

**Menopausal Hormone Therapy, 24-Hour Movement Behaviours, and Cardiovascular Risk
in Postmenopausal Women: A cross-sectional secondary data analysis of the WARM Hearts
cohort study**

by

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Abstract

Background: Postmenopausal women face a heightened risk of cardiovascular disease due to hormonal and aging-related physiological changes. Menopausal hormone therapy (MHT) is often prescribed to manage vasomotor and other menopause-related symptoms, but its cardiovascular (CV) safety profile remains debated. Current evidence suggests that the health effects of MHT may vary by hormone type, route of administration, and timing of initiation. Meanwhile, 24-hour movement behaviours such as physical activity (PA), sleep, and sedentary time are independently associated with CV risk. However, few studies have focused on MHT and these three movement behaviours in tandem regarding their influence on CV outcomes in postmenopausal women.

Objectives: The first objective was to replicate and extend previous work from our research group by evaluating associations between the route of unopposed estrogen MHT and CV outcomes using a larger sample size and incorporating 24-hour movement behaviours into analyses. The second objective was to assess whether CV outcomes differ by MHT usage history, hormone type, and route of administration, and to evaluate whether movement behaviours account for more variation in CV risk than MHT exposures.

Methods: A cross-sectional secondary analysis was conducted using baseline data from 929 postmenopausal women in the Women's Advanced Risk-assessment in Manitoba (WARM) Hearts cohort. MHT exposure was classified by usage history (former or current usage), hormone type (combined estrogen-progestogen or unopposed estrogen), and route of administration (oral, transdermal, or vaginal). Movement behaviours were assessed via wrist-worn accelerometry and included daily moderate-to-vigorous PA (MVPA), stationary time, and sleep duration. Outcomes included arterial stiffness (e.g., aortic pulse wave velocity; aPWV), blood pressure, the Framingham Risk Score (FRS), waist circumference (WC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and fasting glucose. Group differences were assessed via ANOVA and Kruskal-Wallis tests. Hierarchical multivariable linear regression models examined associations between MHT exposures and CV outcomes, adjusting for physiological and sex and gender-related covariates.

Results: Increasing the sample size corroborated most findings from the original publication, in which oral unopposed estrogen MHT was associated with greater arterial stiffness and systolic blood pressure than vaginal use and controls. New analyses indicated that former MHT usage

and oral MHT usage were associated with relatively less favourable CV outcomes compared to controls, current users, and vaginal users, particularly for aPWV and FRS. The type of MHT was not consistently associated with CV outcomes. However, associations between MHT and CV outcomes were statistically but not clinically significant, and average values for these variables were within normal ranges for all user groups. In regression models for both objectives, adding movement behaviours significantly improved model fit beyond MHT exposures for most CV outcomes. MVPA showed stronger associations with cardiovascular outcomes than any MHT exposure and was linked to more favourable 10-year CVD risk, arterial stiffness, blood pressure, waist circumference, and metabolic profiles.

Conclusion: MHT use does not appear to confer clinically significant CV risk in a cohort of healthy Canadian postmenopausal women. Furthermore, the relationships between MHT and CV were often better explained by other variables, particularly movement behaviours. MVPA was the strongest and most consistent predictor of CV health in this analysis. Therefore, regardless of MHT use, postmenopausal women should focus on meeting the MVPA recommendations articulated in the Canadian 24-hour movement guidelines to promote CV health and prevent CVD. These findings can contribute to the ongoing refinement of clinical guidelines and help postmenopausal women make decisions about MHT usage that are tailored to their unique needs, movement behaviours and treatment goals.

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Dedication

To Amma, Papa, Grandma, and Grandpa.

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List of Abbreviations

24HMG: 24-Hour Movement Guidelines

AIx75: Augmentation index standardized to 75 beats per minute

APOs: Adverse pregnancy outcomes

aPWV: aortic pulse wave velocity

BMI: Body mass index

CV: Cardiovascular

CVD: Cardiovascular disease

D1SBP: Day 1 systolic blood pressure

D1DBP: Day 1 diastolic blood pressure

DBP: Diastolic blood pressure

ENMO: Euclidean Norm Minus One

FRS: Framingham Risk Score

HDL-C: High-density lipoprotein cholesterol

LDL-C: Low-density lipoprotein cholesterol

MET: Metabolic equivalent

MHT: Menopausal hormone therapy

MVPA: Moderate-to-vigorous physical activity

PA: Physical activity

SB: Sedentary behaviour

SBP: Systolic blood pressure

SIB: Sustained inactivity bout

SPT: Sleep period time

StaB: Stationary behaviour

TG: Triglycerides

WARM: Women's Advanced Risk-assessment in Manitoba

WC: Waist circumference

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Chapter 1: Literature Review

1.1 Menopause

Menopause is a natural and nearly universal biological transition in females, defined as the permanent cessation of ovarian follicular activity, concurrent with twelve consecutive months of amenorrhea.¹⁻³ This transition generally occurs between the ages of 45 and 55, with a median age of approximately 51 years in Canada.^{1,4} However, substantial variability in the age of natural menopause exists, with approximately 1-3% of women experiencing primary ovarian insufficiency, defined as menopause occurring before the age of 40 years, and an additional 7-9% undergoing early menopause between the ages of 40 and 45 years.^{1,3}

The transition to menopause is referred to as perimenopause. It represents a dynamic physiological phase characterized by hormonal fluctuations that precipitate irregular menstrual cycles and, often, the emergence of menopause-associated symptoms.^{1,5} Vasomotor symptoms, colloquially known as hot flashes and night sweats, affect 50-80% of women, may manifest several years prior to the final menstrual period, and can persist for several years afterwards.^{6,7} Other bothersome symptoms include sleep disturbances, urogenital symptoms (e.g., vaginal dryness, dyspareunia, overactive bladder), cognitive challenges (e.g., 'brain fog'), stress, anxiety, and depressive symptoms.^{1,2,7-9}

Beyond the symptomatic burden, menopause represents a window during which biological aging exerts profound effects on health in multiple bodily systems. A decline in circulating estrogen levels precipitates adverse changes in lipid profiles, vascular compliance, insulin sensitivity, visceral adiposity, and endothelial dysfunction, collectively contributing to an elevated risk of cardiovascular disease (CVD).^{2,5,10-14} Early menopause (whether occurring naturally or surgically) and primary ovarian insufficiency further amplify the risk of coronary heart disease, heart failure, and stroke, potentially by up to 50%, or by 3% for every one-year decrease in age at menopause.^{2,5,15} Moreover, the reduction in estrogen levels appears to heighten susceptibility to osteoporosis, cognitive decline, and anxiety and depression.¹⁶⁻¹⁸

Several modifiable factors influence both the timing of menopause and its subsequent health implications. Among women in the Canadian Longitudinal Study on Aging, smoking, lower socioeconomic status, lower education, and existing cardiovascular (CV) comorbidities

were associated with earlier onset of menopause, while obesity, current employment, and alcohol consumption were linked to delayed onset.⁴ Lifestyle interventions, including physical activity (PA) promotion, smoking cessation, a balanced diet, and cognitive behavioural therapy, are emphasized as critical strategies for managing symptoms of menopause and reducing long-term risk of CVD, cancer, and osteoporosis.^{1,9,12}

While optimizing lifestyle behaviours remains a fundamental strategy for promoting healthier aging during and after menopause, other medical approaches targeting the hormonal changes underlying these risks have been pursued. Menopausal hormone therapy (MHT) is one of the more commonly studied interventions in menopause research due to its potential to alleviate symptoms and modify long-term health trajectories.

1.2 Menopausal Hormone Therapy

For over 80 years, MHT has been recognized as a potential treatment for alleviating menopause-related symptoms and preventing certain long-term health risks.¹⁹ Current women's health guidelines, including those from the Society of Obstetricians and Gynaecologists of Canada, recommend MHT as a first-line treatment for vasomotor symptoms and as a preventive strategy for osteoporosis in women without contraindications.^{20–24}

Estrogen therapy was first introduced in clinical practice in the 1930s and 1940s, initially for symptom relief.^{25,26} In 1941 and 1942, conjugated equine estrogens were formally approved in Canada and the US, respectively, for treating menopausal symptoms.^{25,26} By the 1960s and early 1970s, MHT usage was growing more prominent, accelerated by continued evidence for symptom relief, as well as a popular narrative that estrogen therapy was a cure for a supposed 'loss of femininity' occurring with menopause.^{26,27} However, concerns emerged in the mid-1970s when unopposed estrogen use (i.e., without the use of progestogens to balance the effects of estrogen) was linked to an increased risk of endometrial cancer, prompting the widespread adoption of combined estrogen-progestogen regimens for women with an intact uterus.^{25–28} Throughout the 1980s and 1990s, MHT continued to be widely prescribed, supported by trials such as the Postmenopausal Estrogens Progestins Interventions (PEPI) trial in 1995, which indicated favourable CV effects.^{26,27,29}

Perceptions and prescription trends for MHT shifted dramatically with the publication of the Women's Health Initiative results in 2002, which reported increased risks of breast cancer, stroke, and other CV events among MHT users.³⁰ Widespread concern about these findings ensued, evidenced by actions such as the US Food and Drug Administration issuing “black box” warnings on MHT products (which are strict warnings to patients and healthcare providers about possible hazards associated with the product).^{31,32} Additionally, media reports of the Women's Health Initiative findings, which did not adequately describe the limitations of the study (e.g., findings were not statistically significant, the participants were over 10 years post-menopause on average, and only a single estrogen and progestogen type and dose were tested), contributed to widespread fear and a sharp decline in MHT prescribing.^{25–27,33–37} These declines were observed in Manitoba, Québec, and internationally in the US, Australia, New Zealand, Wales, the Netherlands, Finland, France, Spain, Germany, and South Korea.^{38–49}

In retrospect, re-analyses of Women's Health Initiative data and findings from subsequent trials such as KEEPS⁵⁰, ELITE⁵¹, and DOPS⁵² have demonstrated that the risks and benefits of MHT may depend on the timing of initiation relative to the onset of menopause.²⁶ Early initiation of MHT (within 10 years of menopause) may confer CV benefits, whereas late initiation may be more harmful – a concept coined the “timing hypothesis.”^{53,54} Furthermore, different types of hormone combinations and formulations, dosages, and routes of administration also may differentially influence health outcomes.⁵⁵ In 2026, the general expert consensus is that MHT can be a safe and highly effective treatment option for most women to manage bothersome menopause symptoms, as evidenced by contemporary clinical guidelines and the recent removal of the “black-box” labelling on MHT by the US Food and Drug Administration.^{20,22,31,32,56,57}

Despite the evidence clarifying the nuances of MHT safety, public skepticism and fear have persisted.^{58–61} Studies have found that women's decisions regarding MHT use are affected by concerns about cancer and CVD risk, perceptions of MHT from family and friends, and, importantly, knowledge and awareness of the efficacy of MHT.^{59–61} In a 2019 narrative review, Dr. Robert Reid also identified several factors contributing to the fear of MHT, which included (1) media publicity and misinformation; (2) lack of statistical literacy; and (3) distrust of corporations and “big pharma” in general.⁶² Researchers can help address the first two points by continuing to accumulate evidence and by reporting findings transparently. Comprehensible

effects of more informed public health recommendations and actions on MHT uptake, such as continual updates to clinical guidelines and the removal of “black box” warnings, remain to be seen. However, researchers from the UK and Sweden observed increases in MHT use in these countries between 2015 and 2021 (with the exception of 2020 due to COVID-19), concurrent with earlier guideline updates and research.^{63,64} Therefore, continued efforts to expand the evidence base on MHT and improve knowledge translation and mobilization are warranted.

Beyond postmenopausal women themselves, healthcare providers may be reluctant to prescribe MHT despite these advancements in knowledge and clinical guidelines.^{65–68} Willingness to prescribe MHT may be influenced by the comprehensiveness of medical education, medical specialization, and the extent to which healthcare providers understand current best practices.^{65,66,68} The quality of healthcare counselling is thus an important area to improve, as women seeking aid in managing menopausal symptoms may not be receiving the most current and accurate information.^{59,61} The persistent caution and unfamiliarity with MHT has potential consequences, in that continued underutilization of MHT may negatively impact the health and quality of life of many postmenopausal women.^{27,62} When updates are made to clinical guidelines, clarity and completeness of information must be emphasized, and knowledge mobilization strategies must be optimized.

As previously mentioned, various types of MHT formulations, including estradiol, conjugated equine estrogens, synthetic progestins, and micronized progesterone, as well as different routes of administration (e.g., oral, transdermal, or vaginal routes), further complicate assessments of risk and benefit.^{20,21,55} For example, transdermal administration may offer a lower risk of thromboembolic events and more favourable cardiometabolic effects compared to oral formulations.⁵⁵ Oral MHT undergoes first-pass metabolism in the liver, stimulating the synthesis of various hepatic proteins, including procoagulant factors and inflammatory markers.^{69,70} This hepatic stimulation increases clotting factors (such as factors VII and VIII), C-reactive protein, triglycerides (TG), and other metabolites, contributing to an elevated thrombotic risk profile.^{69,70} In contrast, transdermal estrogen bypasses first-pass metabolism and the subsequent hepatic stimulation, resulting in a potentially safer CV and thrombotic risk profile. Accordingly, current best practices advocate for individualized MHT type, route, and dose selection based on patient risk profiles and therapeutic goals.^{20,55,61}

Previous work from our research group (Kalenga et al., 2022) examined how the route of unopposed estrogen therapy relates to CV outcomes in a subset (N = 278) of postmenopausal women who participated in the Women's Advanced Risk-assessment in Manitoba (WARM) Hearts Study (Clinical Trial: NCT03938155).^{71,72} Women using oral unopposed estrogen therapy had significantly higher systolic and diastolic blood pressure compared to controls and those using transdermal and vaginal formulations.⁷¹ The findings align with published evidence suggesting that the route of administration may be an important determinant of CV risk. However, this study was limited by its sample size, focus on a single hormone formulation (unopposed estrogen), and lack of adjustment for lifestyle movement behaviours. Furthermore, the analyses were conducted during the COVID-19 pandemic and, therefore, could only consider the first 328 participants who were recruited. The WARM Hearts trial has since been completed, with a final total of 1018 participants. Given these limitations and the established recognition that lifestyle factors contribute to CV risk, there is a need to re-examine these associations with a larger sample and a more comprehensive set of exposures.

Movement behaviours such as PA, sedentary behaviour (SB), and sleep are well-established, independent contributors to CVD risk.^{2,73–75} Reflecting this evidence, the Canadian 24-Hour Movement Guidelines (24HMG) for adults aged 18-64 and those aged 65 and older were released in 2020, replacing the 2011 Canadian Physical Activity Guidelines.^{76,77} Unlike their predecessor – which focused solely on moderate-to-vigorous PA (MVPA), muscle- and bone-strengthening activities, and balance training (for adults aged 65 and older) – the 24HMG emphasizes movement behaviours across the full 24-hour day.^{76,77} They incorporate additional recommendations for SB and sleep, which influence health independently and interactively.⁷⁶

Despite this growing understanding, much less is known about how 24-hour movement behaviours influence health outcomes in the context of MHT, representing an important but understudied area of research. It is possible that movement behaviours better explain benefits and risks to CV health previously attributed to hormonal changes alone. However, most studies to date have examined MHT usage without adequately considering 24-hour movement behaviours. Meanwhile, the international Menopause Priority Setting Partnership has recently emphasized the need to better understand the role of lifestyle behaviours in supporting health during menopause transition.⁷⁸ Since MHT and lifestyle behaviours might independently influence CV

and overall health, investigating their effects together would provide a more comprehensive understanding of the safety and efficacy of MHT and support more personalized intervention strategies for postmenopausal women. The following sections will discuss the current evidence on the role of PA, SB, and sleep in postmenopausal health in combination with MHT usage.

1.3 Physical Activity, MHT, and Postmenopausal CV Health

PA is a central component of CVD prevention and overall healthy ageing.⁷³ For postmenopausal women, engaging in regular PA has been linked to improvements in CVD incidence and mortality, lipid profiles, insulin sensitivity, vascular compliance, body composition, musculoskeletal health, and psychological well-being, all of which help counteract the physiological changes that occur during and after the menopausal transition.^{74,79–83} The Canadian 24HMG recommends that all adults, including older women, engage in at least 150 minutes of MVPA and several hours of light-intensity PA per week to support health outcomes.⁷⁶

Despite the well-known benefits, approximately 55% of Canadian adults do not meet the recommended amount of PA outlined in the 24HMG for a multitude of intersecting reasons.⁸⁴ For example, older age, female sex, lower education, lower income, and childcare responsibilities have all been associated with lower PA levels among participants in the Canadian Health Measures Survey.⁸⁴ The menopausal transition may also play a role in declining PA levels.^{85–87} In the Montreal-Ottawa New Emerging Team study, energy expenditure and PA levels decreased among Canadian females transitioning from pre-menopause to post-menopause over a 5-year period.⁸⁵ A follow-up sub-study of this data found a similar trend over the 10-year window surrounding their final menstrual period, where the number of years since this period was negatively associated with pre-menopause PA levels.⁸⁶ Metabolic changes associated with age and the post-menopause period, including a decrease in resting energy expenditure, loss of fat-free mass, as well as declines in estrogen, were reasons hypothesized by the authors to explain the trend of decreasing energy expenditure.⁸⁵ However, since there is evidence that PA declines with both age and during the menopausal transition, it is difficult to disentangle how much of these decreases can be explained by physiological and functional changes occurring with age among males and females, compared to menopausal-related changes and other socioecological factors relevant to this life stage that are experienced by females and not males. For instance, menopausal symptoms; lack of time, energy, and money; family responsibilities; insufficient

guidance from healthcare practitioners; insufficient knowledge about the benefits of PA; and community safety concerns have been identified as barriers to PA in postmenopausal women.^{87,88}

The body of research examining how PA may associate with MHT to influence CV outcomes remains limited and highly heterogeneous (Table 1a; Table 1b).^{89–113} That is, existing studies differ widely in design, MHT regimens, and PA protocols and measurements, contributing to inconsistent and conflicting findings regarding their independent and combined effects on health outcomes. It should be noted that, in the listed studies, PA was an explicit exposure of interest, and not simply a confounding variable (a summary of all studies that adjust for movement behaviours in their analyses is beyond the scope of this thesis). Despite the heterogeneity, these studies provide insights that have helped inform the rationale and direction of this thesis. For example, evidence from 34,212 participants of the California Teachers Study revealed that postmenopausal women who met the American Heart Association PA guidelines and concurrently used MHT had stroke risks comparable to never-users of MHT.¹¹³ Conversely, MHT users who were inactive had significantly higher stroke risk. These findings suggest that PA may attenuate the adverse cerebrovascular effects associated with MHT.

Several groups of researchers have explored how MHT and PA may influence blood pressure (BP) and hemodynamics through exercise interventions. Analyses of a single randomized controlled trial (reported by Cardoso Jr. et al. in 2011 and Oneda et al. in 2014) suggested that a 6-month aerobic training program prevented the rise in daytime diastolic blood pressure (DBP) otherwise attributed to unopposed oral estrogen therapy.^{90,92} Oral estrogen also appeared to blunt exercise-related reductions in muscle sympathetic nerve activity and improvements in blood flow, collectively suggesting that unopposed oral estrogen may interfere with some of the vascular benefits typically gained from aerobic exercise.^{90,92} Conversely, results from the DREW trial showed no difference in BP between the exercise intervention and control groups, although the results for this outcome were not stratified by MHT usage status, despite 45% of the study group being current users.¹⁰³ An 8-week aerobic exercise intervention in another study improved heart rate variability and lowered resting heart rate, independent of MHT use.¹⁰⁴ Similarly, three additional trials reported improvements in BP and vascular function following aerobic training, with no evidence that MHT use altered these effects.^{93,105,107} However, in a trial where women were randomized to placebo, unopposed oral estrogen, or

unopposed transdermal estrogen before undergoing the same 12-week exercise program, both oral and transdermal estrogen enhanced flow-mediated dilation after training compared to the placebo, but BP improvements occurred only in the transdermal group, indicating a possible beneficial interaction between MHT and PA that is route-specific.⁹⁴

Observational studies have also investigated differences in hemodynamic outcomes by MHT status and PA levels. In a large Swedish cohort (n = 6917), ever-users of MHT had more favourable CV profiles, including lower BP, regardless of self-reported PA levels, suggesting that MHT confers vascular benefits independent of lifestyle factors.¹¹⁴ Another study found that MHT was associated with lower DBP, while habitual PA was independently linked to lower systolic blood pressure (SBP), SBP variability, and a blunted BP response to exercise, with no interaction effects between MHT and PA reported.⁹⁵ In contrast, a different study found that endurance-trained women had lower age-related increases in vascular resistance, but MHT use had no association.⁹⁶ Lastly, a study investigating vascular stiffening found that both MHT and regular PA were independently associated with greater carotid arterial compliance, indicating that each may help attenuate vascular stiffening with age.¹¹⁰ Evidently, there is considerable variability in how MHT may influence vascular function, with some evidence of route-specific effects but no consistent pattern in its interaction with exercise-induced outcomes.

Another set of trials and observational studies examined associations between MHT and PA on lipid profiles. Randomized trials have shown that MHT alone may improve high-density lipoprotein cholesterol (HDL-C) and reduce low-density lipoprotein cholesterol (LDL-C) and total cholesterol, although it may also raise TG levels, particularly with oral formulations.^{93,97–99,106} Exercise training consistently appeared to improve total cholesterol and LDL-C, with one study suggesting a synergistic benefit when combined with MHT.⁹⁷ However, the other trials reported no additional lipid improvements beyond those achieved by either intervention alone. One cross-sectional study found that the combination of MHT and regular PA may yield the most favourable lipid ratios and oxidative markers.⁸⁹ Meanwhile, other studies identified that the best lipid profiles were present in women with higher fitness and PA levels, independent of MHT usage^{100,111}, or that MHT and PA each independently improve lipid profiles.^{101,114}

The effect of MHT on exercise-induced changes in body composition has also been studied. Two trials with structured PA interventions reported significant increases in lean mass

and reductions in fat mass among postmenopausal women randomized to an exercise program, independent of MHT usage.^{102,115} Other studies have identified independent beneficial associations between both MHT and regular PA with metrics such as visceral fat, waist circumference, waist-to-hip ratio, and lean tissue, although no synergistic effects were observed.^{99,106,108} These findings suggest that, while MHT may not amplify exercise-induced changes in body composition, it may help maintain or support these physiological adaptations.

Several studies have shown that CV fitness improves with exercise training regardless of MHT status. Peak oxygen uptake ($\text{VO}_{2\text{peak}}$) refers to the highest measured value of oxygen consumption during graded exercise testing and can be used to estimate CV fitness, particularly when a true $\text{VO}_{2\text{max}}$ is not achieved.¹¹⁶ $\text{VO}_{2\text{max}}$ represents the maximal physiological limit of oxygen uptake, indicated by a plateau in oxygen uptake despite increasing workload, while $\text{VO}_{2\text{peak}}$ is considered a valid alternative when a plateau cannot be confirmed.¹¹⁶ Multiple trials have found that aerobic training improves CV fitness outcomes such as $\text{VO}_{2\text{max}}$, $\text{VO}_{2\text{peak}}$, and submaximal heart rate and VO_2 in exercising participants, independent of MHT usage.^{93,99,103,104,107} However, a different exercise trial found that, although MHT and aerobic training increased $\text{VO}_{2\text{peak}}$, gains were significantly smaller in the unopposed estrogen-treated group, suggesting a blunting of adaptation.⁹¹ Moreover, in the trial comparing placebo, oral estrogen, and transdermal estrogen with concomitant aerobic training, only those receiving oral estrogen experienced increases in $\text{VO}_{2\text{peak}}$ following the exercise intervention, suggesting that exercise responses may be specific to the route of administration.⁹⁴ Given the inconsistent findings, further research is needed to determine whether MHT affects physiological adaptations to aerobic exercise over time or vice versa.

Lastly, two more observational studies examined metabolic profiles and coronary artery calcification, yielding mixed results. In one study, MHT use was associated with lower fasting insulin but was also linked to reduced insulin sensitivity, whereas physically active women (particularly those engaging in vigorous-intensity PA) had the most favourable metabolic profiles, suggesting that PA may exert stronger benefits than MHT in this domain.¹⁰⁹ In contrast, another study found that MHT users had significantly lower coronary artery calcification scores than non-users, independent of PA.¹¹² However, the association between PA and artery

calcification varied by MHT status: while PA was linked to lower artery calcification in MHT non-users, it was paradoxically associated with higher calcification among MHT users.

Collectively, these findings (summarized in Tables 1a and 1b) call attention to the complexity of MHT-PA interactions. While some data suggest additive or synergistic benefits, others indicate that MHT may blunt or modify expected exercise responses, and some studies report no measurable effect at all. Factors such as hormone type, route, timing, and individual fitness or health status likely contribute to these discrepancies. Several limitations in the current evidence base should be acknowledged. Aside from the handful of controlled trials that employed supervised interventions, all observational and cohort studies that estimated habitual PA patterns did so using self-report measures.^{89,95,96,101,109–114} This introduces potential for recall bias and measurement error. Additionally, most of the cited studies were conducted 15 to 30 years ago, raising concerns about the relevance of their findings to contemporary populations and MHT formulations. Indeed, most studies did not stratify or adjust for differences in hormone type, dose, route, or duration of MHT use.^{89,95,96,99–103,105,108–114} Lastly, the possibility of “healthy user bias” is a pertinent concern, particularly in observational studies where MHT users may differ from non-users in socioeconomic status, health behaviours, or access to care, all of which could confound associations with PA or health outcomes.^{117–119}

Overall, the available evidence suggests that PA is beneficial for postmenopausal women regardless of hormone status. However, the degree to which MHT modifies the physiological response to exercise, and conversely, whether regular exercise influences the body’s responses to MHT, remains incompletely understood. Further research is needed to clarify whether lifestyle behaviours can buffer MHT-associated risks, augment its benefits, or produce distinct outcomes in combination.

1.4 SB, MHT, and Postmenopausal CV Health

SB is increasingly recognized as an independent health risk factor, particularly among aging populations, and research interest has increased accordingly.¹²⁰ According to the Sedentary Behaviour Research Network, SB is defined as any waking behaviour characterized by an energy expenditure of less than or equal to 1.5 metabolic equivalents (METs) while in a sitting or reclining posture.¹²¹ This is a precise definition that should not be conflated with terms such as

physical inactivity (defined as insufficient PA to meet current guidelines) or stationary behaviour (referring to any waking behaviour involving no ambulation, regardless of energy expenditure).^{121,122} Under these definitions, one can achieve the recommended amount of SB but fail to meet the PA recommendation (i.e., physical inactivity), or vice versa. This distinction is important because both behaviours appear to have independent effects on health.¹²² For example, Chen's (2024) Master's thesis, which analyzed WARM hearts data, reported different relationships with CV outcomes depending on whether participants met PA guidelines only, SB guidelines only, or both.¹²³ Furthermore, SB has also been independently linked to elevated CVD risk, vascular dysfunction, metabolic markers, and cognitive impairment in older adults.^{75,83,124–126}

The Canadian 24HMG recommend limiting sedentary time to less than 8 hours per day for adults of all ages, emphasizing the importance of breaking up prolonged sitting and limiting recreational screen time to under 3 hours per day.⁷⁶ Despite these recommendations, device-based studies suggest that the health risk threshold may be slightly higher when SB is measured objectively with an accelerometer rather than subjectively by self-reported questionnaires. For example, a meta-regression analysis involving over 1 million participants revealed that the risk of all-cause mortality increased more steeply above 9 hours of accelerometer-measured sedentary time per day compared to lower thresholds.¹²⁷ A follow-up meta-regression of older adult populations supported this threshold, showing similar risk elevations beginning at or just above 9 hours of daily SB.¹²⁸ This discrepancy likely reflects differences between self-reported and device-measured estimates, as self-reported methods tend to underestimate total sedentary time.¹²⁹ Given that most SB research to date has relied on self-reported measures, adopting a 9-hour threshold may provide a more pragmatic and evidence-aligned cut-point for accelerometer-based analyses.¹³⁰ Still, among Canadians, data show that females aged 50 – 64 accumulate a mean of 9.9 hours of SB per day (95% CI: 9.6 – 10.2), with slightly higher estimates among females aged 65 – 79 (mean 10.2 h/day; 95% CI: 9.9 – 10.4).¹³¹

Recent reviews have further established SB as a key contributor to cardiometabolic and CV risk in older adults. For instance, high levels of sedentary time have been associated with increased all-cause and CV mortality, particularly among those with low PA levels.^{76,126,130} In fact, breaking up long periods of SB with short bouts of MVPA, or incorporating bouts of high-

intensity PA throughout the day in general, may both offset the negative health effects of SB.^{132–137} Still, other health outcomes are deleteriously impacted by SB. For example, SB is linked to diminished physical function, cognitive decline, and poorer mental health in older adults, although these effects may have been exacerbated during the COVID-19 pandemic.¹²⁴ Other studies have demonstrated that greater sedentary time and longer uninterrupted sitting bouts were independently associated with higher carotid-femoral pulse wave velocity, a marker of arterial stiffness.⁷⁵ Similarly, Williams et al. (2021) summarized mechanistic links between SB and impaired vascular remodelling, noting that prolonged sitting may reduce hemodynamic shear stress and contribute to endothelial dysfunction.¹²⁵

Unlike PA, SB was not the central focus of any of the identified studies involving it as a behaviour (Table 1a; Table 1b). Instead, SB was typically operationalized as baseline inactivity, either to ensure participants were untrained prior to an exercise intervention or to serve as a non-active control group. Consequently, outcomes reported in “sedentary” participants reflect either the absence of exercise or the isolated effects of MHT. For example, two observational studies compared MHT use among sedentary women yielded somewhat conflicting results. Ryan et al. (2002) found that sedentary MHT users had lower insulin sensitivity than nonusers, while Perry et al. (1998) observed more favourable lipid and adiposity profiles in MHT users, suggesting potential but inconsistent cardiometabolic effects.^{138,139} Several studies discussed in Chapter 1.3, which treated SB as the absence of PA, suggested that MHT may independently influence some CV markers in inactive women, including lipid profiles, body composition, and hemodynamics.^{90,91,93–95,97,99,101,106,108–110,113} While this design allows for isolation of MHT and exercise effects, it offers limited insight into SB as an independent behavioural exposure. Since most studies did not measure SB directly, its role in modifying MHT-related CV outcomes is still unknown. More studies are needed to assess SB directly and objectively, treating it as a distinct behavioural exposure rather than a passive comparator to PA. A summary of these studies incorporating SB in their research on MHT is outlined along with the studies on PA and MHT in Tables 1a and 1b.

Evidently, SB remains underexplored in menopause research. Despite recognizing its health risks, it is rarely assessed in conjunction with MHT use in observational studies or clinical trials. As such, understanding whether MHT can buffer (or magnify) the physiological harms of SB or whether SB may diminish (or augment) the potential effects of MHT should be a priority

of women's health research. Clarifying these interactions is important given the increasing prevalence of SB with age and the unique hormonal environment of postmenopausal women.

Table 1a. Summary of Trials on PA and/or SB with CV Outcomes.

Authors, Date	Sample size and population	Trial Details	MHT regimen	PA measurement	SB measurement	CV outcome	Findings
Aragão et al., 2014 ¹⁰²	158 postmenopausal women (88 exercise, 70 control); age range 42-68; 58% used MHT	12-month RCT; exercise group: supervised exercise sessions 3x/week for 1 hour; control group: maintain usual lifestyle	Not specified (MHT use self-reported; no dosage or route reported)	Structured program; AT (50-84% HRR), RT (70-80% 1RM), FT	Not measured; sedentary lifestyle inferred at baseline; control group maintained habitual activity	Body composition (BMI, fat mass, muscle mass)	Exercise significantly improved lean mass and reduced visceral fat; no interaction with MHT, suggesting an independent effect of exercise
Binder et al., 1996 ⁹⁷	71 healthy, sedentary postmenopausal women, aged 60-72 years	11-month RCT; 4 groups: Control, exercise only, MHT only, and exercise + MHT	0.625 mg/day oral CEE (Premarin), + 5 mg MPA for 13 days every 3 months	Structured program: 3-5 sessions/week of AT at 65-85% max HR	All participants sedentary at baseline; control group maintained usual activity	Serum lipids (TC, HDL-C, LDL-C, TG); BP; body composition; VO2max	Exercise reduced TC and LDL-C; MHT increased HDL-C and TG, decreased LDL-C; combined MHT + exercise elicited the best outcomes, maintaining all benefits and prevented MHT-related rise in TG
Cardoso et al., 2011 ⁹⁰	47 sedentary, hysterectomized, postmenopausal women, aged 45-60; healthy, normotensive, non-obese, nonsmokers	6-month double-blind RCT with 4 groups: placebo + control; ET + control; placebo + AT; ET + AT	1 mg/day oral E2V (vs. placebo)	Structured program: cycling 3x/week, 20-60 mins at 56-83% VO2peak	All participants sedentary at baseline; control group maintained usual activity	24h ambulatory BP; VO2peak	ET increased 24h, daytime, and nighttime BP. AT improved VO2peak and mitigated ET-induced BP increases.

Authors, Date	Sample size and population	Trial Details	MHT regimen	PA measurement	SB measurement	CV outcome	Findings
Cardoso et al., 2014 ⁹¹	42 sedentary, hysterectomized, healthy postmenopausal women aged 45-60	6-month double-blind RCT with 4 groups: placebo + control; ET + control; placebo + AT; ET + AT	1 mg/day oral E2V (vs. placebo)	Supervised cycling 3×/week (20–60 min); intensity set at respiratory compensation point	All participants sedentary at baseline; control group maintained usual activity	VO ₂ AT, VO ₂ RCP, VO ₂ peak, BP and HR	AT improved VO ₂ measures but gains in VO ₂ AT and VO ₂ RCP were smaller with ET. ET lowered resting HR and had no effect on BP.
Church et al., 2007 (DREW trial) ¹⁰³	464 sedentary, overweight or obese postmenopausal women aged 45-75 (BMI 25-43; SBP 120-159.9 mmHg)	6-month RCT; 4 groups: non-exercise control, 4-, 8-, and 12-kcal/kg/week exercise doses	Baseline MHT use recorded but formulation not specified	Supervised treadmill or cycle ergometer exercise 3–4×/week at 50% VO ₂ peak	Participants sedentary at baseline (< 20 min PA on < 3 days/week; < 8000 steps/day); daily steps tracked with pedometers	Absolute VO ₂ peak, relative VO ₂ peak, BP, waist circumference	VO ₂ peak measures improved with increasing exercise dose, but unaffected by MHT use. BP showed no significant changes.
Green et al., 2004 ⁹⁹	48 sedentary postmenopausal women (18 on MHT, 30 non-MHT)	HERITAGE Family Study; pre-post design; 20-week aerobic training program	Unopposed CEE; dose and route not reported	AT: supervised cycling, 55% VO ₂ max for 30 min/day, 3x/week; gradual progression	Participants were sedentary at baseline	Abdominal visceral fat, waist circumference, waist to hip ratio, lipid profiles, BP, metabolic syndrome status, VO ₂ max	MHT users had lower visceral fat, WC, waist to hip ratio, and more favourable lipid profiles. Exercise improved VO ₂ max but had a minimal effect on metabolic syndrome. No additive benefit of MHT plus AT observed

Authors, Date	Sample size and population	Trial Details	MHT regimen	PA measurement	SB measurement	CV outcome	Findings
Heikkinen et al., 1997 ⁹⁸	78 healthy postmenopausal women (aged 49-55)	2-year RCT with stratified exercise subgroups; compared 2 E2V + MPA regimens vs placebo, with and without exercise	Oral sequential E2V (2 mg) plus MPA (10-20 mg) in two dosing schedules	Combined AT and RT: 1x/week supervised RT plus 2x/week self-directed AT	Not reported	Anerobic threshold, TC, LDL-C, HDL-C, TG	MHT improved TC and LDL in year 1; no significant effects on HDL-C or TG. Anaerobic threshold declined over time with no effect of MHT or exercise
Jurca et al., 2004 ¹⁰⁴	88 sedentary postmenopausal women; mean age ranged from 56.0 to 57.4 depending on group; BMI 25-40; SBP 120-159.9 mmHg; 56% using MHT	8-week RCT; aerobic exercise group vs control group	Self-reported current use: unopposed ET or combined therapy; not manipulated in trial	Supervised moderate-intensity AT: treadmill or cycling, 3-4x/week (~44 mins/session) at 50% VO2max	All participants sedentary at baseline; control group maintained usual activity	HRV, resting HR	Exercise significantly improved HRV and reduced resting HR. MHT did not influence these responses.
Kirwan et al., 2003 ¹⁰⁵	38 postmenopausal women with CAD; age 53-71; stratified by MHT status (18 on MHT, 20 not)	26-week cardiac rehab program with stratification by MHT use	Self-reported oral unopposed ET or combined therapy for at least 1 year; route and dose varied	Supervised AT: progressive walking 5x/week, 45-60 min/session at 65-75% VO2peak	Not reported	VO2peak, anerobic threshold, submaximal HR and cardiac output, calf blood flow, vascular conductance	MHT users had higher VO2peak at baseline but showed similar training responses. Improvements in VO2peak, anaerobic threshold, and vascular function occurred regardless of MHT status

Authors, Date	Sample size and population	Trial Details	MHT regimen	PA measurement	SB measurement	CV outcome	Findings
Lara et al., 2010 ¹⁰⁶	34 healthy, postmenopausal women, mean age 50 ± 2.7 years.	4-month crossover study; assessed association between PA levels, body composition, and metabolic variables before and after MHT	non-oral (3 mg/day intranasal estradiol daily and 200 mg/day vaginal micronized progesterone for 14 days/month) or daily low-dose oral (oral estradiol 1 mg and drospirenone 2 mg/day) preparations	Objective (pedometer); participants categorized as active (>6000 steps/day) or inactive (≤ 6000 steps/day)	Objective (pedometer step count); “inactive” defined as ≤ 6000 steps/day	WC, waist-to-hip ratio, body fat %, TC, LDL-C, HDL-C, TG, fasting glucose	After 4 months of MHT, both active and inactive women had reduced WC, waist-to-hip ratio, TC, and LDL-C. However, body fat % was lower in active vs inactive women. Negative correlations between step count and anthropometric measurements were only observed post-MHT
Lindheim et al., 1994 ⁹³	101 healthy, sedentary, postmenopausal women aged 42-59	6-month RCT. 4 groups: Control, exercise, CEE, or CEE + exercise	CEE 0.625 mg/day on days 1-25 of each month	AT: supervised treadmill and stationary cycling at $\sim 70\%$ max HR, 3x/week, 30 mins/session	All participants sedentary at baseline; control group maintained usual activity	VO2max, SBP, TC, TG, LDL-C, HDL-C, HDL/LDL ratio	CEE alone decreased TC, TG, and LDL-C and increased HDL/LDL ratio. Exercise improved VO2max and lipid profile except HDL-C. VO2max increased in exercise and CEE + exercise groups. SBP decreased in

Authors, Date	Sample size and population	Trial Details	MHT regimen	PA measurement	SB measurement	CV outcome	Findings
							all groups. No additive effect for CEE + exercise
Moreau et al., 2013 ⁹⁴	36 sedentary postmenopausal women aged 45-65, plus 7 estrogen-deficient, postmenopausal, endurance-trained controls	RCT with 12 weeks of MHT assignment (placebo, oral E2, transdermal E2) followed by 12 weeks of exercise while continuing assigned treatment	Oral E2 (1 mg/day) or transdermal E2 patch (0.05 mg/day)	AT: endurance walking, 40-45 mins/day, 5-7 days/week, at 65-80% max HR, for 12 weeks	Not reported	Flow-mediated dilation, SBP, VO2peak	E2 alone increased FMD; FMD improved further with AT in both E2 groups but not placebo. VO2peak increased only in oral E2 group. SBP decreased only in transdermal E2 group. Endothelial benefits of AT were ET-dependent
O'Donnell et al., 2006 ¹⁰⁷	23 healthy, sedentary postmenopausal women, mean age 57	12-week RCT; 11 participants on MHT, 12 on placebo	Oral 17 β -estradiol (1 mg/day) with cyclic micronized progesterone (200 mg/day for 10 days per month)	AT: walking 5 days/week, 45 minutes/session at 70-80% peak HR	All participants sedentary at baseline; control group maintained usual activity	Submaximal HR, VO2, stroke volume, cardiac output; total peripheral resistance; VO2peak; ventilatory threshold; resting and peak ischemic calf blood flow	CV improvements (increased VO2peak, and ventilatory threshold, decreased submaximal HR and VO2) occurred with training regardless of MHT. MHT did not alter central or

Authors, Date	Sample size and population	Trial Details	MHT regimen	PA measurement	SB measurement	CV outcome	Findings
							peripheral adaptations.
Oneda et al., 2014 ⁹²	45 healthy, hysterectomized, postmenopausal women, mean age 51	6-month RCT with 4 groups: placebo + control; ET + control; placebo + AT; ET + AT	Oral E2V, 1 mg/day	AT: cycling 3x/week, 20-50 min/session, intensity progressed from anaerobic threshold to respiratory compensation point	All participants sedentary at baseline; control group maintained usual activity	Forearm blood flow, HR, BP	AT increased forearm blood flow in placebo and MHT groups. HR decreased only in the ET + AT group. BP was unaffected by MHT or AT.
Teixeira et al., 2003 ¹⁰⁸	233 sedentary postmenopausal women aged 40-66	1-year RCT; exercise vs non-exercise, stratified by MHT use; MHT regimens varied	Participant-prescribed MHT; majority used oral unopposed ET (32%) or oral combined therapy (48%). 14% used transdermal routes.	RT and AT: 3x/week, supervised, 60-75 mins/session, including strength exercises and aerobic circuits with progressive intensity	All participants sedentary at baseline; control group maintained usual activity	Body composition (lean soft tissue, fat tissue, BMI, % body fat)	MHT alone preserved lean soft tissue but did not reduce fat tissue. Exercise increased lean soft tissue in all women and decreased fat tissue only in those on MHT. Effects of exercise on body composition exceeded those of MHT alone.

Abbreviations: MHT, menopausal hormone therapy; PA, physical activity; SB, sedentary behaviour; CV, cardiovascular; RCT, randomized controlled trial; HRR, heart rate reserve; AT, aerobic training; RT, resistance training; FT, flexibility training; BMI, body mass index; SBP, systolic blood pressure; CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate; HR, heart rate; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; BP, blood pressure; ET, estrogen therapy; E2, estradiol; E2V, estradiol valerate; VO₂AT, VO₂ at anaerobic threshold; VO₂RCP, VO₂ at respiratory compensation point; WC, waist circumference; TC/HDL-C, total cholesterol to high-density lipoprotein cholesterol ratio; HRV, heart rate variability; CAD, coronary artery disease

Table 1b. Observational Studies on PA and/or SB and CV Outcomes

Authors, Date	Study details	Sample size and population	MHT regimen	PA measurement	SB measurement	CV outcome	Findings
Brown et al., 2000 ¹⁰⁹	Cross-sectional study examining insulin sensitivity in postmenopausal women by MHT use and PA level	60 healthy postmenopausal women (mean age 64 ± 5); groups: sedentary, physically active (non-competitive aerobic exercise), or athletic (competitive runners)	Oral MHT used for at least 2 years; 66% combined therapy; 34% unopposed ET	Subjective (self-reported activity/training history). Classification: sedentary, active, athletic)	Subjective (grouped based on at least 2 years without structured activity)	Insulin sensitivity index, fasting insulin, and intravenous glucose tolerance	MHT associated with lower fasting insulin but reduced insulin sensitivity and glucose tolerance. VPA showed the greatest insulin sensitivity index. PA had stronger positive effects than MHT alone; no added benefit of combining PA and MHT
Haddock et al., 1998 ¹⁰⁰	Cross-sectional data from the Aerobics Center Longitudinal Study examining the relationship between fitness and CV risk with MHT usage	283 nonsmoking, postmenopausal women, mean age 53.0 ± 7.1 .	Self-reported: no MHT, unopposed estrogen, or combined therapy	Maximal treadmill test; fitness measured as total time to exhaustion (proxy for VO2max)	Not directly measured; all participants considered relatively sedentary at baseline	TC, HDL-C, TC/HDL-C, TG, fibrinogen	Higher fitness linked to better lipid and fibrinogen profiles, independent of MHT use. MHT modified the fitness-TC/HDL association but not other outcomes
Hagberg et al., 2003 ¹⁰¹	Cross-sectional; assessed associations between MHT,	60 postmenopausal women; mean age ranged from 61 to 66. Women were	Unopposed ET or combined therapy; stable use for	Subjective (group classification based on habitual PA)	Subjective (self-report of at least 2 years without structured activity)	TC, LDL-C, HDL-C, TG, TC/HDL-C	MHT improved lipid profiles in sedentary and moderately active women.

Authors, Date	Study details	Sample size and population	MHT regimen	PA measurement	SB measurement	CV outcome	Findings
	PA level, and lipids	sedentary, moderately active, or endurance trained; approximately half in each group were on MHT	at least 2 years				Endurance-trained women had the most favourable lipid profiles. There was no added benefit of combining MHT with AT.
Hunt et al., 1997 ⁹⁶	Cross-sectional study comparing MHT and AT in relation to BP and hemodynamics	66 healthy women, aged 21-72, pre- and postmenopausal, sedentary and endurance-trained, with and without MHT	Various estrogen-based regimens; women classified as current MHT users or non-users; duration, route, dose, and type not specified	Self-reported endurance training (distance and hours/week)	Subjective (self-report of at least 2 years without structured activity)	SBP, DBP, cardiac output, stroke volume, systemic vascular resistance, total blood volume	MHT was not associated with differences in BP. Endurance training is linked to preserved cardiac output and lower age-related increases in vascular resistance. No additive benefit of MHT with PA.
Lawler et al., 2002 ⁸⁹	Cross-sectional; examined effects of MHT and PA on lipids	34 healthy, nonsmoking, postmenopausal women (age 50-60) divided into 4 groups: NSD (no MHT, sedentary); NEX (no MHT, exercising); ESD (MHT, sedentary); EEX (MHT, exercising)	Estrogen-based regimens for at least 2 years; duration, route, type, and dose not specified	Subjective; self-reported regular PA (at least 30 mins/session for at least 3 days/week)	Inferred via group categorization; sedentary groups did not engage in structured PA	TC, HDL-C, LDL-C, TG, LDL/HDL ratio, HDL-C oxidation	MHT with regular PA (EEX group) associated with highest HDL-C, lowest LDL/HDL ratio, and lower HDL oxidation compared to NEX group. Neither MHT nor PA alone showed the same benefits. No significant

Authors, Date	Study details	Sample size and population	MHT regimen	PA measurement	SB measurement	CV outcome	Findings
							differences in LDL-C or TG across groups.
Moreau et al., 2003 ¹¹⁰	Cross-sectional; examined MHT and PA on arterial compliance	69 pre- and postmenopausal women. Postmenopausal women were approx. 58-64 years of age. Divided into sedentary and trained groups.	Varied regimens; oral or transdermal unopposed ET and combined therapy	Subjective; trained participants reported habitual aerobic PA for at least 5 years	Subjective; did not perform regular exercise of any type	Carotid arterial compliance	MHT and regular PA independently associated with higher carotid arterial compliance, suggesting each may offset age-related vascular stiffening.
Perry et al., 1998 ¹³⁹	Cross-sectional; examined fat distribution and coronary risk factors in sedentary women with and without MHT usage	84 sedentary, overweight, postmenopausal women; 33 MHT users (mean age 50.1 ± 5.2) and 51 nonusers (mean age 52.5 ± 7.8)	0.625 mg CEE daily and 10 mg MPA for 10 days of each month	Not examined	All women were described as sedentary but unclear how this was measured	TC, HDL-C, LDL-C, TG, central adiposity, BMI	MHT use was associated with lower central adiposity, and TC, and higher HDL-C, raising the possibility that MHT may mitigate some adverse effects of SB; no difference in LDL-C by MHT group.
Pettee et al., 2007 ¹¹¹	Cross-sectional; examined the relationship between PA, lipid proteins, and MHT use	485 postmenopausal women (mean age 56.9 ± 2.9 years); 286 MHT users, 196 nonusers	Varied; unopposed ET and combined therapy; route and dose not reported	Self-reported leisure PA (via Modifiable Activity Questionnaire)	Not explicitly reported on	TC, LDL-C, HDL-C, TG	PA associated with favourable lipid profiles regardless of MHT status. Improvements in HDL and LDL size and

Authors, Date	Study details	Sample size and population	MHT regimen	PA measurement	SB measurement	CV outcome	Findings
							concentration were seen only in MHT nonusers; MHT may blunt some benefits of PA on lipoproteins.
Ryan et al., 2002 ¹³⁸	Cross-sectional; examined differences in insulin sensitivity by MHT status in sedentary women	28 obese, sedentary, postmenopausal women aged 50 – 70 years	Varied; unopposed ET and combined ET; oral routes	Not examined	Subjective; self-reported less than 20 mins PA twice per week	VO2max, body composition, insulin resistance, fasting glucose, fasting insulin	Sedentary women using oral MHT had lower insulin sensitivity than sedentary nonusers, even after controlling for abdominal obesity, MHT may adversely impact metabolic health in inactive women
Shakir et al., 2004 ¹¹⁴	Cross-sectional analysis of women in the Women's Health in the Lund Area cohort; examined CV risk factors by MHT status and lifestyle behaviours	6917 Swedish women; 492 premenopausal, 3600 postmenopausal without MHT, 2816 postmenopausal with ever usage of MHT	Not specified; divided into ever usage and never usage	Self-reported questionnaire	Self-reported questionnaire: SB only examined in relation to working behaviours (i.e., sedentary work, light PA work, heavy PA work)	BMI, waist-to-hip ratio, SBP, DBP, HDL-C, LDL-C, TG, TC, CV events	Ever-users had more favourable CV risk profiles, but PA did not differ between MHT users and non-users, which suggests that MHT is related to CV benefits independent of PA
Stevenson et al., 1997 ⁹⁵	Cross-sectional; compared BP variables in	52 healthy, non-obese, postmenopausal	Varied; majority used oral combined	Subjective (Stanford Physical	Inferred sedentary status based on lower	Casual, 24-h ambulatory, daytime and	PA associated with lower SBP, lower SBP

Authors, Date	Study details	Sample size and population	MHT regimen	PA measurement	SB measurement	CV outcome	Findings
	physically active vs sedentary postmenopausal women and in MHT users and nonusers	women (18 highly active runners; 34 sedentary or minimally active controls); 25 used MHT (8 active, 17 controls)	therapy; others used ET alone or transdermal preparations. Used for at least 1 year.	Activity Questionnaire)	PA (Control group)	nighttime SBP and DBP; BP variability; BP response to exercise	variability, and a blunted SBP response to exercise. MHT associated with lower DBP and reduced DBP load. No interaction reported.
Weinberg et al., 2012 ¹¹²	Cross-sectional; examined the association of MHT with atherosclerosis independent of PA and other lifestyle factors	544 postmenopausal women, asymptomatic of heart disease, who were referred for coronary artery calcium screening to measure CV risk; aged 50-80; 46.3% were MHT users	Only divided into users and non-users; route, type, dose, duration not specified	Self-reported via Baecke questionnaire	Not reported	CAC	MHT associated with lower CAC; PA showed opposite associations depending on MHT use, with higher PA linked to lower CAC in nonusers, and higher PA paradoxically associated with higher CAC among MHT users
Zhong et al., 2020 ¹¹³	Cross-sectional; examination of relationship between PA and stroke risk by MHT usage in the California	34212 postmenopausal women in the California Teachers Study	Only divided into users and non-users; route, type, dose, duration not specified	Self-reported via baseline and follow-up questionnaires; categorized by whether they met the AHA PA guidelines	Self-reported via baseline and follow-up questionnaires; categorized by whether they met the AHA PA guidelines	Stroke	PA appeared to offset increased stroke risk associated with MHT use; physically active women had no elevated stroke

Authors, Date	Study details	Sample size and population	MHT regimen	PA measurement	SB measurement	CV outcome	Findings
	Teachers Study cohort						risk regardless of MHT status, while inactive MHT users had higher risk of stroke over time

Abbreviations: MHT, menopausal hormone therapy; PA, physical activity; SB, sedentary behaviour; CV, cardiovascular; ET, estrogen therapy; VPA, vigorous physical activity; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; AT, aerobic training; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate; CAC, coronary artery calcification; AHA, American Heart Association

1.5 Sleep, MHT, and Postmenopausal CV Health

Sleep duration is a core component of the Canadian 24HMG, which recommends 7-9 hours of high-quality sleep per night for adults aged 18-64, and 7-8 hours for adults aged 65 and older.⁷⁶ Research has shown a U-shaped or J-shaped association between sleep duration and CV health, with both short and long sleep outside of the recommended range conferring greater CV risk.^{140–146} The 24HMG also indicate that sleep must be high quality, as poor sleep quality, including frequent awakenings and difficulty maintaining sleep, has also been independently associated with increased CVD risk.^{76,145}

Sleep disturbances are among the most common complaints during and after the menopausal transition, affecting up to 60% of women, with nighttime awakenings being the most frequent complaint.^{147,148} Disturbances are likely explained by hormonal fluctuations and the presence of menopausal symptoms, such as vasomotor symptoms.^{149,150} For example, while aging itself impacts sleep, there is evidence that hormonal fluctuations (i.e., declines in estradiol and increases in follicle-stimulating hormone) are associated with worsening sleep quality.¹⁴⁸ Menopausal sleep issues can impair quality of life, work productivity, and CV and overall health, and they often persist for many years after the menopausal transition.^{151,152} In the Study of Women's Health Across the Nation, women with persistently short sleep (5 hours per night) over midlife had a higher risk of CVD events compared to those sleeping 6 hours, although this finding was marginally significant after adjustment.¹⁴³ Additionally, American women with chronic sleep maintenance insomnia reported significantly poorer quality of life, reduced daily functioning, and higher usage of healthcare resources, including hospital emergency department visits, even after adjusting for comorbidities.¹⁵² American peri- and postmenopausal women have also been shown to be more likely than premenopausal women to sleep fewer than 7 hours per night and to report more difficulties initiating or maintaining sleep.¹⁵³

A sizeable body of research has examined the effects of MHT on sleep. Findings suggest that MHT, especially when including progesterone, improves objective and subjective sleep parameters.^{150,154–158} For example, studies have shown that micronized and non-micronized progesterone increases sleep duration, enhances sleep efficiency, and reduces nocturnal awakenings.^{159–161} A 2022 meta-analysis from Pan et al. confirmed modest improvements in

subjective sleep quality among MHT users, particularly those with vasomotor symptoms.¹⁶² However, they suggested no beneficial effects on sleep duration among MHT users.

Evidence points to multiple mechanisms that may influence sleep through MHT. First, progesterone – particularly micronized progesterone – appears to have sleep-promoting effects, potentially through GABAergic pathways.^{155,156,162} Second, sleep improvements may result indirectly from reduced vasomotor symptoms and night sweats, which can contribute to nocturnal awakenings.^{157,163} Third, transdermal estrogen may offer more stable serum estradiol levels and higher bioavailability than oral administration, which could promote better sleep.¹⁶² Fourth, MHT may modulate melatonin secretion timing or circadian rhythms, though findings are not well established.¹⁶⁴ Lastly, estrogen may also enhance sleep through effects on other neurotransmitter systems, including serotonin and acetylcholine pathways.^{149,156}

Despite several promising mechanisms by which MHT may enhance sleep, these findings should be interpreted with caution. Many of the positive effects have been reported in studies relying on subjective outcomes, and although these measures are important, a discrepancy has been observed between subjective assessments and objective measures, such as polysomnography and accelerometry.^{149,157,158} While some RCTs reported improvements in sleep fragmentation and slow-wave sleep, others found negligible or even adverse effects on sleep architecture.^{161,165–167} Some evidence even indicates that MHT may influence physiological aspects of sleep as measured by polysomnography, without necessarily leading to perceptible improvements in self-reported sleep satisfaction among peri- and postmenopausal women.¹⁶⁸

Although the effects of MHT on sleep have been widely studied, only seven published studies were identified that examined both MHT and sleep in relation to CV outcomes (Table 2).^{169–175} Two randomized trials suggested that MHT and sleep are associated with cardiometabolic outcomes in postmenopausal women, and that MHT may elicit outcomes independent of sleep, although no interaction effects were explored.^{170,171} A 12-week controlled trial found that women receiving estradiol plus drospirenone reported fewer sleep complaints and experienced reductions in SBP, waist circumference (WC), fasting insulin, and insulin resistance compared to the placebo group, particularly among those with elevated baseline BP.¹⁷¹ The other trial reported that women randomized to either oral conjugated equine estrogens or transdermal estradiol experienced smaller increases in BMI over time compared to placebo, despite similar

reductions in self-reported insomnia.¹⁷⁰ Conversely, data from the Nurses' Health Study I and II showed that women under age 60 who slept five hours or less per night had consistently higher rates of prevalent and incident hypertension compared to those with longer sleep durations.¹⁷² These associations remained significant regardless of MHT use, indicating that MHT did not attenuate or modify the increased CV risk associated with insufficient sleep in this cohort.¹⁷²

Experimental sleep studies have also offered insight into the role of MHT in CV autonomic regulation during sleep.^{169,173–175} In a series of trials, Virtanen et al. (2000, 2008, 2024) investigated the effects of estradiol on polysomnography-derived measures of heart rate variability.^{173–175} In the 2000 trial, estradiol lowered heart rate during wakefulness and non-REM sleep but did not affect heart rate variability or interact with sleep stages, suggesting increased vagal tone without altering sleep-related autonomic patterns.¹⁷⁴ The 2008 trial found that estradiol reduced the complexity of nonlinear heart rate variability, particularly during slow-wave and REM sleep, which may reflect adverse CV effects independent of sleep stage.¹⁷⁵ Most recently, a sleep disturbance protocol showed that MHT had no effect on heart rate variability or its response to disturbed sleep in peri- or postmenopausal women, indicating limited interaction between MHT and sleep disturbance on heart rate variability.¹⁷³ Lastly, a within-participants sleep restriction study from a different research group showed that restriction was associated with increased LDL-C in women on MHT, though the absence of a non-treatment group limited conclusions about the hormone's effects.¹⁶⁹

Several limitations characterize the current body of evidence on MHT and sleep in relation to CV outcomes. Four of the seven publications involved relatively small sample sizes, fewer than 50 participants in total, which limits statistical power and generalizability.^{169,173–175} Three studies relied on self-reported sleep measures rather than objective measurements.^{170–172} This is especially notable given the discrepancy between the two types of measurement in the observed effects of MHT on sleep.¹⁴⁹ Healthy user bias is, again, another concern in sleep studies, as women who choose to use MHT may differ fundamentally from non-users in their health behaviours.^{119,176} This was illustrated by Mirer et al. (2015), who analyzed longitudinal sleep data from midlife women in the Wisconsin Sleep Cohort and found that an apparent protective effect of MHT on sleep-disordered breathing disappeared after 2002, when the Women's Health Initiative reported increased cardiovascular risk with MHT.¹⁷⁶ This shift

suggests that earlier associations were likely due to healthy user bias, with healthier women more likely to use MHT before the risks became widely known.¹⁷⁶ Furthermore, only two studies examining MHT and sleep in relation to CV outcomes were published within the past 10 years, meaning some evidence and data may be outdated.^{170,173} This is particularly relevant given Mirer et al.'s (2015) findings, as studies conducted before and after 2002 may yield skewed results due to shifts in MHT usage patterns.¹⁷⁶ Finally, two of the identified studies did not examine differences in outcomes by MHT type, dose, or route of administration.^{169,172}

Overall, while MHT appears to offer modest improvements in sleep, especially among women with vasomotor symptoms, its impact on CV outcomes is less clear. Few studies have directly assessed whether MHT-related improvements in sleep translate into meaningful CV benefits, and even fewer have tested whether sleep and MHT interact to influence CV risk. Experimental evidence suggests that MHT may affect CV physiology during sleep, but these effects often seem to occur independently of sleep stage or quality. Observational findings also show limited support for the idea that MHT buffers the CV risks associated with short or poor-quality sleep. These gaps highlight the need for more targeted research that examines how MHT and sleep parameters jointly impact CV health in postmenopausal women. Better understanding this relationship could help refine the risk-benefit profile of MHT and inform more personalized approaches to treatment.

Table 2. Summary of Studies Investigating Sleep and MHT on CV Outcomes

Author, Date	Study Design	Sample size and population	MHT regimen	Sleep Measurement	CV Outcome	Findings
Cintron et al., 2017 ¹⁷⁰	RCT (KEEPS ancillary study) evaluating plasma OxA levels during and after 4 years of MHT, with follow-up 3 years post-treatment.	74 healthy, recently menopausal white women (within 3 years at enrollment), median age 53	Randomized to one of the 3 following groups: (1) oral CEE (0.45 mg/day) plus a placebo transdermal patch; (2) transdermal 17 β -E2 (50 micrograms/day) plus a placebo pill; (3) placebo pills and patch. Women in the active treatment groups also received oral micronized progesterone (200 mg) for the first 12 days of each month.	Subjective only: Menopausal insomnia symptoms (4-point scale: none to severe), assessed at baseline, 6 months, and annually; no objective sleep measures used.	Plasma OxA (neuropeptide involved in regulating arousal, wakefulness, and appetite) levels (ng/mL), self-reported insomnia severity, BMI, waist circumference, health-related QOL	Oral CEE and transdermal E2 experienced smaller increases in BMI compared to placebo, despite similar reductions in self-reported insomnia Post-treatment, OxA correlated weakly with waist circumference. Effects of MHT on OxA appear independent of perceived sleep improvements.
Gambacciani et al., 2011 ¹⁷¹	12-week RCT comparing MHT to control on quality of life, metabolic parameters and blood pressure in	52 postmenopausal women under age 60 not using MHT in the past year	Randomized to one of 2 groups: (1) 17 β -estradiol (1 mg/day) + drospirenone (2 mg/day); (2) calcium (control)	Subjective, using the WHQ at baseline, 6 weeks, and 12 weeks.	WHQ outcome domains (sleep VMS, anxiety, sexual behaviour, depressed mood, somatic symptoms);	WHQ scores for sleep problems decreased significantly with MHT versus both baseline and control. Improvements

Author, Date	Study Design	Sample size and population	MHT regimen	Sleep Measurement	CV Outcome	Findings
	postmenopausal women.				SBP, DBP, WC, insulin resistance (HOMA index)	coincided with improvements in SBP (in women with baseline SBP 130-139 mmHG), WC, blood insulin, and insulin resistance. MHT could jointly benefit sleep and cardiometabolic risk in symptomatic women.
Gangwisch et al., 2013 ¹⁷²	Longitudinal cohort study using data from the Nurses' Health Study I (NHS-I) and II (NHS-II), investigating associations between self-reported sleep duration and hypertension prevalence and incidence	Three cohorts: 1986 NHS-I: 82,130 women; 2000 NHS-I: 71,658 women; 2001 NHS-II: 84,674 women. Ages ranged from 25–79 years. Only female registered nurses in the U.S.	Self-reported MHT status (never, past, current) included as a covariate and effect modifier. No specific regimen information provided.	Subjective; sleep duration self-reported on questionnaires and categorized as ≤5, 6, 7 (reference), 8, or ≥9 hours per night.	Prevalence and 6-year incidence of physician-diagnosed hypertension.	Short sleep (≤5 hours) consistently associated with higher hypertension prevalence and increased risk of incident hypertension in women <60 years. MHT use did not significantly modify these associations.

Author, Date	Study Design	Sample size and population	MHT regimen	Sleep Measurement	CV Outcome	Findings
Kerkhofs et al., 2007 ¹⁶⁹	Within-participant sleep restriction experimental study; participants underwent baseline, 3 nights of 4-hour sleep restriction, and 1 recovery night.	10 healthy postmenopausal women aged 55–65, all on hormone therapy	2 women using unopposed estrogen, 8 using combined therapy; no other specifics reported	Objective: Sleep restricted under lab supervision; EEG confirmed adherence.	Blood lipids, leukocyte counts	After 3 nights of restricted sleep, TC, LDL-C, WBC, neutrophils, and monocytes increased significantly, despite MHT use. As all participants were on MHT, it is unclear what role it played in the results.
Virtanen et al., 2000 ¹⁷⁴	Randomized, double-blind, placebo-controlled crossover trial; 3 months of transdermal MHT vs. placebo with 1-month washout; polysomnography and HRV measured at the end of each phase.	43 healthy postmenopausal women (hysterectomized); ages 47–65.	(1) Transdermal E2: women <56 yrs used 1.5 mg gel while women ≥56 yrs used 50 µg patch; (2) placebo; each for 3 months.	Objectively via PSG	HR, HRV, and oxygen saturation across sleep stages	MHT decreased heart rate during wake and non-REM sleep, but had no effect during REM sleep; however, it did not alter HRV in any stage. While sleep stage strongly influenced HRV, MHT did not interact with sleep stage to modify HRV patterns, suggesting MHT elevates overall vagal tone without

Author, Date	Study Design	Sample size and population	MHT regimen	Sleep Measurement	CV Outcome	Findings
						modulating sleep-related autonomic shifts.
Virtanen et al., 2008 ¹⁷⁵	Randomized, double-blind, placebo-controlled crossover trial examining effects of MHT on nocturnal nonlinear HRV	43 healthy, hysterectomized postmenopausal Finnish women, aged 47–65	Transdermal E2 (gel for <56 years; patch for ≥56 years), each for 3 months with a 1-month washout	Objectively via PSG	Nonlinear HRV: ApEn, Poincaré plot SD1/SD2, and fractal scaling exponents ($\alpha1/\alpha2$)	MHT decreased ApEn, particularly during slow-wave sleep; SD2 decreased during slow-wave and REM sleep; SD1 trended lower in slow-wave sleep; These effects were additive rather than interactive with sleep stages; i.e., MHT and sleep each independently influenced HRV. Authors interpret these changes as potentially detrimental to CV health during sleep.
Virtanen et al., 2024 ¹⁷³	Secondary analysis of a randomized, double-blind, placebo-	26 healthy climacteric women (14 perimenopausal, 12	Perimenopausal: Cyclic oral E2V 2 mg ($\pm$ 1 mg norethisterone); Postmenopausal:	Three consecutive PSG nights pre- and post-treatment	HRV (time, frequency, and nonlinear domains) measured from	Sleep disturbance slightly increased vagal HRV in postmenopausal women at baseline

Author, Date	Study Design	Sample size and population	MHT regimen	Sleep Measurement	CV Outcome	Findings
	controlled trial with repeated sleep disturbance protocol	postmenopausal); aged ~48 and ~63 years, respectively	Continuous oral E2V 2 mg + norethisterone 0.7 mg; Placebo	(adaptation, reference, and externally disturbed night via IV line)	full overnight ECG	but had no effect in those receiving MHT. However, effects were small, inconsistent, and not observed across all groups, indicating limited interaction between MHT and sleep disturbance on HRV.

Abbreviations: MHT, menopausal hormone therapy; CV, cardiovascular; RCT, randomized controlled trial; KEEPS, Kronos Early Estrogen Prevention Study; OxA, Orexin A; CEE, conjugated equine estrogens; E2, estradiol; BMI, body mass index; QOL, quality of life; WHQ, Women's Health Questionnaire; VMS, vasomotor symptoms; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; HOMA, Homeostatic Model Assessment for Insulin Resistance; NHS, Nurses' Health Study; EEG, electroencephalogram; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cells; PSG, polysomnography; HR, heart rate; HRV, heart rate variability; REM, rapid eye movement; ApEn, approximate entropy; E2V, estradiol valerate; IV, intravenous; ECG, electrocardiogram

1.6 Physiological Mechanisms Linking Female Sex Hormones, 24HMG, and CV Health

As mentioned in Section 1.1, estrogen has been proposed to influence several physiological factors relevant to CV health. Declining estrogen concentrations are associated with unfavourable changes in lipid metabolism, reduced arterial elasticity, decreased insulin sensitivity, greater visceral fat accumulation, and impaired endothelial function.^{2,5,10–12,14} Furthermore, compared to age-matched men, premenopausal women typically have better vascular function and lower CVD.^{13,14,177} A possible mechanism explaining this relationship is that estrogen seems to affect vascular smooth muscle ion channel activity and stimulates nitric oxide production through the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signalling pathway.^{177–179} Nitric oxide is well known for being an important vasodilator that protects against atherosclerotic changes by reducing vascular smooth muscle cell proliferation, platelet aggregation, and platelet adhesion.¹⁸⁰ In addition to nitric oxide, estrogen also seems to increase the availability of prostacyclin and endothelium-derived hyperpolarizing factors, which also contribute to vascular relaxation.¹⁸⁰ Progestogens might further be involved in these effects by inhibiting smooth muscle proliferation and migration and amplifying the actions of estrogen.¹⁷⁹ Estrogen may also help regulate inflammation by decreasing some pro-inflammatory markers, which can, in turn, influence CV risk. For example, estradiol may suppress interleukin-6 gene expression, and higher estradiol levels have been associated with significantly lower C-reactive protein levels in premenopausal women.^{181,182}

Like estrogen, PA is also involved in the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signalling pathway and nitric oxide production.^{14,183,184} Exercise performed at a range of durations and intensities increases blood flow and shear stress on the endothelium, which stimulates endothelial nitric oxide synthase via PI3K/Akt signalling and elevates nitric oxide levels.¹⁷⁷ Regular PA also has well-known benefits for lipid metabolism, BP regulation, insulin sensitivity, and body composition.^{74,79} Regarding more direct relationships between female sex hormones and PA, in a controlled trial of postmenopausal women, significant improvements in endothelial function following endurance training were observed only among those treated with estradiol and not in those receiving placebo, suggesting that estradiol may be necessary for optimal vascular adaptation to exercise.^{14,94} Therefore, these shared pathways provide a

physiological rationale for examining hormone exposure via MHT and PA together, as both appear to influence endothelial function and vascular health through overlapping mechanisms.

Although SB is by definition not the direct opposite of PA (being distinct from physical inactivity), it is characterized by a hemodynamic environment that may counteract hormone- and PA-related vascular effects.^{121,185} Prolonged sitting leads to low and oscillatory shear stress in the lower extremity arteries, which suppresses endothelial nitric oxide synthase phosphorylation and reduces nitric oxide bioavailability.^{185,186} This differs from the effects of estrogen and PA, which, as mentioned, support nitric oxide production through shear stress and the PI3K/Akt pathway.¹⁷⁷ In addition, SB has been linked to pro-inflammatory markers such as interleukin-6 and C-Reactive Protein, fibrinogens, and tumour necrosis factor alpha (TNF- α).¹⁸⁵ Observational studies show that these associations may be stronger in women than in men, with higher interleukin-6 and fibrinogen levels reported in one study and more pronounced C-reactive protein and interleukin-6 responses, even after adjustment for covariates such as adiposity, in another.^{187,188} These sex differences could partly reflect hormonal influences, including estrogen.¹⁸⁵ As a result, SB may exacerbate endothelial dysfunction and inflammatory processes in the context of declining estrogen in menopause.

Sleep influences estrogen and progesterone levels, both through central mechanisms involved in sleep regulation and through pathways linked to respiratory function and sleep-disordered breathing. Brain regions that regulate sleep-wake cycles have estrogen receptors, and declining estrogen levels have been shown to disrupt serotonergic and noradrenergic neurotransmission, reduce melatonin production, and increase thermoregulatory instability.^{149,163} These changes can lead to difficulty initiating and maintaining sleep, and may be compounded by vasomotor symptoms and mood swings.^{149,163} Estradiol levels associate with both objective and subjective sleep measures, with lower or more rapidly fluctuating Estradiol levels linked to poorer sleep efficiency, shorter sleep durations, and sleep-disordered breathing.¹⁸⁹ This aligns with clinical observations that women who experience abrupt hormonal changes, such as those with bilateral oophorectomy, often report more severe sleep problems.^{189,190}

Progesterone decline has also been linked to sleep disturbances; lower levels of progesterone and its metabolite allopregnanolone have been associated with reduced sleep efficiency, shorter sleep duration, shallower sleep, and sleep-disordered breathing.¹⁸⁹

Progesterone appears to exert sedative and hypnotic effects that mimic those of GABA receptor modulators, promoting sleep and reducing arousal.^{189,191} In addition, progesterone may reduce sleep-disordered breathing by stimulating respiration via steroid receptor-mediated pathways in the central nervous system (although this was demonstrated in female cats) and by promoting upper airway muscle activity in female humans.^{192,193} Therefore, disruptions in sleep linked to declining estrogen and progesterone are clinically relevant because, as described in Section 1.5, sleep disturbances and sleep-disordered breathing are established risk factors for CVD.^{76,140–142,145} In other words, pathways linking sleep to CVD and those linking hormonal exposures to CVD may be related.

Considering all the above-described relationships, it is important to consider hormonal changes, including those elicited by MHT and 24HMG together when examining CV health in postmenopausal women.

Chapter 2: Methods

2.1 Statement of the Problem

CVD remains a leading cause of death among women in Canada and worldwide, with risk increasing significantly after menopause due to both hormonal fluctuations and aging-related physiological changes.^{11,194} Although MHT has been studied extensively in women's health, there is conflicting evidence regarding its safety and efficacy.^{21,195} Moreover, several unknowns remain about the shared influence of MHT and movement behaviours on CV risk. To the best of my knowledge, no studies have explicitly assessed the contributions of the major movement behaviours of PA, SB, and sleep, in tandem with MHT use, on CV health.

Many of the large and seminal trials that have informed current prescribing guidelines and perceptions were not designed or intended to investigate movement behaviours.^{58,62,196,197} If included, these variables served as confounders (not as the main exposure variable), and acknowledgement in their respective publications was minimal.^{29,30,51,198–201} Notably, the highly influential publications from the Women's Health Initiative have been critiqued because, among other reasons, models that adjusted for lifestyle confounders such as PA were either not reported or dismissed in favour of the more compelling unadjusted findings.^{30,33,34,201,202} It is unreasonable to expect a single trial to account for all possible confounders, but the absence of and disregard for movement behaviours are considerable limitations in studies of MHT and CV health.

Examination of supplementary data from a 2020 systematic review and meta-analysis on the effects of MHT on CVD indicated that only 7 of the 47 included observational studies adjusted for any movement behaviours in their analyses.^{203–210} 5 of these 7 studies found no association between MHT usage and adverse CV outcomes after adjusting for covariates (Appendix Table 1).^{203,206–209} The remaining 2, both of which analyzed data from the same cohort, found that adverse outcomes were only found in women with pre-existing hypertension and diabetes, and not in women without these conditions.^{204,205}

Much of the literature reviews on MHT consulted for this thesis (including systematic and narrative reviews of evidence, indications, and contraindications for use) also variably included movement behaviours in their recommendations and conclusions; when they were

included, it was often in passing rather than as a focal point of the message.^{19,53,57,61,150,211–215} However, other authors and groups, including The Menopause Society (formerly known as the North American Menopause Society) and the International Menopause Society, have stated that primary prevention of CVD through lifestyle modification and pharmacological interventions must be prioritized during the menopausal transition, irrespective of MHT usage, for better or worse.^{21–24,55,56,216,217} The International Menopause Society, in particular, expressly advocates lifestyle-based health promotion strategies during menopause, with MHT prescribed as an add-on as needed and when indicated.^{24,56}

Meanwhile, the 2024 Menopause Priority Setting Partnership identified key unresolved questions for clinicians, researchers, and menopausal women. The question “What lifestyle changes (e.g. [...], exercise, [...]) benefit people at different stages of menopause? How can people be supported to make these changes?” was among the 10 priorities published.⁷⁸ In their 2022 position statement, The Menopause Society also called for more research on “the long-term benefits and risks on women’s health of lifestyle modification...if chosen in addition to or over hormone therapy for VMS, bone health, and CVD risk reduction.”²² Evidently, there is an established need to better understand how modifiable behaviours such as PA, SB, and sleep relate to health outcomes during menopause, with or without MHT usage.

As mentioned in Section 1.2, a previous publication from our research group, authored by Kalenga et al. and based on data from the Women’s Advanced Risk-assessment in Manitoba (WARM) Hearts cohort, examined the association between the route of unopposed estrogen therapy and CV markers, including blood pressure and arterial stiffness.⁷¹ That study reported that women using oral estrogen therapy had significantly higher SBP and DBP compared to those using non-oral estrogen therapy and those who had never used MHT.⁷¹ These results align with published findings suggesting that the route of administration may be a key factor influencing CV outcomes in MHT users.^{21,26,55,69} However, there were limitations to the analysis in our earlier work.⁷¹ First, it was conducted using a subset of the WARM Hearts cohort, who were recruited before COVID-19 public health interventions interrupted research data collection on March 23, 2020. As a result, data were available for only 328 of the participants, whereas the full WARM Hearts cohort comprises 1018 participants as of December 22, 2022. Secondly, for the purposes of the Kalenga et al. study, only data on unopposed estrogen MHT users were analyzed,

despite available data on combined estrogen-progestogen therapy, progestogen-alone, and other formulations of hormone therapy. Finally, the previous work by Kalenga et al. did not adjust for lifestyle movement behaviours. These limitations restrict the applicability of findings to broader clinical and public health contexts.

The problems and gaps outlined above are summarized as follows: (1) the safety and efficacy of MHT is controversial; (2) the relationships between MVPA, SB, and sleep in tandem with MHT usage are unknown (3) seminal randomized controlled trials on MHT were not designed or intended to account for movement behaviours; (4) few observational studies on MHT, including those published by our research group, have acknowledged or adjusted for movement behaviours; (5) some published recommendations and reviews do not emphasize movement behaviours as potential confounders of the relationship between MHT and CV health, nor do they recommend them as areas of intervention alongside MHT; and (6) other guidelines and expert recommendations for MHT usage advocate for lifestyle modification, including movement behaviours, as a cornerstone of health promotion and primary prevention of CVD.

To work towards addressing some of these gaps, my thesis uses data from the Women's Advanced Risk-assessment in Manitoba (WARM) Hearts Study (Clinical Trial: NCT03938155)⁷² using data from 1018 postmenopausal women in the cohort. This thesis research leverages validated accelerometer-based assessments of PA, SB, and sleep behaviour in combination with detailed reproductive and CV data. Specifically, it examines whether behaviours targeted by the Canadian 24HMG – PA, SB, and sleep duration – better explain associations with CV factors compared to MHT exposures. By evaluating the independent effects of MHT and 24-hour movement behaviours, this research aims to inform more integrated practical recommendations for postmenopausal women.

2.2 Research Objectives, Questions, and Hypotheses

The following section will outline the research objectives, questions, and hypotheses guiding this thesis.

2.2.1 Objective 1.

Objective 1 was to replicate, rework, and extend the study by Kalenga et al. (2022) by evaluating associations between estrogen MHT route and CV outcomes using an expanded sample size,

using alternative analytical specifications, and by incorporating movement behaviours into analyses. Objective 1 has 4 sub-objectives:

- 1A. Replicate the study Kalenga et al. (2022) using the complete sample (a larger sample size) from the WARM Hearts cohort, without adding predictors or altering model structure.
- 1B. Rework analyses from Kalenga et al. (2022) and Objective 1A using alternative variable operationalizations and reporting strategies.
- 1C. Expand group comparisons from Kalenga et al. (2022) and Objectives 1A and 1B by testing differences across estrogen MHT routes in a broader set of variables, including movement behaviours (MVPA, StaB, and sleep).
- 1D. Expand regression models from Kalenga et al. (2022) and Objectives 1A and 1B by adding movement behaviours and examining additional outcomes, as well as assessing the relative contribution of movement behaviours in explaining variance in CV outcomes.

Objective 1D has 3 sub-objectives:

- 1D.1 Add movement behaviours to the original model structure presented in Kalenga et al. (2022) in a second block, using the same exposure definitions, covariates, and outcomes.
- 1D.2 Using the same exposure definitions, original outcomes, and new outcomes (FRS, WC, HDL, LDL, TG, glucose), construct unadjusted models by entering MHT estrogen route in one block, followed by movement behaviours in a second block.
- 1D.3 Using the same exposure definitions, original outcomes, new outcomes, and an alternate set of covariates, construct adjusted models by entering covariates in one block, followed by estrogen MHT route in a second block, and movement behaviour in a third block.

The corresponding research questions and hypotheses developed to address Objective 1 are presented in Table 3.

2.2.2 Objective 2.

Objective 2 is to extend the analyses from Objective 1 by examining CV outcomes across alternative MHT exposure definitions and by quantifying the incremental and relative contributions of movement behaviours within hierarchical regression models, in order to determine whether movement behaviours explain CV risk more effectively than MHT exposures. Objective 2 has 2 sub-objectives:

2A. Examine group differences in demographic variables, movement behaviours, and CV outcomes across various MHT exposure definitions.

2A.1. To compare demographic variables, movement behaviours, and CV outcomes across groups defined by MHT history (never usage/controls, former usage, current usage).

2A.2. To compare demographic variables, movement behaviours, and CV outcomes across groups defined by MHT type (controls, combined estrogen-progestogen, unopposed estrogen).

2A.3. To compare demographic variables, movement behaviours, and CV outcomes across groups defined by MHT route of administration (controls, oral, transdermal, vaginal).

2B. Use regression models to evaluate the extent to which movement behaviours improve model fit beyond covariates and MHT usage, and to compare the relative explanatory value of individual MHT and movement predictors.

2B.1. To evaluate associations between MHT history (controls, former usage, current usage) and CV outcomes, and to assess the incremental and relative contribution of movement behaviours in explaining variance in these outcomes using hierarchical regression models.

2B.2. To evaluate associations between MHT type (controls, combined estrogen-progestogen usage, unopposed estrogen usage) and CV outcomes, and to assess the incremental and relative contribution of movement behaviours in explaining variance in these outcomes using hierarchical regression models.

2B.3. To evaluate associations between MHT route of administration (controls, oral usage, transdermal usage, vaginal usage) and CV outcomes, and to assess the

incremental and relative contribution of movement behaviours in explaining variance in these outcomes using hierarchical regression models.

The corresponding research questions and hypotheses developed to address Objective 2 are presented in Table 3.

Table 3. Research Questions and Hypotheses.

Objective	Question	Hypothesis
1	In replicating, reworking, and extending Kalenga et al. (2022), what is the association between unopposed estrogen MHT route and CV outcomes, and to what extent do movement behaviours contribute to explaining variance in these outcomes?	Unopposed estrogen MHT route will be associated with CV outcomes, but movement behaviours will contribute more substantially to the explanation of variance in these outcomes, regardless of sample size or variable operationalization.
1A	When replicating the analytical framework of Kalenga et al. (2022) in a larger sample, are associations between unopposed estrogen MHT route and CV outcomes reproduced?	Associations between unopposed estrogen MHT route and CV outcomes will persist after increasing the sample size.
1B	Do associations between unopposed estrogen MHT route and CV outcomes persist when alternative variable operationalizations are applied?	Associations between unopposed estrogen MHT route and CV outcomes will persist when alternative variable operationalizations are applied.
1C	Do group differences across unopposed estrogen MHT routes extend to a broader set of CV outcomes and behavioural predictors, including MVPA, StaB, and sleep duration?	CV outcomes (including the original outcomes proposed by Kalenga et al. and newly introduced outcomes) and movement behaviours will differ across unopposed estrogen MHT route groups.
1D	To what extent do movement behaviours contribute to the explanation of variance in CV outcomes beyond unopposed estrogen MHT route?	Movement behaviours will account for greater variance in CV outcomes compared to unopposed estrogen MHT route.

1D.1	When movement behaviours are added to the original model structure of Kalenga et al. (2022), do they improve model fit beyond unopposed estrogen MHT route and covariates?	When added to the original model structure of Kalenga et al. (2022), movement behaviours will better explain the variance in CV outcomes compared to unopposed estrogen MHT route and covariates.
1D.2	In unadjusted hierarchical models, does the addition of movement behaviours after unopposed estrogen MHT route explain additional variance in original and newly introduced CV outcomes?	In unadjusted models, movement behaviours (both collectively and individually) will explain a greater proportion of variance in original and newly introduced CV outcomes beyond unopposed estrogen MHT route.
1D.3	In adjusted hierarchical models including covariates, unopposed estrogen MHT route, and movement behaviours, what is the relative contribution of each block of predictors and each individual variable in explaining CV outcomes?	In adjusted hierarchical models, movement behaviours (both collectively and individually) will explain a greater proportion of variance in original and newly introduced CV outcomes beyond an alternative set of covariates and unopposed estrogen MHT route.
2	Across alternative MHT exposure definitions, do demographic characteristics, movement behaviours, and CV outcomes differ between groups, and do movement behaviours explain CV risk more effectively than MHT exposures within hierarchical regression models?	CV outcomes will differ across alternative MHT exposure definitions; however, movement behaviours will account for greater variance in CV risk than MHT exposures and covariates in hierarchical regression models
2A	Do demographic characteristics, movement behaviours, and CV outcomes differ across alternative MHT exposure definitions?	Demographic characteristics, movement behaviours, and CV outcomes will differ across groups defined by alternative MHT exposure definitions.

2A.1	Do demographic variables, movement behaviours, and CV outcomes differ across groups defined by MHT history (controls, former, current)?	Variables of interest will differ across MHT history groups (controls, former, current).
2A.2	Do demographic variables, movement behaviours, and CV outcomes differ across groups defined by MHT type (controls, combined estrogen-progestogen, unopposed estrogen)?	Variables of interest and movement behaviours will differ across MHT type groups (controls, combined estrogen-progestogen, unopposed estrogen).
2A.3	Do demographic variables, movement behaviours, and CV outcomes differ across groups defined by MHT route of administration (never use, oral, transdermal, vaginal)?	Variables of interest and movement behaviours will differ across MHT route groups (controls, oral, transdermal, vaginal).
2B	To what extent do movement behaviours improve model fit beyond covariates and MHT exposures, and how do their contributions compare to those of individual MHT predictors?	Movement behaviours will improve model fit beyond covariates and MHT exposures and will demonstrate greater explanatory value than MHT exposures.
2B.1	When MHT history (controls, former, current) is modeled in relation to CV outcomes, do movement behaviours provide additional explanatory value beyond MHT exposure and covariates?	When MHT history is modelled in relation to CV outcomes, movement behaviours (individually and collectively) will explain a greater proportion of variance beyond MHT exposure and covariates.
2B.2	When MHT type (controls, combined estrogen-progestogen, unopposed estrogen) is modeled in relation to CV outcomes, do movement behaviours provide additional explanatory value beyond MHT exposure and covariates?	When MHT type is modelled in relation to CV outcomes, movement behaviours (individually and collectively) will explain a greater proportion of variance beyond MHT exposure and covariates.

2B.3	When MHT route (controls, oral, transdermal, vaginal) is modeled in relation to CV outcomes, do movement behaviours provide additional explanatory value beyond MHT exposure and covariates?	When MHT route is modelled in relation to CV outcomes, movement behaviours (individually and collectively) will explain a greater proportion of variance beyond MHT exposure and covariates.
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2.3 Research Design

This thesis follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (see Appendix B for the STROBE checklist. A cross-sectional secondary analysis was conducted using data from approximately 1018 postmenopausal females enrolled in the WARM Hearts cohort. A detailed protocol paper for the WARM Hearts study was published by Rose et al. in 2021.⁷² The study received ethical approval from the University of Manitoba Research Ethics Board (H2019:063) and the St. Boniface Research Review Committee (RRC/2019/1833). The purpose of the WARM Hearts study is to determine whether a selection of traditional and novel non-invasive CVD risk factors can predict adverse health outcomes in community-dwelling older women. The study employs a prospective, observational design, with follow-up analyses of participants' health data five years after data collection. Currently, only the baseline cross-sectional data are available; the five-year health administrative data for the cohort will be available in 2028.

The WARM Hearts study recruited a total of 1018 women aged 55 years and older using a convenience sampling approach. Participants were primarily recruited through community outreach, including radio interviews, media advertisements, and presentations on CV health at community events. Individuals who expressed interest were asked to contact the research team by phone or email. Eligibility screening was then conducted via telephone to determine whether participants met the inclusion criteria. These criteria will be described in Chapter 2.4. Eligible participants attended two in-person research visits scheduled 8 to 14 days apart. The first visit took place at the Active Living Centre at the University of Manitoba, and the second was held at the Asper Clinical Research Institute at St. Boniface Hospital in Winnipeg, Manitoba. Between these visits, participants were given a take-home package containing an accelerometer, a stool sampling kit, and questionnaires to complete prior to the second visit. All the assessments conducted during the data collection process are summarized in Table 4.

Table 4. Summary of WARM Hearts Assessments (Adapted from Rose et al., 2021).

Assessment	Measurement Tool
Day 1 (University of Manitoba)	
Demographic information	Questionnaire (age, sex, gender)
Medical history	Questionnaire (medical history and CV-related testing)
Cognition	MoCA
Body composition	BIA (InBody 270); waist circumference; BMI
Grip strength	Hand dynamometer
Gait speed	5-metre walk test
Fried frailty phenotype	Self-reported exhaustion, unintentional weight loss; Paffenbarger Physical Activity Scale
Physical function	Senior Fitness Test
Aerobic fitness	6-minute walk test, with HRV assessed with HR monitor and PA characteristics assessed with accelerometer
PHIN	Collected via questionnaire
Take-home assessments	
Demographic information	Questionnaire
CV risk factors	Questionnaire (smoking status, medications, history of CV disease)
Reproductive health	Questionnaire (menstrual history, contraception use, pregnancy history, menopause status, VMS, MHT use)
PA characteristics	Accelerometer worn for approximately 7 days
PA levels	International Physical Activity Questionnaire (IPAQ)
Gut microbiome	EasySampler stool sample kit
Quality of life	EQ-5D-5L and EQ-VAS
Self-esteem	Self-Esteem Scale
Gender information	GENESIS-PRAXY Gender Questionnaire
Sleep quality	PSQI
Nutritional status	SCREEN II
Self-compassion	Self-compassion Scale

Health anxiety	Health anxiety subscale of the Multidimensional Health Questionnaire
Day 2 (Asper Clinical Research Institute)	
Fasting blood sample	Phlebotomy
Depression symptoms	Patient Health Questionnaire-9
Arterial stiffness	Mobil-O-Graph NG
Resting blood pressure	Mobil-O-Graph NG
Blood pressure response to moderate exercise	Mobil-O-Graph NG

Abbreviations: CV, cardiovascular; MoCA, Montreal Cognitive Assessment; BIA, bioelectrical impedance analysis; BMI, body mass index; HRV, heart rate variability; HR, heart rate; PA, physical activity; PHIN, personal health information number; VMS, vasomotor symptoms; MHT, menopausal hormone therapy; EQ-5D-5L, EuroQol 5-Dimension 5-Level; EQ-VAS, EuroQol Visual Analogue Scale; GENESIS-PRAXY, GENdEr and Sex determinantS of cardiovascular disease: From bench to beyond-Premature Acute Coronary Syndrome; PSQI, Pittsburgh Sleep Quality Index; SCREEN II, Seniors in the Community: Risk Evaluation for Eating and Nutrition V.II.

Recruitment and data collection were conducted in four phases between October 10, 2019, and December 22, 2022. These phases were interrupted by three separate pauses due to the COVID-19 pandemic, including the initial shutdown in March 2020 and subsequent suspensions in November 2020 and December 2021 (Table 5). Despite these disruptions, the study ultimately enrolled and collected data from 1018 participants by December 22, 2022.

Table 5. Participant Recruitment and Completion Between COVID-19 Disruptions

Start date of recruitment and data collection	End date of recruitment and data collection	Participants recruited, cumulative (N)	Participants completed data collection, cumulative (N)
October 10, 2019	March 23, 2020	480	240
<i>Shutdown 1</i>			
September 16, 2020	November 10, 2020	480	331
<i>Shutdown 2</i>			
October 2, 2021	December 20, 2021	522	423
<i>Shutdown 3</i>			
February 1, 2022	December 22, 2022	1018	1018

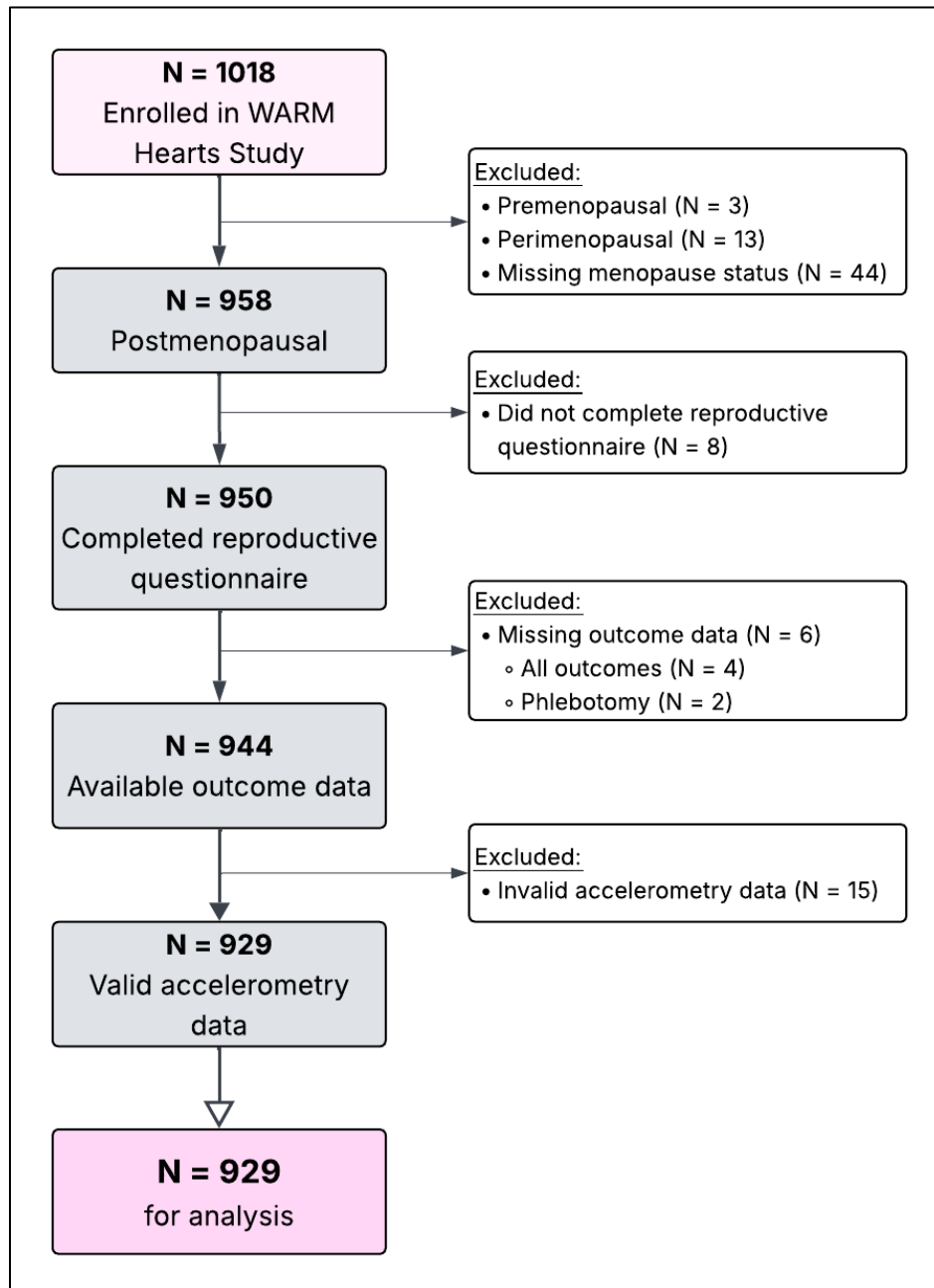
2.4 Inclusion and Exclusion Criteria

As described in the published protocol paper, the inclusion criteria for the WARM Hearts study were women aged 55 and older who possessed a Manitoba Personal Health Information Number.⁷² The exclusion criteria were previous hospitalization or treatment for ischaemic heart disease, acute myocardial infarction, stroke/transient ischaemic attack, percutaneous coronary intervention, coronary artery bypass surgery, congestive heart failure, peripheral artery disease, congenital heart defects, and arrhythmia. Additionally, women were excluded from participation if they had received medical advice against PA or had previously participated in the Assessment of Large and Small Artery Elasticity for the Early Detection of Cardiovascular Disease study (NCT02863211).

In addition to the above criteria for the WARM Hearts study, my thesis further refines the cohort using a secondary set of inclusion and exclusion criteria. To be included in the analyses, women must have self-identified as postmenopausal (self-reported cessation of menstruation for at least 12 months); completed a reproductive history, including MHT usage data; have available data on CV health markers; and have recorded at least 4 days and nights of valid accelerometry data for MVPA, SB, and sleep. Among MHT users, those who had reported any usage, regardless of duration, were included. This is because there is limited and inconsistent evidence that the duration of MHT adversely affects CV health in human females, and therapeutic effects typically

occur early and do not appear to depend on the duration of treatment.^{57,195,218,219} Participants were excluded from the analysis if they self-identified as premenopausal or perimenopausal. After applying these criteria, 929 participants remained for analysis (Figure 1).

Figure 1. Study Flowchart.



2.5 Measurements

2.5.1 Menopausal Hormone Therapy Usage and Additional Reproductive Health Data

Participants completed a detailed self-report questionnaire that captured their lifetime reproductive history and menstrual characteristics. Items included age at menarche and menopause, current menstrual status, cycle regularity, and typical period length, intensity, and symptoms (e.g., clotting, interference with daily life). Menopausal status was self-classified as premenopausal, perimenopausal, or postmenopausal, with additional detail on the cause of menopause (natural, surgical, or treatment-induced). Pregnancy history was assessed, including total number of pregnancies and outcomes (e.g., miscarriage, stillbirth, live birth), along with any adverse pregnancy outcomes (APOs) such as gestational diabetes or pre-eclampsia. Participants were additionally asked about breastfeeding, fertility challenges, and any reproductive health conditions (e.g., endometriosis, polycystic ovarian syndrome, diagnosed early menopause, etc.). Information on hormonal contraception use, such as type (e.g., pill, intrauterine device, patch), duration, and brand, was also collected. Participants reported their history of vasomotor symptoms, including whether they had ever experienced them, whether symptoms were ongoing or had resolved, as well as their severity, onset, and duration.

MHT use was assessed in as much detail as participants could recall, including whether they had used estrogen-only, progestogen-only, or combined formulations. For each type, participants indicated the route of administration (e.g., oral, skin cream/gel, patch, vaginal), approximate dates of use, dosage, frequency of administration, and current usage status. However, most participants were unable to recall the specific dose and frequency of their MHT regimens, and so these variables were not included in the present analyses. The self-report data were instead used to derive summary variables reflecting MHT exposure, timing, and hormone type. Still, while efforts were made to clarify responses, many participants expressed uncertainty regarding the formulation or route used, particularly for therapies initiated many years ago. This introduces potential for recall bias and exposure misclassification. Future studies may benefit from linkage to pharmacy or medical records to enhance classification accuracy.

2.5.2 Accelerometry Data

2.5.2.1 Accelerometry Protocol

To objectively assess PA, SB, and sleep, participants in the WARM Hearts study were asked to wear a wrist-mounted accelerometer (ActiGraph GT3X+; ActiGraph, Pensacola, FL, USA) for seven consecutive days. The ActiGraph GT3X+ is a triaxial accelerometer with a dynamic range of $\pm 6g$ and a sampling frequency of 90 Hz. Although the Actigraph monitor's sampling frequencies can be set anywhere in the range from 30 Hz to 100 Hz, frequencies in multiples of 30 Hz (30, 60, or 90 Hz) are the most accurate.^{220,221} Since higher frequencies are more sensitive, the 90 Hz sampling rate was chosen because it can enhance detection of low-intensity movements in free-living environments and is well-suited for older adult populations.^{220,221}

The device was worn continuously on the non-dominant wrist (24 hours/day), starting at 6:00 AM on the day of the first research visit and ending at 6:00 AM on the eighth day. Participants returned the accelerometer to research staff at their second research visit. Participants were instructed to wear the device at all times, including during sleep, and to remove it only during prolonged water-based activities such as swimming or bathing. Concurrently, participants completed an Activity Monitor Logbook to help verify data quality and increase the accuracy of data processing.²²² The logbook included instructions for wearing the accelerometer properly and prompted participants to document the times at which they got into bed, fell asleep, woke up, and got out of bed, to the nearest minute. They were also instructed to record daytime naps and periods when they removed the monitor, along with the reason for doing so (e.g., showering, swimming, washing dishes, etc.).

The placement of the monitor on the wrist was chosen over locations such as the thigh or hip based on evidence of higher compliance among research participants, higher accuracy in quantifying sleep, the ability to capture upper-extremity movements, and better capture of low-intensity behaviours in free-living older adult populations.^{220,223,224} Furthermore, the accelerometer was worn on the non-dominant wrist instead of the dominant wrist to reduce misclassification of SB as light activity, which might occur when upper limb movements (e.g., writing, using electronic devices) occur during seated tasks.²²⁴

Participants were required to wear the accelerometer for ≥ 16 hours per day (i.e., worn for 67% of the 24-hour day, allowing up to 8 hours of non-wear time per 24 hours) for ≥ 4 days to be included in subsequent analyses using the accelerometry data. Although 10 hours is a more commonly used minimum threshold for a valid wear day in accelerometer studies, shorter wear durations are associated with greater underestimation of time spent in SB and PA.^{225–227} For example, McGrath et al. (2017) reported that SB was underestimated by over 2.5 hours per day when using a 10-hour cut-off compared to a 14-hour reference.²²⁶ Several recent studies have adopted a 16-hour threshold, including those using the UK BioBank cohort.^{228–230} Additionally, Sagelv et al. (2023) standardized wear time to 16 hours in their pooled analysis of four international cohort studies, reflecting its growing use as an alternative to the traditional 10-hour cut-off and its potential to improve accuracy in estimating daily movement behaviours.²³¹ Because this thesis focused on 24-hour movement behaviours, a 16-hour threshold would also better capture the full range of daily activity. Furthermore, increasing the minimum wear time from 10 to 16 hours in this cohort excluded only three additional participants, thereby minimizing the trade-off between sample size and measurement accuracy described in previous publications.²²⁷ For the sleep window, a proportional rule was applied during data cleaning, where participants were excluded if they did not achieve a wear time of $\geq 67\%$ during the sleep period window for ≥ 4 nights.

2.5.2.2 Data Processing: GGIR Overview

Researchers have increasingly recognized the value of device-based measurement for assessing movement behaviours.²³² These methods offer far greater detail than self-report tools, capturing minute-by-minute movement across multiple days and avoiding common pitfalls like recall bias and social desirability bias.²³³ To maximize the potential of raw acceleration data, particularly in studies involving diverse device brands, open-source and standardized processing methods are strongly recommended.^{234,235}

GGIR is an open-source R package designed to meet this need and make accelerometry analyses more accessible to researchers.^{236–238} Unlike the proprietary “count” metrics historically used in commercial devices, which are derived from manufacturer-specific algorithms, GGIR processes raw accelerometry data directly in milligravity (mg) units.^{224,237} This is a notable strength of GGIR, as “counts” lack a universal definition and are determined by device hardware,

filtering choices, epoch length, and proprietary algorithms.^{239,240} This means that the same movement can yield widely different outputs across devices and studies, and a reliance on proprietary “count” algorithms can hinder reproducibility, cross-study comparability, and population-level surveillance.²³⁹ By contrast, the mg units that GGIR can handle are based on gravitational acceleration and can therefore be calibrated anywhere in the world, which facilitates harmonization across populations and devices. As such, GGIR enables the application of customized PA intensity thresholds, supports data from multiple accelerometer brands, and additionally includes built-in tools for autocalibration and quality control.^{237,241,242} Because of these advantages, GGIR is now widely used in population health research and is part of a broader shift toward more harmonized, evidence-based analysis of movement behaviour, being cited by over 500 studies to date. In this thesis, all accelerometry data were processed using GGIR to ensure methodological consistency, transparency, and alignment with current best practices.

Raw accelerometer data were initially downloaded using ActiLife software (version 6.13.4), saved in both .gt3x and .csv formats, and then processed using the GGIR package (version 3.0-3) in R (version 4.3.2).^{237,243} GGIR converts triaxial acceleration signals into a single gravity-corrected vector magnitude using the Euclidean Norm Minus One (ENMO) metric, where $ENMO = \sqrt{x^2 + y^2 + z^2} - 1g$. Negative ENMO values were rounded to zero, and values were averaged over 5-second epochs and expressed in milligravity units (1 mg = 0.0098 m/s²) for analysis.

GGIR comprises five sequential processing functions: Part 1 (g.part1) through Part 5 (g.part5).²³⁷ In Part 1, raw accelerometer files are loaded, and device-specific information are automatically extracted (e.g., brand, file format, file header content). The g.calibrate function is used to estimate and correct for any sensor calibration error based on deviations from expected gravitational signals.²⁴² Raw triaxial acceleration values were then converted into ENMO units and averaged into 5-second epochs for analysis. Non-wear time was detected using a 60-minute window with 15-minute moving increments. A time window was classified as non-wear if the standard deviation was less than 13 mg on at least two axes, and the range of values was less than 50 mg on all axes. These thresholds are designed to identify periods of little to no movement that likely reflect when the device was removed.²³⁶ Data were processed in 24-hour blocks, using midnight to midnight to classify the start and end of one day. In simpler terms,

g.part1 loads and calibrates the data, extracts basic movement signals, and identifies when the device was not worn.

In part 2, GGIR generates detailed summaries of each participant's activity patterns. For this study, data were summarized over standard 24-hour windows (midnight to midnight) across all valid days. Metrics include time spent in light, moderate, and vigorous activity, average acceleration, and the timing of the least and most active 5-hour per day. As mentioned, a day was considered valid if it contained ≥ 16 hours of wear time; only participants with ≥ 4 valid days were included in the final analyses.

Sleep parameters are estimated in parts 3 and 4. In part 3, GGIR identifies periods of likely sleep based on sustained inactivity bouts (SIBs). For this thesis, we utilized the default SIB detection algorithm proposed by van Hees et al. (2015), which defines a SIB as any period during which the change in the wrist's z-angle does not exceed 5 degrees for at least 5 consecutive minutes.²³⁸ Other specific parameters set to detect sleep in GGIR will be described in Chapter 2.5.2.5. The part 3 output is then passed to the part 4 functions, where the sleep period is optionally refined using participant-reported bedtimes and wake times from their sleep logs recorded in the Activity Monitor Logbooks, and comprehensive sleep data is generated. The sleep variables generated from part 4 include sleep onset time, wake time, total sleep duration, wake after sleep onset, and sleep efficiency, as well as indicators of data quality and non-wear time, and whether participant logbook entries were used in the final estimates.

Lastly, in part 5, GGIR combines the PA outputs from part 2 and the sleep estimates from part 4 to classify time spent across multiple movement behaviour categories. By default, this includes 16 distinct time-use classes, which account for combinations of activity intensity (inactive, light, moderate, vigorous), time of day (waking hours vs. sleep window), and whether the behaviour occurred in bouts of specific length (e.g., 1-minute bouts, 10-minute bouts, unbouted, etc.). Users can define activity intensity thresholds and bout characteristics, such as the minimum bout duration or a specific acceleration cutoff, to classify moderate-intensity PA. Part 5 also segments the data into daily windows, using either a calendar day (e.g., midnight to midnight) or a "waking" day (e.g., from wake time to next wake time). For each day, it calculates the total duration, number of bouts, and mean acceleration for each class. The outputs are saved as .csv summary files and visualized in PDF format for further review.

2.5.2.3 Physical Activity Data Processing in GGIR

PA intensities were defined using published acceleration cut-points validated in older adults with wrist-worn accelerometers. Based on Sanders et al. (2019), activity less than or equal to 57 mg was classified as sedentary (less than or equal to 1.5 METs), light PA was defined as 58-104 mg (1.5-2.9 METs), and activity at least 104 mg was classified as MVPA (equal or greater than 3 METs).²⁴⁴ Sanders et al. did not propose a specific threshold for vigorous activity (equal to or greater than 6 METs), which is not an issue for this analysis, as it only concerns activities of moderate intensity or higher. However, for the sake of data transparency and planning for possible future analyses, we also incorporated the vigorous activity cut point proposed by Bammann et al. (2021) of at least 254 mg into the GGIR pipeline, although it will not be used when reporting results.²⁴⁵

These cut-points were selected based on their use in studies involving non-dominant wrist-worn accelerometers in adults over 55 years of age, which aligns with the protocol and population characteristics of the WARM Hearts cohort. Sanders et al. developed thresholds using GENEActiv devices worn on the non-dominant wrist in a sample of adults aged 60 to 86 years, while Bammann et al. used ActiGraph devices (the same model used in WARM Hearts) in adults with a mean age of 62.9 years.^{244,245} Therefore, both studies are methodologically and demographically relevant. Once applied in GGIR, these thresholds were used to classify PA intensity across the 24-hour cycle, and GGIR automatically aggregated the time spent in each intensity category across all valid wear days for each participant.

In accelerometer research, a bout refers to a continuous period of activity at a specified intensity for a defined duration. Previously, Canadian and international PA guidelines recommended that MVPA be accumulated in bouts lasting at least 10 minutes. This was reflected in the 2011 Canadian Physical Activity Guidelines and consistent with positions from the World Health Organization and the U.S. Department of Health and Human Services.^{76,77} However, in contrast to the lack of evidence actually supporting a strict 10-minute bout requirement to achieve positive outcomes, accumulating evidence from observational studies demonstrated that shorter bouts of MVPA (less than 10 minutes) are associated with health benefits.⁷⁶ This resulted in the 10-minute minimum bout requirement being removed from the most recent update of the

Canadian 24HMG, which instead emphasized the importance of accumulating movement throughout the day, rather than in strictly defined windows.⁷⁶

Aligning with these updates, MVPA was operationalized in this thesis as time spent above 104 mg in bouts of at least 1 minute. This reflects evidence suggesting that, while MVPA of any duration is linked to lower 5-year mortality risk, accumulating MVPA in bouts of at least 1 minute is associated with greater risk reduction than very short, unbouted activity.¹³⁵ A 1-minute minimum was also consistent with recent accelerometer-based studies that examined MVPA in older adults using non-dominant wrist-worn devices.^{230,246,247} Furthermore, consistent with the rationale for using the non-dominant wrist, applying a minimum bout length may help reduce the likelihood that isolated or incidental arm movements, such as fidgeting, brushing teeth, or writing while seated, are misclassified as MVPA.²²⁴ Therefore, the GGIR output variable *dur_day_MVPA_bts_1_min_pla* was used to capture average daily MVPA.

2.5.2.4 Sedentary and Stationary Behaviour Data Processing in GGIR

As described in Chapter 1.5, the Sedentary Behaviour Research Network defines SB as “any waking behaviour characterized by an energy expenditure less than or equal to 1.5 METs, while in a sitting, reclining, or lying posture.”¹²¹ This differs from physical inactivity, which was defined as “an insufficient physical activity level to meet present physical activity recommendations,” such as not achieving 150 minutes of MVPA per week in adults.¹²¹ Stationary behaviour (StaB), a related but broader term, was defined as “any waking behaviour done while lying, reclining, sitting, or standing, with no ambulation, irrespective of energy expenditure.”¹²¹ The key distinction between these definitions lies in posture and intensity: SB and StaB are posture-based, whereas physical inactivity is intensity-based and refers to the absence of sufficient MVPA. Unlike SB, StaB includes sitting, standing still, and other low-movement behaviours that may not meet the postural criteria for SB but do match the energy requirements. These definitions, while conceptually distinct, often blur in practice, particularly when posture cannot be directly measured. This has led to debate in the literature about whether they are truly distinct constructs or if they simply reflect overlapping patterns of low-movement behaviour when measured using accelerometry.^{122,248}

Still, StaB, although newer and less frequently used in epidemiological studies and guidelines, is arguably a more accurate term to use in studies that utilize wrist-worn

accelerometers, which cannot detect posture.¹²¹ Despite its limitations, wrist-worn devices are widely used in movement behaviour research due to evidence of higher compliance rates and the ability to detect short and sporadic movements that may be missed by self-report or posture-sensitive devices worn on the hip or thigh.^{220,223,224,227} Consequently, because standing still and sitting quietly can produce similar acceleration data on the surface, posture-based distinctions cannot be inferred in studies using wrist-worn devices. In recognition of the limitation, GGIR classifies the lowest intensity level of behaviour as inactivity rather than SB, explicitly avoiding the latter term to acknowledge that posture is not assessed.²³⁶ This low-acceleration, non-ambulatory time aligns closely with the conceptual definition of StaB.

In this thesis, the term stationary behaviour (StaB) will be used moving forward to more accurately describe the construct captured by wrist-worn accelerometry. While this diverges from the terminology used in some public health guidelines, it reflects the practical limitations of the device and aligns with calls for construct clarity in accelerometry studies.^{121,249} This distinction is supported by evidence from a study that used thigh-worn monitors to differentiate between sitting and standing and found that both were independently and negatively associated with aerobic fitness.²⁵⁰ In other words, their findings suggest that standing is distinct from SB, and both may have negative implications for CV health compared to PA. Additionally, another study demonstrated that time spent in StaB, regardless of posture, is associated with elevated CVD and mortality risk, with sitting independently conferring greater risk than standing.²⁵¹ Grouping sitting and standing together under the broader term StaB is, therefore, both methodologically appropriate and necessary to accurately reflect the construct measured in this thesis. Referring to this time as SB would misleadingly suggest that only sitting or lying is being captured, when in fact, standing still is also likely included in the accelerometry data.

StaB was operationalized as the average daily time spent below 57 mg of acceleration in a 1-minute bout, using the GGIR output variable *dur_day_IN_bts_1_min_pla*.²⁴⁴ A 1-minute bout duration was chosen to align with the MVPA definitions used in this thesis. StaB was treated as a continuous variable, rather than dichotomized based on guideline cutoffs, to support a more nuanced investigation of its association with CV risk across the full behavioural range. Additionally, since the 24HMG define SB in a posture-based way and counts standing as light-

intensity PA, the StaB construct does not map cleanly onto these binary thresholds, further justifying a continuous rather than categorical approach.

2.5.2.5 Sleep Data Processing in GGIR

As previously described, GGIR uses a two-step process to detect sleep: initial identification of the sleep period time window (SPT-window) using SIBs (Part 3), followed by optional refinement based on participant-reported sleep times, and generation of interpretable sleep variables, including sleep duration and estimated non-wear time during the SPT-window (Part 4). In this thesis, SPT-window detection was guided by participants' self-reported sleep logs, provided via the *loglocation* argument. Additionally, the parameter *sleepwindowType* = "*TimeInBed*" was set to instruct GGIR to use the full in-bed interval (from reported bedtime to final wake time) as the primary sleep window. In this configuration, any SIB that fully overlaps with the in-bed period is classified as sleep, allowing for the estimation of sleep onset latency and sleep efficiency by distinguishing between time in bed and time asleep. On nights when logbook entries were missing, GGIR automatically defaulted to the HDCZA algorithm, which was developed for studies that utilize wrist-worn accelerometer data but do not incorporate sleep logs and has been validated against polysomnography (PSG).²⁵²

After data processing was complete, individual nights were manually inspected for each participant, and participants were excluded if they had less than 4 nights with at least 67% wear time during the SPT-window. Moreover, if the algorithm-generated sleep duration was clearly inconsistent with the logbook entries, it was manually corrected. Sleep episodes outside of the SPT-window were coded as daytime naps, and a total sleep duration variable was created by summing nocturnal and nap sleep averages (*dur_spt_sleep_min_pla* + *dur_day_srnap_min_pla*). The sleep detection algorithms used here have been validated against PSG and sleep diaries in adult samples, supporting their accuracy for estimating sleep parameters in free-living settings.^{238,252–254}

2.5.3 CV Risk Factors

2.5.3.1 Framingham Risk Score

The Framingham Risk Score (FRS) is a clinical algorithm used to estimate an individual's likelihood of developing CVD over the next ten years. It was originally derived from the Framingham Heart Study, a landmark longitudinal cohort initiated in 1948 that enrolled over 5,000 adults aged 28 to 62 from Framingham, Massachusetts, to study risk factors for CVD.²⁵⁵ The study has since expanded across multiple generations and continues to inform the understanding of CV risk.

The FRS incorporates a range of clinical and behavioural predictors. Variables considered in the original and most recent revised model included age, sex, SBP, DBP, total cholesterol, HDL-C, LDL-C, triglycerides (TG), BMI, smoking status, diabetes status, and use of antihypertensive medications.^{256,257} This thesis follows the most current method outlined by D'Agostino et al. (2008), using eight inputs: age, sex, SBP, total cholesterol, HDL-C, smoking status, diabetes status, and use of antihypertensive medication. These values were collected during the participants' two study visits and entered into the Framingham prediction equation, producing a percentage score that represents the individual's estimated 10-year CVD risk.^{257,258}

The model has demonstrated strong predictive utility, with each of the eight risk factors showing a statistically significant relationship with incident CV events in the original Framingham cohort and the Framingham Offspring Study cohort ($p < 0.001$).²⁵⁷ Although Ko et al. (2020) found that the FRS overestimated CVD risk in a large, multiethnic Canadian sample, it remains one of the most widely used and accessible tools for risk stratification in both research and clinical settings.²⁵⁹

2.5.3.2 Anthropometry

Anthropometric measurements were collected during the first research appointment to assess body size and composition, which are known predictors of CV risk and mortality.^{260–262} Height was measured to the nearest 0.5 cm using a portable Seca stadiometer by trained staff. Waist circumference was assessed at the level of the superior iliac crest according to Canadian Society for Exercise Physiology guidelines.^{263,264} Body composition, including weight and body fat percentage, was assessed using bioelectrical impedance analysis with the InBody 270 device.^{265,266} Participants stood barefoot on the analyzer platform with their arms held slightly away from their bodies to ensure accurate impedance readings. The device calculates BMI (in

kg/m²) using measured height and body mass and provides additional estimates of lean mass and fat mass.

2.5.3.3 Blood Pressure

Blood pressure was assessed using the Mobil-O-Graph PWA, a validated oscillometric device commonly used in clinical and research settings for non-invasive measurement of SBP and DBP.^{267,268} Following Canadian Cardiovascular Society guidelines, participants were seated comfortably and rested for at least five minutes prior to measurement.²⁶⁹ A blood pressure cuff was placed on the left upper arm, unless contraindicated (e.g., recent surgery), in which case the right arm was used. Blood pressure values were recorded in millimetres of mercury (mmHg).

On the first day of the study, a single reading of SBP and DBP was obtained as a safety clearance measure prior to initiating the day's exercise protocols. These measurements will be referred to as D1SBP (day 1 systolic blood pressure) and D1DBP (day 1 diastolic blood pressure) for the remainder of this thesis. If D1SBP was greater than or equal to 160 mmHg or D1DBP was greater than or equal to 90 mmHg, participants were given 5 minutes to relax before repeating the measurement. If the values exceeded the thresholds again, the active portions of testing were not performed, and the research assistant recommended that the participant see their primary care provider for medical clearance.

On the second day of the study protocol, three consecutive BP readings were taken with the participant seated and their arm supported at heart level. The average of the second and third readings of SBP and DBP were recorded.

2.5.3.4 Arterial Stiffness

Arterial stiffness was assessed at the second study visit using the Mobil-O-Graph PWA. Arterial stiffness is an indicator of vascular aging and is independently associated with increased CV risk, including coronary artery disease, stroke, left ventricle hypertrophy, atrial fibrillation, and heart failure.^{270,271} With age, the large elastic arteries (e.g., the aorta and carotid arteries) lose compliance, and they become less able to buffer the pressure wave generated by each heartbeat. This causes reflected pressure waves to return to the heart earlier in the cardiac cycle, during systole, which raises central SBP and increases the workload on the heart.²⁷⁰ These vascular changes can be quantified using non-invasive indices such as pulse wave velocity and

augmentation index, which are gaining traction as markers of CV health.^{271,272} The Mobil-O-Graph measured aortic pulse wave velocity (aPWV; m/s) and augmentation index adjusted to a heart rate of 75 beats per minute (AIx75; %).

aPWV obtained from the Mobil-O-Graph has shown acceptable accuracy in comparison to intra-aortic catheterization and cardiac MRI.^{273,274} AIx75 serves as a complementary measure of arterial tone and wave reflection, especially relevant in younger or normotensive adults.^{270,275} Evidence suggests that both aPWV and AIx75 can predict CV events and all-cause mortality^{276–278} In the WARM Hearts cohort, Kalenga et al. (2022) found no adjusted differences in aPWV or AIx75 between unopposed estrogen users and controls, though group comparisons showed higher values among oral estrogen users compared to non-oral estrogen users.⁷¹

2.5.3.5 Phlebotomy

Fasting blood samples were collected during the second research visit. Participants fasted for 12 hours prior to phlebotomy, during which 15 mL of blood was drawn by a trained phlebotomist and separated into four tubes: a serum silica tube (1 × 4 mL), a lithium heparin tube (1 × 4 mL), and two ethylenediaminetetraacetic acid (EDTA) tubes (2 × 3 mL)⁷². Whole blood from the serum silica tube was snap frozen and stored at –80°C. Following coagulation and centrifugation at 2,000 × g for 10 minutes, serum was aliquoted and similarly stored. Plasma was isolated from the EDTA and lithium heparin tubes using the same centrifugation procedure, with eight aliquots stored at –80°C. Analyses of LDL-C, HDL-C, TG, and fasting blood glucose were performed using lithium heparin plasma. These traditional biomarkers are incorporated into the Framingham Risk Score and interpreted using the CCS guidelines.²⁷⁹

2.6 Variables

All the variables described below are presented in Tables 6 through 9 and summarized in Table 10.

2.6.1 Menopausal Hormone Therapy Usage

MHT usage was categorized based on self-report into never-users and ever-users, which were comprised of former MHT users and current MHT users (Table 6). Former users had

indicated that they had previously used MHT but were not using it at the time of data collection. Current users were actively using any form of MHT at the time of data collection.

Table 6. MHT Usage Status Summary.

MHT Usage Status	N	Percent (%)
Never	660	71.0
Ever	269	29.0
<i>Former</i>	<i>173</i>	<i>18.7</i>
<i>Current</i>	<i>96</i>	<i>10.3</i>
Total	929	100.0

Abbreviations: MHT, menopausal hormone therapy

2.6.2 Menopausal Hormone Therapy Type

Participants were classified into one of five categories based on the type of hormone they reported using: unopposed estrogen, combined estrogen-progestogen, progestogen only, multitype, or other/unknown (Table 7). Participants were assigned to the multitype category if they reported using more than one distinct hormone type (e.g., both unopposed estrogen and combined therapy) over time, in accordance with categorization rules described in previous cohort studies.^{280–282} Since a goal of the analyses in this thesis is to explore whether the type of MHT influences CV outcomes, assigning individuals who had used multiple formulations of MHT to a single hormone-type group (e.g., unopposed estrogen) could obscure potential differences attributable to specific formulations and introduce exposure misclassification. Additionally, individuals who report using multiple MHT formulations may differ systematically from those who used a single formulation. For example, usage of multiple formulations may reflect differences in treatment response or symptom severity over time. This is in contrast to Kalenga et al. (2022), where hormone type was defined using an “ever-use” approach, whereby individuals who had ever used unopposed estrogen (regardless of if they also used a different formulation) were assigned to a single hormone-type category. In this thesis, multitype participants were identified descriptively but excluded from analytic models examining hormone type in Objective 2.

When filling out the MHT usage history survey, participants were presented with predefined hormone type categories (i.e., estrogen-only, progestogen-only, or combined

estrogen-progestogen therapy) or they had the option to select “Other” and provide a free-text response. Estrogen-only responses were re-coded as unopposed estrogen for easier interpretation and consistency with terminology used in previous publications.^{28,197,213,283}

A total of 39 participants self-reported their hormone therapy use in the “Other” category. Upon review of the free-text entries, many appeared to reference estrogen-based therapies (e.g., Vagifem, Premarin, Estrogel); however, incomplete product names, unclear formulations, and missing contextual details limited the ability to reliably recode these cases. To avoid misclassification bias, these “Other” responses were combined with participants who had selected “Unsure of Type” to create one “Other/Unknown” category. Similar strategies have been used in previous epidemiologic cohort studies. For example, two groups of authors analyzing the Norwegian NOWAC cohort and the California Teachers Study, respectively, retained “unknown” or “other” MHT groups when participant reports could not be confidently categorized.^{284,285} Therefore, a conservative strategy was used for this analysis to preserve participants’ self-reported answers without overinterpreting vague or incomplete information. This approach also allows for the retention of these cases in descriptive analyses while maintaining transparency in exposure classification.

Table 7. MHT Type Summary.

MHT Type	N	Percent (%)
Control (No MHT)	660	71.0
Combined therapy user	70	7.5
Unopposed estrogen user	101	10.9
Progestogen-only User	4	0.4
Other/Unknown	47	5.1
Multitype User	47	5.1
Total	929	100.0

Abbreviations: MHT, menopausal hormone therapy

Despite their inclusion in summary tables, participants in the “Other/Unknown” group (n = 47) will be excluded from regression models to reduce classification error. The progestogen-only group (n = 4) will also be excluded from modelling due to its extremely small sample size.

2.6.3 Menopausal Hormone Therapy Route

MHT route of administration was categorized based on participant responses into categories of oral (pill), patch, skin cream/gel, vaginal (e.g., vaginal rings, intrauterine devices, tablets), multi-route (if more than one route was reported), or unsure (Table 8). Participants who reported more than one route of MHT were classified as “multi-route” users in accordance with the criteria for MHT multitype users described in 2.6.2. Patch or skin cream/gel responses were combined into one “transdermal” category, in line with the approach of Kalenga et al. (2022).⁷¹

Table 8. MHT Route of Administration Summary.

MHT Route	N	Percent (%)
Control (no MHT)	660	71.0
Oral	97	10.4
Transdermal	47	5.1
Vaginal	61	6.6
Multi-route	48	5.2
Unsure of Route	16	1.7
Total	1018	100.0

Abbreviations: MHT, menopausal hormone therapy

Participants reporting use of multiple hormone routes of administration were identified descriptively but excluded from analytic models examining hormone route. Inclusion of participants with heterogenous exposure histories would complicate interpretation and introduce exposure ambiguity. Participants who were unsure of their MHT route (n = 16) were also excluded from regression analyses. Since this study specifically aims to examine the physiological effects of different administration routes, including participants without route information would limit the ability to draw accurate conclusions about route-specific associations with CV outcomes.

2.6.4 Movement Behaviours

Movement behaviours were assessed using accelerometry, as described in Section 2.5.2. These behaviours will be operationalized as follows: MVPA will be quantified as the average

minutes per day; sleep duration will be calculated as the average number of hours slept per day (including naps); and StaB will be estimated as the average number of hours per day spent inactive or stationary. While the Canadian 24HMG utilize weekly totals, MPVA is reported here as a daily average to account for variations in accelerometer wear time (4-7 days) and avoid the bias associated with extrapolating weekly volumes from shorter observation periods. Most participants (N=635; 68.4%) recorded 7 valid days of accelerometer wear time. The remainder (N=294, 31.6%) had 4 to 6 days of valid wear time. Therefore, nearly a third of the values would need to be extrapolated, which could introduce bias. As mentioned, StaB serves as a proxy for SB, acknowledging the limitations of accelerometry in distinguishing between different postures.

2.6.5 CV Outcomes

Primary outcomes include aPWV, AIx75, SBP, DBP, and FRS. The first four of these measures were selected to replicate the analysis conducted by Kalenga et al. (2022).⁷¹ In the original study, the SBP and DBP values reflected the first blood pressure measurements obtained during the study protocol on day 1 (D1; referred to as D1SBP and D1DBP for the remainder of this thesis), which were primarily used as pre-exercise safety screening.

Secondary outcomes include additional CV markers previously explored in MHT research (some of which are also components of the FRS), including waist circumference (WC), HDL-C, LDL-C, TG, and fasting glucose.^{29,70,214,286,287} These prior studies have reported mixed associations between MHT use and these markers, with evidence of both protective and adverse effects. All outcomes will be treated as continuous variables.

To provide a clinical context for interpreting these results, it is important to evaluate the cohort's observed measurements against established health benchmarks. Table 9 summarizes the normative reference ranges and clinical targets for each primary and secondary outcome, as defined by current CV and metabolic guidelines. Where established targets were not available (i.e., for aPWV and AIx75), recommendations from individual studies and findings from comparable populations were listed.

Table 9. Clinical Reference Ranges for Primary and Secondary Outcomes.

Outcome	Targets and Recommended Ranges	Source
aPWV ^a	< 9-10 m/s	Alecu et al. (2008) ²⁸⁸ ; An et al. (2023) ²⁸⁹
AIx75 ^a	Approximately 22-28% ^b (Increases with age; lower is better)	Paiva et al. (2020) ²⁹⁰
SBP	≤ 130 mmHg	Hypertension Canada (2025) ²⁹¹
DBP	≤ 80 mmHg	Hypertension Canada (2025) ²⁹¹
FRS	Low Risk: < 10% Intermediate-Risk: 10-19.9% High Risk: ≥ 20%	CCS Guidelines (2021) ²⁶⁹
WC	< 88 cm	Health Canada ²⁹²
HDL-C	> 1.3 mmol/L	Ottawa Heart Institute ²⁹³ ; Statistics Canada (2020) ²⁹⁴
LDL-C ^c	Normal-low elevation: ≤ 1.8-3.5 mmol/L Moderate elevation: 3.5-5.0 mmol/L High elevation: > 5.0 mmol/L	CCS Guidelines (2021) ²⁶⁹
TG	< 1.8 mmol/L	Ottawa Heart Institute ²⁹³
Fasting Glucose	Hypoglycemia: < 3.0-3.9 mmol/L Normal: 4.0-6.0 mmol/L Prediabetes: 6.1-6.9 mmol/L Diabetes: ≥ 7.0 mmol/L	Diabetes Canada (2018) ²⁹⁵

Abbreviations: aPWV, aortic pulse-wave velocity; AIx75, augmentation index standardized to 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; CCS, Canadian Cardiovascular Society.

^a No established target values for Canadians have been published to date.

^b Population was Brazilian women with no cardiovascular risk factors.

^c The CCS uses broad LDL-C thresholds to guide the initiation or intensification of lipid-lowering therapy. Clinical concern is evaluated in the context of multiple factors, and thus there is no single or specific target.

2.6.6 Covariates

Primary models were adjusted for the following covariates: Age, education level (no degree/certificate/diploma or high school education vs. postsecondary education), age at menopause onset, type of menopause (natural/spontaneous vs medically/surgically induced), history of vasomotor symptoms, and primary household earner status. These variables were selected based on their established associations with CV outcomes and MHT usage. Additional

variables, such as BMI, history of APOs, MHT duration, and MHT timing, were entered into sensitivity analyses; these variables are described in Chapter 2.6.6.1 and Chapter 2.7.4.2.

2.6.6.1 Sex Neutral Physiological Covariates

Several sex-neutral physiological covariates (variables that are relevant regardless of sex) were initially considered for inclusion in regression models, including age, BMI, history of hypertension, and average mean arterial pressure. These variables were selected a priori based on established associations with CVD risk and prior work in this area, including the analytical approach used by Kalenga et al. (2022).⁷¹ Age was included as a covariate in models for most outcomes in Objective 1 and Objective 2, given its influence on CV risk through cumulative vascular, metabolic, hormonal, autonomic, and inflammatory changes across the life course.²⁹⁶ Age is also known to affect movement behaviours and may also affect MHT uptake patterns.^{20,84-87,131,297} However, age was excluded from models that directly replicate Kalenga et al. and from models in which the outcome measure is calculated using age; this will be described further in Chapter 2.7.2.2.

Other physiological variables (BMI, history of hypertension, and mean arterial pressure) were evaluated and included as covariates in models addressing Objective 1, but not Objective 2. BMI can predict CV morbidity and mortality, with excess adiposity linked to dyslipidemia, hypertension, and insulin resistance, all of which elevate CVD risk.^{298,299} Consistent with this rationale and the thesis objectives, BMI was included as a covariate in Objective 1A, 1B, and 1D.1 analyses to mirror the analytical approach of Kalenga et al. (2022).⁷¹ However, BMI was excluded from regression models in Objective 2, which incorporated movement behaviours, to avoid overadjustment bias.³⁰⁰ Overadjustment bias has been defined as “control[ling] for an intermediate variable (or a descending proxy for an intermediate variable) on a causal path from exposure to outcome,” which can obscure the true effects of exposure variables.³⁰⁰ Since BMI plausibly lies downstream of several exposures, including movement behaviours, controlling for BMI could obscure the effects of movement behaviours on CV outcomes. Therefore, BMI should arguably be excluded from analyses investigating movement behaviours as exposure variables.

Mean arterial pressure and history of hypertension were included in the Objective 1 replication analyses to maintain consistency with Kalenga et al. (2022).⁷¹ However, they were not retained in the models under Objective 2 for three reasons. First, their inclusion in Objective

1 was primarily methodological rather than conceptually central to the research questions under Objective 2. Second, these variables would only be applicable to a subset of models (i.e., for aPWV and AIx75), reducing comparability across outcomes. Third, retaining them would increase model complexity without materially advancing the interpretation of the primary relationships of interest. Accordingly, they were not retained in the Objective 2 models.

2.6.6.2 Female Sex-Specific Covariates

Age at menopause, a history of experiencing vasomotor symptoms, and type of menopause may influence both CV risk and possibly MHT use. Early menopause has been associated with a higher risk of coronary heart disease and stroke, possibly due to prolonged estrogen deficiency and related metabolic or vascular changes.³⁰¹ Females who experience early menopause may also be encouraged to initiate MHT to manage symptoms or mitigate health risks associated with estrogen deficiency.^{20,22,24} Similarly, vasomotor symptoms, regardless of whether they begin before or after menopause, have been linked to increased CV risk and may contribute to decisions around MHT use.³⁰¹ In this study, vasomotor symptoms are operationalized as a binary variable (history of symptoms vs. no history of symptoms).

The type of menopause (spontaneous vs. surgical or medical treatment-induced) can also influence both CVD risk and MHT use. Menopause type will be operationalized as a binary variable indicating spontaneous menopause (yes vs. no). Spontaneous menopause refers to the natural cessation of menstruation unrelated to medical intervention. Most of the participants in this sample reported spontaneous menopause (N=758). Women who do not fall into this category (N=171) reported, for example, bilateral (N=70) or partial oophorectomy (N=5), hysterectomy (N=27), endometrial ablation (N=27), cancer-treatment-induced menopause (via chemotherapy or radiation therapy; N=8), or other health conditions or considerations (N=34) resulting in cessation of menses. The addition of this variable acknowledges that surgical or induced menopause can be associated with more abrupt hormonal changes and higher CV risk, which may influence both MHT initiation and CV outcomes.^{302,303} For example, among participants of the Canadian Longitudinal Study on Aging, women who experienced surgical menopause had greater CV risk as determined by the FRS compared to women who experienced spontaneous menopause.³⁰⁴ Similarly, a cross-sectional study among Iranian females found that those who experienced surgical or chemotherapy treatment-induced menopause had higher odds of CVD

and coronary heart disease compared to those who experienced spontaneous menopause.³⁰⁵ Interestingly, in a pooled analysis of over 200,000 females across 10 international studies, this trend was modified by MHT usage: those who experienced surgical menopause but did not use MHT had a higher risk of incident CVD compared to their counterparts who did have a history of using MHT.³⁰²

However, it should also be noted that menopause type and age at menopause are often related, where women experiencing surgical or treatment-induced menopause are typically younger than women who experience spontaneous menopause.³⁰² Still, the authors of the pooled analysis found that even after adjusting for age at menopause, there was still an influence of the type of menopause on incident CVD, where spontaneous menopause was associated with lower CVD risk compared to women who experienced surgical menopause at the same age.³⁰² Therefore, both age at menopause and type of menopause will be considered in the main analyses.

2.6.6.3 Social and Gender-related Covariates

Socioeconomic and psychosocial gender-related factors are increasingly recognized as important contributors to CVD in women. To align with the Canadian Institutes of Health Research Sex- and Gender-Based Analysis Plus guidelines, this study included two gender-related variables: (1) *primary household earner* (a binary variable indicating whether the participant is the main income provider in their household), and (2) *educational attainment* (a binary variable indicating whether the participant completed high school and/or postsecondary education).

Evidence suggests that women who experience financial strain or who serve as primary earners often face higher stress levels, reduced access to care, and limited time for health-promoting behaviours, all of which may increase CV risk.^{306,307} In Canada, these disparities persist despite a universal healthcare system, disproportionately affecting women's CV health.³⁰⁶ Educational attainment is also a well-established predictor of CVD. Canadian individuals with lower education levels have significantly higher odds of CVD, independent of other factors such as income, smoking status, and BMI.³⁰⁸ Education was entered into models as a binary variable indicating achievement of a postsecondary education; high school education and no degree/certificate/diploma were merged together (rather than modelled separately) due to issues

with multicollinearity. Including social- and gender-related variables in analyses helps control for social determinants that may confound associations between MHT, lifestyle behaviours, and CV outcomes.

Table 10. Summary of Variables.

Type	Variable	Operationalization	Units
MHT Exposures	MHT usage	Control (Never usage) Former usage Current usage	-
	MHT type	Control (Never usage) Combined estrogen-progestogen Unopposed estrogen	-
	MHT route	Control (Never usage) Oral Transdermal Vaginal	-
Movement Behaviour Exposures	MVPA	Continuous	Average minutes/day
	StaB	Continuous	Average hours/day
	Sleep duration	Continuous	Average hours/day
Primary outcomes	aPWV	Continuous	m/s
	AIx75	Continuous	%
	SBP	Continuous	mmHg
	DBP	Continuous	mmHg
	FRS	Continuous	% (10-Year CV Risk)
Secondary outcomes	WC	Continuous	WC
	HDL-C	Continuous	mmol/L
	LDL-C	Continuous	mmol/L
	TG	Continuous	mmol/L
	Glucose	Continuous	mmol/L
Outcomes used in Objective 1 Only	D1SBP	Continuous	mmHg
	D1DBP	Continuous	mmHg

Covariates used in Objective 1 Only	History of hypertension	Binary (yes/no)	-
	Mean arterial pressure	Continuous	mmHg
	BMI	Continuous	kg/m ²
Covariates used in Objective 1 and/or Objective 2	Age	Continuous	Years
	Age at menopause	Continuous	Years
	Spontaneous menopause	Binary (yes/no)	-
	History of VMS	Binary (yes/no)	-
	Primary household earner status	Binary (yes/no)	-
	Highest education	No degree/certificate/diploma or High School education vs. Postsecondary education	-

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; CV, cardiovascular; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; D1SBP, day 1 systolic blood pressure; D1DBP, day 1 diastolic blood pressure; BMI, body mass index; VMS, vasomotor symptoms.

2.7 Statistical Analyses

Preliminary data cleaning and preparation were performed in Microsoft Excel (Version 2511), including applying exclusion criteria (described in section 2.4) and verifying data quality and formatting. Diagnostic checks were conducted for both group comparisons and linear regression models. Group comparisons for continuous variables were assessed via one-way ANOVA unless assumptions of normality (assessed via Shapiro-Wilk test) and homogeneity of variance (Levene's test) were violated. Kruskal-Wallis tests and Welch's ANOVA were used as alternatives applied when the assumptions of normality and homogeneity of variance were violated, respectively.

For linear regression models, assumptions of linearity (via visual inspection of P-P plots, and Q-Q plots), homoscedasticity (via visual inspection of scale-location plots), normality of residuals (via visual inspection of a histogram of standardized residuals), and multicollinearity (via Variance Inflation Factor) were assessed. Missing data were handled via listwise deletion within each model. In this analysis, most missing data were observed for two specific covariates, age at menopause and primary earner status. These data may be considered missing-not-at-random, meaning that missingness is related to both the variable itself and other unobserved variables.^{309–311} For example, age at menopause values were likely missing because participants could not recall an accurate age, and participants may have preferred not to disclose information about income status for other unknown reasons. Multiple imputation has not been recommended to handle missing-not-at-random data, therefore listwise deletion was used.^{309–311} Additionally, one implausible fasting glucose value (0.608 mmol/L) was identified; the participant with this value was excluded from analyses with glucose as the outcome.

To quantify the magnitude of observed differences by MHT exposure groups, effect sizes were calculated using Eta-squared (η^2) for ANOVA and Epsilon-squared (ϵ^2) for Kruskal-Wallis tests. These metrics estimate the proportion of variance in the tested variable attributable to the grouping variable (e.g., MHT exposure).³¹² While these effect sizes are reported for completeness, they are not utilized as the primary criterion for interpretation. Instead, findings are evaluated against normative and clinical guidelines (e.g., 24HMG, Table 9) and/or compared to findings from studies using similar populations, as per recommendations in literature on statistical methods.^{313,314}

For regression models, unstandardized (B) and standardized (β) coefficients are reported. Unstandardized coefficients represent the absolute change in the outcome variable (e.g., mmHg or m/s) for every one-unit increase in the predictor, maintaining the original clinical scales. In contrast, standardized coefficients translate these effects into standard deviation units, allowing for comparisons of the relative predictive strength between, for example, different movement behaviors and MHT exposures within the same model. In models utilizing log-transformed outcomes, a one-unit increase in the predictor multiplies the expected value of the outcome by e^β ; interpretations can also be quickly estimated, where a one-unit increase in the predictor approximates a $100 \times \beta$ % change in the outcome.³¹⁵

All analyses were conducted using R (version 4.4.1) and SPSS (version 29). A two-tailed alpha level of 0.05 was used for statistical significance, although exact p-values are reported for completeness.

2.7.1 Descriptive statistics

Descriptive statistics were used to summarize participant demographics, MHT exposures, 24-hour movement behaviours, and CV outcomes. Continuous variables are reported as means $\pm$ standard error (in Objective 1A only), means $\pm$ standard deviation or medians with interquartile ranges, depending on their distribution. Categorical variables are presented as frequencies and percentages.

2.7.2 Objective 1 Statistical Analyses

As outlined in Chapter 2.2.1, Objective 1 was to replicate, rework, and extend the study by Kalenga et al. (2022) by evaluating associations between estrogen MHT route and CV outcomes using an increased sample size, using alternative analytical specifications, and by incorporating movement behaviours into analyses. Table 11 summarizes all the changes made from the original analyses from Kalenga et al. in each sub-objective.

Objective 1 focused on participants with any history of unopposed estrogen MHT use and controls (i.e., MHT never-users), expanding the sample from N=55 ever-unopposed-estrogen users and N=223 controls in Kalenga et al. (2022), to N=153 ever-unopposed-estrogen users and N=660 controls in this thesis.⁷¹ Of note, this categorization of unopposed estrogen MHT usage

includes individuals who reported use of more than one MHT regimen (i.e., “multitype” users), whereas the number of participants who used exclusively unopposed estrogen was smaller in the full sample (N=101). Additionally, 6 participants included in the original analyses by Kalenga et al. (2022) were excluded from this thesis due to missing data.

2.7.2.1 Objective 1A Statistical Analyses

Objective 1A replicates Kalenga et al. directly, with the main difference being the larger sample size (total N=278 in Kalenga et al. to total N=813 in this thesis).⁷¹ The outcomes examined were aPWV, AIx75, systolic and diastolic blood pressure. As described in Chapter 2.5.3.3, two sets of blood pressure measurements were taken during the WARM Hearts study: D1SBP and D1DBP, which were obtained for pre-exercise safety clearance; and the day 2 SBP and DBP measurements, calculated as the mean of the second and third measurements (of three total trials).⁷² In Kalenga et al., the D1SBP and D1DBP values were used.⁷¹ Therefore, for methodological consistency with Kalenga et al., the D1SBP and D1DBP values were examined in Objective 1A. Accordingly, the outcomes examined for Objective 1A are aPWV, AIx75, D1SBP, and D1DBP. In all subsequent analyses, the averaged day 2 SBP and DBP values were used.

Baseline differences across routes of unopposed estrogen administration (oral, transdermal, vaginal) and controls were assessed using one-way ANOVA with Bonferroni post-hoc corrections. Group comparisons were performed using ANOVA regardless of the distribution of the outcome variables, to replicate the approach of Kalenga et al.⁷¹

Multiple linear regression models were then constructed to assess associations between route of administration and CV outcomes, using the control group (MHT never-users) as the reference category. A second set of models among MHT users only were also fit, comparing oral users (reference category) to transdermal and vaginal users. Covariates were selected *a priori* based on Kalenga et al. (2022) and established clinical relevance; no stepwise selection procedures were used.⁷¹ Specifically: D1SBP and D1DBP models were adjusted for age and BMI; aPWV models were adjusted for age, mean arterial pressure, age at menopause onset, history of vasomotor symptoms, and history of hypertension; AIx75 was adjusted for age at menopause onset, history of vasomotor symptoms, and history of hypertension. Model fit was reported and assessed using the R^2 and adjusted R^2 values. Standardized and unstandardized

regression coefficients were reported to facilitate interpretation of effect sizes and to allow comparison of the relative contribution of individual predictors within each model.

2.7.2.2 Objective 1B Statistical Analyses

Objective 1B builds upon Objective 1A by employing alternative variable operationalizations and minor changes to the model structure. The outcomes for Objective 1B are aPWV, AIx75, D1SBP, D1DBP, SBP, and DBP.

Group comparisons were conducted using the same statistical procedures described for Objective 1A. Regression models were also constructed in the same way, with the exception that age was excluded as a covariate when modelling aPWV. This change was made because age is incorporated into the Mobil-o-Graph algorithm used to derive aPWV values; including age as a covariate would therefore risk statistical overadjustment.^{268,273,316,317} However, a replication of the remaining models in this thesis with age included were conducted as sensitivity analyses and are described in Chapter 2.7.4.2 and Chapter 3.4.3.

2.7.2.3 Objective 1C Statistical Analyses

Objective 1C is to expand the group comparisons from the previous Objectives by testing differences across unopposed estrogen MHT routes in a broader set of variables, including additional outcomes (FRS, WC, HDL-C, LDL-C, TG, and glucose) and movement behaviours (MVPA, StaB, sleep).

Assumptions of ANOVA were assessed via Levene's test, the Shapiro-Wilk test, and visual inspection of histograms (raw data and standardized residuals), PP plots, and QQ plots. Welch's ANOVA or Kruskal-Wallis tests were used as non-parametric alternatives for outcomes where assumptions of homogeneity of variance and assumptions of normality were violated. Dunn's tests with a Bonferroni correction were used for post-hoc analyses following Kruskal-Wallis tests. Visual inspection of histograms and results from the Shapiro-Wilk test indicated that mean arterial pressure, StaB, sleep duration, SBP, and LDL-C met normality assumptions and were analyzed using one-way ANOVA. DBP followed a normal distribution but violated Levene's test and thus was tested using Welch's ANOVA. The remaining outcomes (age, age at menopause, MVPA, aPWV, AIx75, FRS, WC, HDL-C, TG, and glucose) violated the Shapiro-Wilk test and were thus assessed using Kruskal-Wallis tests.

2.7.2.4 Objective 1D Statistical Analyses

Objective 1D is to expand the regression models from the previous Objectives by adding movement behaviours and examining additional outcomes, as well as assessing the relative contribution of movement behaviours in explaining variance in CV outcomes. To address this objective, hierarchical multiple linear regression models will be constructed.

Hierarchical linear regression is a regression method where predictors are entered into models in steps, or “blocks,” based on theory and prior literature rather than on decisions made by statistical software.^{318,319} The goal is to assess the incremental change in model fit between each block of variables on the outcome, typically measured by R^2 , Adjusted (Adj.) R^2 , and the change in F-statistics. Generally, control variables with a known relationship to the outcomes of interest are entered in preliminary blocks, followed by blocks containing the predictors of interest.³¹⁸ Recommendations support hierarchical regression as a theory-based alternative to stepwise methods, which can produce unstable models that reflect chance patterns in the sample, and dismiss prior literature and theory.^{318,320–322} By structuring the model in conceptually defined blocks, hierarchical regression clarifies the unique contribution of each domain of interest. Hierarchical linear regression has been applied in studies where CVD was the outcome³²³ and where MHT was an exposure²⁸³, both of which used block-wise entry to structure their models.

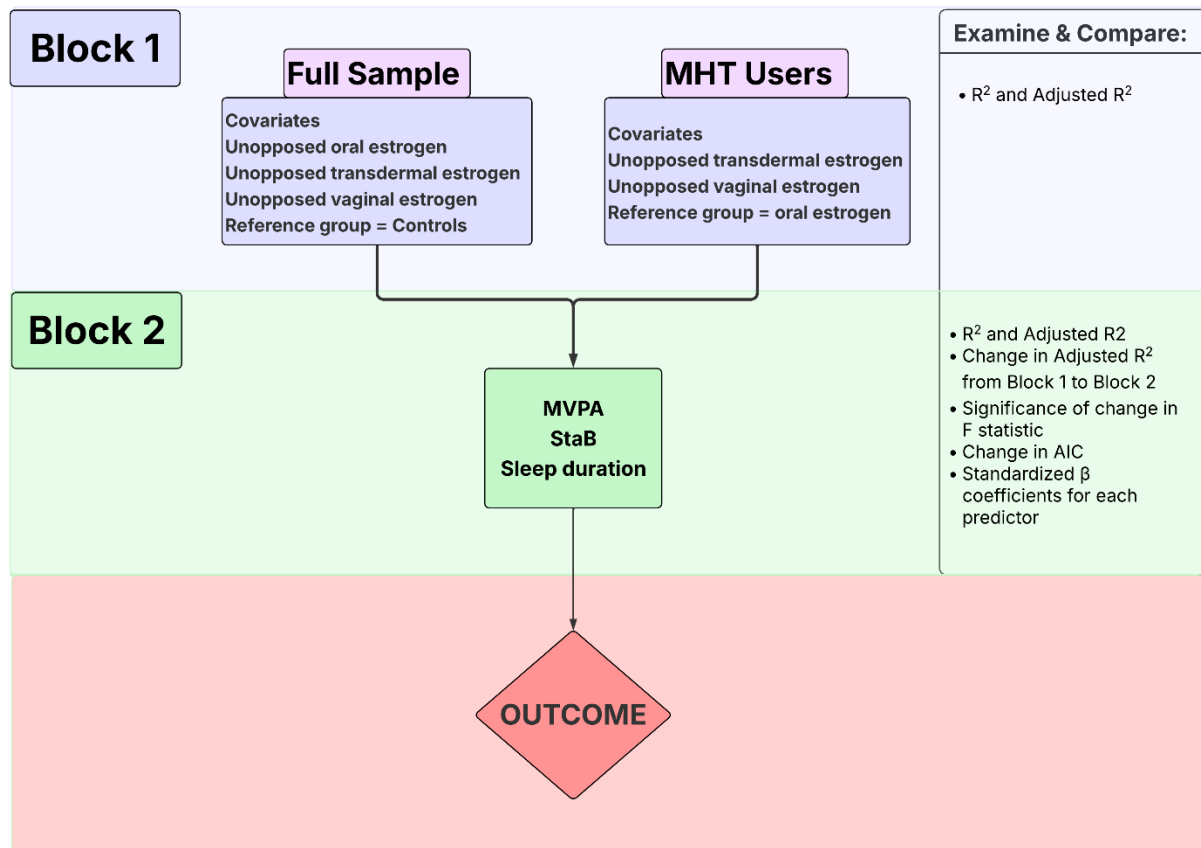
When hierarchical models are used (Objective 1D and Objective 2B), model fit was evaluated by the change in F statistic and Adjusted R^2 values, unstandardized (B) and standardized (β) beta coefficients and 95% confidence intervals for each included variable, as well as the Akaike Information Criterion (AIC). Adjusted R^2 values are interpreted instead of R^2 values because the latter will always increase when new predictors are added to a model, thus would artificially inflate the estimated goodness-of-fit.³²⁴ This would be especially problematic when using a hierarchical structure, as each additional block would always appear “better” than previous blocks, regardless of the true relevance of the additional predictors. Adjusted R^2 values are an unbiased measure that correct for the number of predictors in the model, which can help prevent overfitting.³²⁵ Adjusted R^2 values may fall below zero due to the adjustment penalty; such values do not indicate negative explanatory power, but simply that the model fits the data poorly.³²⁴ Similarly, AIC is a measure of the balance between model fit and model parsimony, in

which models are penalized for including many predictors if they do not substantially improve model fit.^{326,327} The “best” model will have the lowest AIC.

Visual inspection of regression diagnostics indicated that model assumptions were generally met across outcomes. Residuals were approximately normally distributed, and there were no substantial deviations from linearity or homoscedasticity for most outcomes. VIFs were within acceptable limits. However, a concerning right-skew was observed for FRS, TG, and fasting glucose, with corresponding deviations in distributions of standardized residuals. Therefore, these three variables were log-transformed for regression analyses (logFRS, logTG, logGlucose). Diagnostic plots following the transformation more closely met the assumptions of linear regression. Descriptive statistics for these variables are presented on the original scale for interpretability.

Objective 1D.1. To address Objective 1D.1, movement behaviours were added to the original model structure from Kalenga et al. in a second block (Figure 2).⁷¹ The outcomes examined were aPWV, AIx75, D1SBP, D1DBP, SBP, and DBP. aPWV was adjusted for mean arterial pressure, history of hypertension, age at menopause, and history of vasomotor symptoms; AIx75 was adjusted for history of hypertension, age at menopause, and history of vasomotor symptoms; and the four blood pressure outcomes were adjusted for age and BMI. In the full sample, the model structure was as follows: *Block 1* included covariates and unopposed estrogen use (oral, transdermal, and vaginal), with never-usage as the MHT reference group; *Block 2* included MVPA, StaB, and sleep. Among MHT users only, the model structure was as follows: *Block 1* included covariates and unopposed estrogen use (transdermal and vaginal), with oral usage as the MHT reference group; *Block 2* included MPVA, StaB, and sleep. The change in model fit from *Block 1* to *Block 2*, as well as the relative contribution of each exposure variable, was assessed using the methods described previously.

Figure 2. Model Structure for Objective 1D.1



Objective 1D.2. To address Objective 1D.2, unadjusted models were constructed in the same manner as Objective 1D.1, but no covariates were included. That is, *Block 1* included MHT usage exposures, and *Block 2* included movement behaviours. Additionally, D1SBP and D1DBP were no longer examined as outcomes. Models were assessed in the same manner. The primary outcomes examined were aPWV, AIx75, SBP, DBP, and FRS. The secondary outcomes examined were WC, HDL-C, LDL-C, TG, and glucose.

Objective 1D.3. Finally, to address Objective 1D.3, adjusted models were constructed, where variables were entered in three blocks. Outcomes examined were the same as Objective 1D.2 (aPWV, AIx75, SBP, DBP). Additionally, an alternative set of covariates was used; the rationale behind these decisions was described in Chapter 2.6.6. Covariates were entered into *Block 1*. This included age, age at menopause, spontaneous menopause, history of vasomotor symptoms,

educational attainment, and primary household earner status, as previously described. However, age was not included in models predicting aPWV and AIx75, because it is part of the calculation of these outcomes. MHT exposure variables were then entered in *Block 2* to evaluate their incremental contribution beyond the covariates. Movement behaviours were finally added in *Block 3*. The change in model fit from *Block 1* to *Block 2* and *Block 2* to *Block 3*, as well as the relative contribution of each exposure variable in *Block 3*, was assessed using the methods described previously.

Table 11. Summary of Changes from Kalenga et al. in Objective 1

Objective	Change from Kalenga et al.	Rationale
1A	Analyzing a larger sample size (Total N increased from 278 to 813)	Larger samples better represent the population and increase precision and statistical power
	6 participants included in the original analyses were excluded from this thesis	Due to missing data for bloodwork parameters (HDL-C, LDL, TG, fasting glucose).
	Reporting model fit	Model fit was not reported in Kalenga et al.
1B	Including the day 2 SBP and DBP values as outcomes in addition to D1SBP and D1DBP.	The day 2 values are likely less variable and could better reflect resting blood pressure under standardized research conditions. The day 1 values were intended as a safety check.
	Removing age as a covariate from models predicting aPWV	Age should arguably not be included as a covariate for aPWV, because age is included in its calculation
	Reporting mean and standard deviation rather than mean and standard error	For consistency with analyses in Objectives 1C, 1D, 2A, and 2B.
	Reporting coefficients for all predictors entered into regression models, including covariates	For completeness.
1C	Adding movement behaviours (MVPA, StaB, sleep) into analyses	Movement behaviours were not included in prior models and may explain some of the variance in outcomes attributed to MHT usage
	Examining additional outcomes (FRS, WC, HDL-C, LDL-C, TG, and glucose)	FRS is a composite measure used to predict 10-year CV risk; Remaining outcomes have previously been explored in MHT research with mixed findings.

1D	Hierarchical linear regression model structure	Allows for assessing the change in model fit when adding different “blocks” of predictors
1D.3	Alternative set of covariates	See Chapter 2.6.6 and Table 10.

2.7.3 Objective 2 Statistical Analyses

Analyses in Objective 2 categorize MHT users more broadly into three separate MHT: (1) MHT usage history (controls/never-users, former users, current users), (2) MHT type (controls/never-users, combined estrogen-progestogen, unopposed estrogen), and (3) route of administration (controls/never-users, oral, transdermal, vaginal). Primary outcomes are aPWV, AIx75, SBP, DBP, and FRS. Secondary outcomes are WC, HDL-C, LDL-C, TG, and glucose.

2.7.3.1 Objective 2A

Objective 2A was to examine group differences in covariates, movement behaviours, and CV outcomes across MHT exposures defined by usage history (Objective 2A.1), type (Objective 2A.2), and route (Objective 2A.3). Differences were assessed in the following variables: age, BMI, mean arterial pressure, age at menopause, MPVA, StaB, sleep duration, aPWV, AIx75, SBP, DBP, FRS, WC, HDL-C, LDL-C, TG, and glucose.

Visual inspection of histograms and results from the Shapiro-Wilk test indicated that mean arterial pressure, StaB, sleep duration, and SBP met normality assumptions and were analyzed using one-way ANOVA for all Objectives. DBP and LDL-C followed normal distributions, but DBP violated Levene’s test when analyzed by MHT usage history (Objective 2A.1), and LDL-C violated Levene’s test when analyzed by MHT type (Objective 2A.2) and route (Objective 2A.3). Welch’s ANOVA was used for these variables in these cases. All remaining continuous variables violated normality assumptions and were therefore analyzed using Kruskal-Wallis tests, with Dunn’s post-hoc tests and Bonferroni correction for multiple comparisons where appropriate.

Furthermore, to examine the association between MHT exposures and categorical variables, Pearson’s chi-square tests of independence were conducted. These tests were conducted primarily to contextualize results from the thesis objectives, rather than to be interpreted as main findings. The following variables were assessed: history of hypertension, sleep apnea, type 1 diabetes, type 2 diabetes, history of adverse pregnancy outcomes, spontaneous menopause,

vasomotor symptoms (experience and severity), postsecondary education (compared to non-postsecondary), and primary earner status. Examinations of MHT type and MHT route were also tested for current or former usage status among ever-users, with controls excluded. The assumption of adequate cell size was evaluated, and all cells had an expected frequency greater than 5. Post-hoc pairwise comparisons of column proportions were calculated, and p-values were adjusted using the Bonferroni correction.

2.7.3.2 Objective 2B

Hierarchical linear regression models were used to address Objective 2B and were structured similarly to the models in Objective 1D. Separate model sets were constructed for each exposure definition: usage history (Objective 2B.1), MHT type (Objective 2B.2), and route of administration (Objective 2B.3). These categories were modelled separately to avoid multicollinearity arising from overlapping categories. For each exposure-outcome pair, regression models were estimated in both the full sample and among MHT users only.

Unadjusted models were first calculated to evaluate associations between MHT exposures and outcomes (*Block 1*). Movement behaviours were then added in a subsequent block (*Block 2*) to assess whether they improved model fit beyond MHT exposure alone. Following unadjusted models, fully-adjusted hierarchical models were constructed. Covariates were entered into *Block 1*, followed by the relevant MHT exposure in *Block 2*, and movement behaviours in *Block 3*. Age was not included in models predicting aPWV, AIx75, or FRS. Model fit was evaluated using the same approach described in Chapter 2.7.4.2. Figures 3 and 4 are visual representations of the unadjusted (Figure 3) and adjusted (Figure 4) model structure to aid understanding.

Figure 3. Unadjusted Model Structure for Objective 2B.

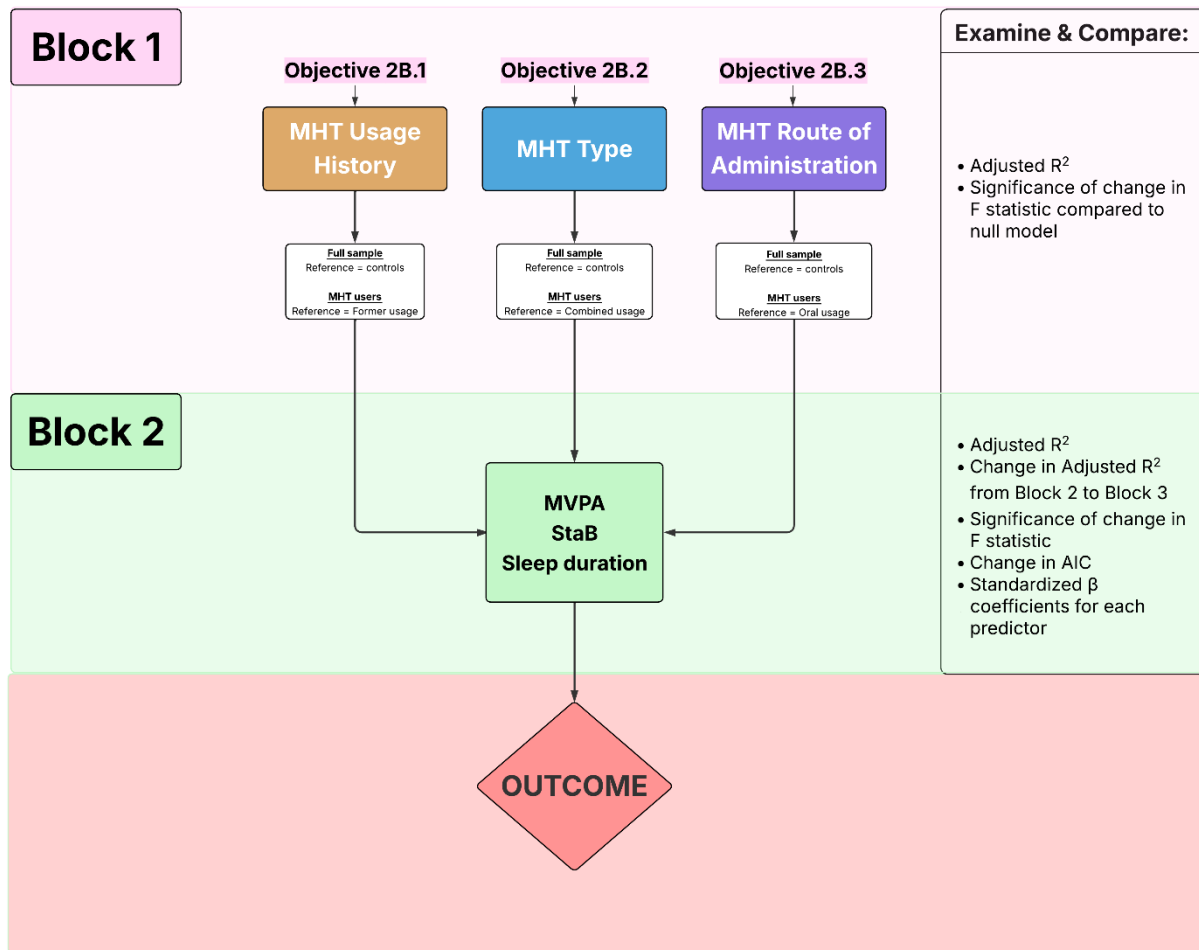
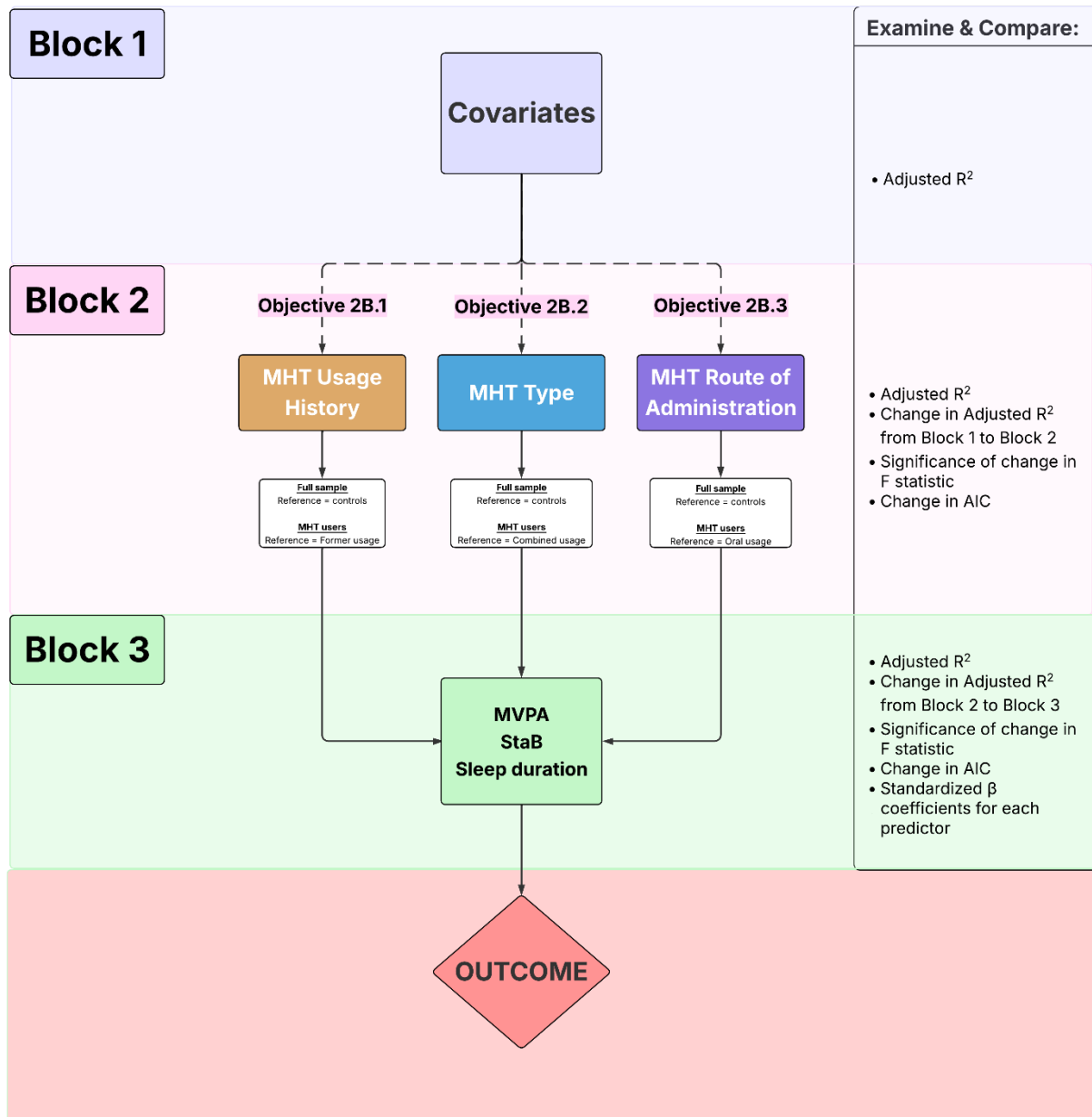


Figure 4. Adjusted Model Structure for Objective 2B.



2.7.4 Additional Considerations and Sensitivity Analyses

2.7.4.1 Notable Variables Dismissed from Models

A number of additional variables were considered for entry into the model as covariates but were dismissed due to lack of available data in our cohort, limited theoretical justification, and/or to avoid overfitting the models.³²⁸

Ethnicity. Ethnicity was not included as a covariate in any models. This variable was not part of the original WARM Hearts data collection protocol.⁷² Early in the study, some participants expressed interest in reporting their ethnicity, prompting the research team to seek and obtain ethics approval to collect this information from subsequent participants. A condition of that approval, however, was that ethnicity would be used as a descriptive variable, and that no analyses would be conducted based on race or ethnicity per se. The cohort is highly homogenous, with 94.9% (N=882) of participants identifying as white, which would preclude meaningful subgroup analyses even if permitted. For these reasons, ethnicity could not be included in analyses.

Duration of MHT Usage. The duration of MHT use was a collected variable but was not included as an exposure variable or covariate in the primary models. There is limited and inconsistent evidence that prolonged treatment duration adversely affects CV health in human females.^{195,218,219} Canadian clinical guidelines recommend individualized treatment and emphasize the timing of initiation rather than the duration of therapy, with duration tailored to symptoms, contraindications, and patient preferences.^{20,57} However, sensitivity analyses related to duration of use will be conducted and are described in Section 2.7.4.2.

Blood Hormone Levels. Circulating hormone concentrations (e.g., estradiol, follicle-stimulating hormone) were not collected as part of the WARM Hearts study protocol.⁷² The lack of these data represents a limitation of the study and should be addressed in future research to allow more precise characterization of hormone levels and their role in CV risk.

Age at Menarche. Age at menarche has been associated with CV events in later life, where menarche earlier or later than age 12 to 13 is associated with higher CV risk.³²⁹ This variable was collected in the WARM Hearts study. The mean age at menarche was 12.8 ± 1.4 years old; the minimum age was 9, and the maximum was 18. Most participants reported ages between 12 and 14 years (n = 627, 67.5%), with few at the extremes (equal or less than 11 years, n = 109; equal or greater than 15 years, n = 88). Many participants (N=104) could not recall their age at the onset of menstruation. However, the accumulating evidence in large epidemiologic studies on the associations between age at menarche and CV events suggests that the relationships may be largely indirect. Earlier menarche could instead reflect factors such as higher childhood BMI and lower physical activity levels, the presence of diseases like diabetes, and adverse psychosocial

exposures, which can persist into adulthood and influence long-term CV risk.^{330–332} Given its possible distal position in the causal pathway and because some of these factors are already accounted for through other variables (i.e., movement behaviours), including age at menarche as a covariate would likely provide limited additional explanatory value and risk overadjustment. Furthermore, there is little to no evidence of a relationship between age at menarche and later MHT use; thus, age at menarche is unlikely to be a confounder for the exposures of interest in this study.³³³ For these reasons, age at menarche was not included in the analyses.

2.7.4.2 Sensitivity Analyses

Sensitivity analyses will repeat analyses while either adding an additional covariate or restricting the sample to different subgroups. All analyses are considered exploratory and should be interpreted with caution.

BMI. BMI was excluded from the regression models in Objective 2B, because including it as a covariate could constitute overadjustment bias, as described in Chapter 2.6.6.1.³⁰⁰ BMI was included as a covariate in sensitivity analyses to evaluate this assumption. Results are described in Chapter 3.4.1.

Accounting for Age. Because three of the five primary outcomes (aPWV, AIx75, and FRS) include age in their calculations, age may confound relationships between MHT usage, movement behaviours, and CV outcomes. For this reason, age was not controlled for in the regression models for these outcomes in Objective 2B. To assess the robustness of primary findings to age-related differences without controlling for age directly, (1) group comparisons were redone stratified by age group (Chapter 3.4.2), and (2) adjusted regression models from Objective 2B were re-fit with age included in the covariate block (Chapter 3.4.3). For the group comparisons, participants were stratified by age 55–64 or age 65 and older. This separation cut-off was chosen for 3 reasons: a) the median age of the entire sample is 64; b) the Canadian 24-hour movement guidelines distinguish between “adults” and “older adults” at age 64 and age 65 respectively; and c) ages 64 and 65 correspond to a scoring threshold within the FRS, where reaching age 65 increases the point allocation.^{76,257,258}

Duration of MHT Usage. Sensitivity analyses were conducted among MHT users to evaluate whether the duration of MHT exposure influenced CV outcomes. Duration was coded as the

maximum number of years on an MHT regimen. Analyses were also limited to participants who were able to recall both the approximate start and end dates of MHT use. This approach was informed by prior literature suggesting elevated CV risk with prolonged MHT exposure, particularly among users who had used MHT for more than 5 years, although the evidence is inconsistent.^{195,218} Results are described in Chapter 3.4.4.

Timing of MHT. To evaluate the timing hypothesis, a binary indicator representing the delayed initiation of MHT was added to the regression models. Timing was calculated as the difference between the age at first reported use of any MHT regimen and the age at menopause. Therefore, only current or former MHT users who were able to recall their age of menopause and the year they started any regimen will be examined. Initiation occurring 10 or more years after menopause (N=31) was entered into the model, with initiation before 10 years serving as the reference category (N=185). Results are described in Chapter 3.4.5.

History of APOs. Because APOs, including hypertensive disorders of pregnancy and gestational diabetes, are associated with higher long-term risks of chronic hypertension, coronary artery disease, stroke, heart failure, and other adverse cardiometabolic profiles, these variables will be included as covariates in sensitivity analyses.^{334,335} This approach is consistent with guidance from the American Heart Association that recognizes APOs as risk factors for later CVD in women.³³⁴ The number of women who experienced at least 1 APO in the current sample is 436, or 46.9% of the sample. APOs experienced by women in this cohort included miscarriages (N=213; 22.9%), stillbirths (N=12; 1.3%) pre-eclampsia (N=36; 3.6%), eclampsia (N=3; 0.3%), gestational hypertension (N=36; 3.9%), gestational diabetes (N=28; 3.0%), pre-term deliveries (N=66; 7.1%), low birth weight babies (N=41; 4.4%), ectopic pregnancies (N=26; 2.8%) and other APOs (N=97; 10.4%) such as placental abruption, hyperemesis gravidarum, and cholestasis of pregnancy. Collapsing these events into a single binary indicator enables analysis of their influence while minimizing the sample-size limitations associated with modelling each APO separately. Regression models will be re-fit with history of APOs included in the covariate block (see Chapter 3.4.6).

2.8 Sex- and Gender-Based Considerations

This study is sex-specific by design, focusing exclusively on postmenopausal individuals assigned female at birth. All participants self-identified as women, and analyses treated biological sex as a defining characteristic. In alignment with the Canadian Institutes of Health Research Sex- and Gender-Based Analysis Plus framework, the study also examined how gender-related social factors, including educational attainment and responsibility for income, may impact CVD risk. These gendered exposures reflect structural and social conditions that can affect health behaviours, access to care, and treatment decisions (such as for MHT use). While biological sex was treated as a constant in this sample, gender-based variables were included as covariates to better contextualize the observed relationships between MHT, movement behaviours, and CV outcomes.

Chapter 3: Results

3.1 Participant Characteristics

A total of 929 participants were eligible for the analyses of this thesis. For completeness, both the means ($\pm$ SD) and medians [Q1, Q3] of the continuous variables are summarized in Table 12. However, the written descriptions and statistical testing of these data use the appropriate parameters for their distributions (i.e., medians and quartiles for skewed variables and means and standard deviations for normally distributed variables).

The included participants had a median age of 64 [60, 69] years and a median BMI of 25.8 [23.2, 29.3] kg/m². Mean arterial pressure was 97 ± 11 mmHg. The median age at menopause was 52 [49, 55] years, which aligns with the estimated Canadian population median of 51.⁴ The women accumulated a median of 20.5 [8.9, 37.4] minutes per day of MVPA and, on average, spent 12.1 ± 1.6 hours per day stationary and 6.5 ± 0.9 hours asleep. Accordingly, the average participant in the sample does not meet the recommended 24HMG targets for any of these three behaviours (using StaB as a proxy for SB).⁷⁶

The overall CV profiles of the WARM Hearts participants were generally consistent with normative values and established target guidelines (Table 9; Table 13). In other words, the participants were generally healthy. The median aPWV was 8.9 [8.3, 9.8] m/s, and 79.2% of participants (N=736) had values below the 10 m/s threshold previously suggested as indicating higher CV risk.^{288,289} The median AIx75 of 21.7% [13.3, 28.7] is similar to other findings in healthy older women.²⁹⁰ The majority of participants were normotensive, with SBP and DBP values of 122 ± 14 mmHg and 77 ± 10 mmHg, respectively.²⁹¹ The median FRS was 6.3% [3.9, 9.6], reflecting low 10-year risk of CVD.²⁶⁹ Only 13.5% of participants (N=135) would be classified as intermediate risk, and 1.4% of participants (N=13) were at high risk as indicated by the FRS. The median WC was 92.5 [85.0, 102.3] cm, which trends above the 88 cm benchmark suggested by Health Canada, indicating high CV risk.²⁹² WC was the only outcome for which a majority of participants (N=626; 67.4%) were outside the target threshold. Values for HDL-C (1.69 [1.42, 2.01] mmol/L), TG (0.98 [0.76, 1.33]) mmol/L, and fasting glucose (5.65 [5.34, 5.99] mmol/L) were all normal.^{293–295} The mean LDL-C of 3.31 ± 0.85 mmol/L approaches the moderately-elevated range, but may not be concerning for individuals with lower global risk

(i.e., FRS < 10%).²⁶⁹ The LDL-C values are also higher than those reported by Statistics Canada for women aged 20-79 in 2019.³³⁶ Even so, over half of the participants (N=552; 59.4%) had normal or only mildly elevated LDL-C.

Categorical variables are presented in Table 12. Most women had completed a postsecondary education (79.2%). A history of hypertension was reported by 22.8%. Type 2 Diabetes was reported by 2.6% of the women, and no women (0%) had Type 1 Diabetes. Sleep apnea was reported by 5.6%. Nearly half (46.9%) reported a history of APOs. Most women experienced spontaneous menopause (81.6%) and/or reported a history of vasomotor symptoms (71.7%). Among the women who reported on household earning status (N=896), 40.3% identified as the primary household earner.

Table 12. Participant Characteristics.

Continuous Variables	N	Mean (SD)	Median [Q1, Q3]
Age (years)	929	65 (6)	64 [60, 69]
BMI (kg/m ²)	929	26.7 (5.2)	25.8 [23.2, 29.3]
Mean Arterial Pressure (mmHg)	929	97 (11)	96 [89, 105]
Age at Menopause (years)	824	52 (5)	52 [49, 55]
MVPA (mins/day)	929	25.4 (21.2)	20.5 [8.9, 37.4]
StaB (h/day)	929	12.1 (1.6)	12.1 [10.9, 13.2]
Sleep duration (h/day)	929	6.5 (0.9)	6.5 [6, 7]
aPWV (m/s)	929	9.1 (1.1)	8.9 [8.3, 9.8]
AIx75 (%)	929	21.3 (10.2)	21.7 [13.3, 28.7]
SBP (mmHg)	929	122 (14)	121 [112, 131]
DBP (mmHg)	929	77 (10)	76 [70, 84]
FRS (% 10-year CV risk)	929	7.0 (4.1)	6.3 [3.9, 8.6]
WC (cm)	929	94.3 (13.3)	92.5 [85, 102.3]
HDL-C (mmol/L)	929	1.75 (0.44)	1.69 [1.43, 2.02]
LDL-C (mmol/L)	929	3.31 (0.85)	3.30 [2.72, 3.89]
TG (mmol/L)	929	1.13 (0.57)	0.98 [0.76, 1.33]
Glucose (mmol/L)	928	5.77 (0.86)	5.65 [5.34, 5.99]
Categorical Variables	N	%	
Education	929		
No degree/certificate/diploma	27	2.9	
High school education	166	17.9	
Postsecondary education	736	79.2	
Sleep apnea	929		
No	877	94.4	
Yes	52	5.6	
Type 1 Diabetes	929		

No	929	100
Yes	0	0
Type 2 Diabetes	929	
No	905	97.4
Yes	24	2.6
History of Hypertension	929	
No	717	77.2
Yes	212	22.8
Ever APOs	929	
No	493	53.1
Yes	436	46.9
Spontaneous Menopause	929	
No	171	18.4
Yes	758	81.6
History of Vasomotor Symptoms	929	
No	263	28.3
Yes	666	71.7
Primary Household Earner	896	
No	535	59.7
Yes	361	40.3
Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; APOs, adverse pregnancy outcomes.		

Table 13. Proportion of Participants within CV Outcome Reference Ranges

Outcome	Freq.	%
aPWV		
< 10 m/s	736	79.2%
> 10 m/s	193	20.8%
AIx75		
≤ 28%	690	74.3%
> 28%	239	25.7%
SBP		
≤ 130 mmHg	696	74.9%
> 130 mmHg	233	25.1%
DBP		
≤ 80 mmHg	600	64.6%
> 80 mmHg	329	35.4%
FRS		
Low Risk (under 10%)	731	78.7%
Intermediate Risk (10.0-19.9%)	125	13.5%

High risk (20% and higher)	13	1.4%
WC		
< 88 cm	303	32.6%
≥ 88 cm	626	67.4%
HDL		
≤ 1.30 mmol/L	133	14.3%
> 1.30 mmol/L	796	82.8%
LDL		
Normal to low elevation (≤ 3.50 mmol/L)	552	59.4%
Moderate elevation (3.50 to 5.00 mmol/L)	347	37.4%
High elevation (≥ 5.00 mmol/L)	30	3.2%
TG		
< 1.8 mmol/L	826	88.9%
≥ 1.8 mmol/L	103	11.1%
Fasting Glucose^a		
Hypoglycemia (≤ 4.0 mmol/L)	0	0.0%
Normal (4.0 - 6.0 mmol/L)	699	75.3%
Prediabetes (6.1-6.9 mmol/L)	186	20.0%
Diabetes (7.0 and higher mmol/L)	43	4.6%

Abbreviations: aPWV, aortic pulse wave velocity; AIx75, augmentation index standardized to 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure, FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides

N = 929 for all outcomes except fasting glucose (N=928)

^a Fasting glucose values within the diabetic range do not automatically warrant a diagnosis of diabetes and additional tests should be conducted to confirm.²⁹⁵

3.2 Objective 1 Results: Replicating and Extending Kalenga et al.

3.2.1 Objective 1A

Objective 1A was to replicate the work of Kalenga et al. using a larger sample size, without adding predictors or altering model structures. Group comparisons using ANOVA (Table 13) and linear regression models (Tables 14 and 15) were conducted to address this objective.

Group Comparisons.

Mean values ($\pm$ SE) for aPWV, AIx75, D1SBP, and D1DBP by unopposed estrogen route of administration in Kalenga et al. (2022) and the present thesis sample are displayed in Table 13. In Kalenga et al., oral unopposed estrogen users had significantly higher aPWV (9.93 ± 1 m/s) than controls (8.85 ± 1 m/s), transdermal users (8.57 ± 1 m/s), and vaginal users (8.80 ± 1 m/s).⁷¹ After increasing the sample size for the present thesis cohort, oral users still had a faster

aPWV (9.7 ± 0.2 m/s) than controls (9.0 ± 0.4 m/s) and vaginal users (8.9 ± 0.1 m/s), but there was no significant difference compared to transdermal usage (9.1 ± 0.2 m/s).

Kalenga et al. reported significantly higher AIX75 values among oral users ($28.9 \pm 2\%$) compared to transdermal users ($16.0 \pm 2\%$) and vaginal users ($21.9 \pm 2\%$).⁷¹ In the larger sample, mean AIX75 values did not differ significantly between groups.

For D1SBP, Kalenga et al. reported higher values among oral users (137 ± 4 mmHg) than among controls (124 ± 1 mmHg), transdermal users (118.2 ± 2 mmHg), and vaginal users (122.8 ± 2 mmHg).⁷¹ In the larger thesis sample, oral users had higher D1SBP (130 ± 2.1 mmHg) than controls (124 ± 0.5 mmHg) and vaginal users (121 ± 1.4 mmHg) but did not differ significantly from transdermal users (124 ± 2.2 mmHg).

Lastly, Kalenga et al. reported higher D1DBP values among oral users (79 ± 2 mmHg) compared to controls (74 ± 1 mmHg), transdermal users (73 ± 1 mmHg), and vaginal users (73 ± 2 mmHg).⁷¹ In the larger sample, mean D1DBP values did not differ significantly between groups.

Table 13. Outcomes by Route of Unopposed Estrogen Administration in Kalenga et al. and the Larger Thesis Sample.

Variable	Data	Control	Oral	Transdermal	Vaginal
aPWV (m/s)	Kalenga et al. (2022)	8.85 (1)	9.93 (1) *	8.57 (1) †	8.80 (1) †
	Thesis (2026)	9.0 (0.4)	9.7 (0.2) *	9.1 (0.2)	8.9 (0.1) †
AIx75 (%)	Kalenga et al. (2022)	20.5 (4)	28.9 (2)	16.0 (2) †	21.9 (2) †
	Thesis (2026)	21.2 (0.4)	21.0 (1.5)	19.7 (1.7)	21.2 (1.1)
D1SBP (mmHg)	Kalenga et al. (2022)	124 (1)	137 (4) *	118.2 (2) †	122.8 (2) †
	Thesis (2026)	124 (0.5)	130 (2.1) *	124 (2.2)	121 (1.4) †
D1DBP (mmHg)	Kalenga et al. (2022)	74 (1)	79 (2) *	73 (1) †	73 (2) †
	Thesis (2026)	74 (0.3)	75 (1.3)	73 (1.3)	72 (1.1)

Abbreviations: aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; D1SBP, day 1 systolic blood pressure; D1DBP, day 1 diastolic blood pressure; SE, standard error

Kalenga et al.: N = 223 (control), 16 (oral), 20 (transdermal), 19 (vaginal)

Thesis (2026): N = 660 (control) 47 (oral), 40 (transdermal), 66 (vaginal)

* p < 0.05 compared to controls

† p < 0.05 compared to oral unopposed estrogen users

No differences observed between controls and vaginal or transdermal users.

No differences observed between vaginal and transdermal users.

Values displayed as mean (SE)

Multiple Linear Regression Models.

Model fit statistics for the thesis sample are shown in Table 14; these parameters were not reported in Kalenga et al.⁷¹ Since several participants did not report their age of menopause, the models that adjust for this variable (aPWV and AIx75) have a smaller sample size (N = 718) than models that do not incorporate it (D1SBP and D1DBP; N = 813). A notable finding from these analyses is that models predicting aPWV were estimated to explain a massive amount of its variance (Adj. $R^2 = 0.93$ in the full sample; Adj $R^2 = 0.94$ in MHT users). As will be shown in findings from Objective 1B (Chapter 3.3.2) and sensitivity analyses (Chapter 3.5.3), this is likely due to the dependence on age in calculating aPWV.²⁷³

Unstandardized regression coefficients from Kalenga et al. and from the present thesis analyses are presented in Table 15. Results are first described for the full sample (controls as the reference group), followed by those for MHT users only (oral use as the reference group).

Full Sample, Coefficients (Controls as Reference Group)

In Kalenga et al., there were no independent associations between oral, transdermal, of vaginal estrogen use and aPWV or AIx75 relative to controls.⁷¹ Oral use was associated with higher D1SBP and D1DBP relative to controls. Transdermal and vaginal usage were not associated with D1SBP or D1DBP relative to controls.

In the larger thesis sample, a significant association between vaginal use and slower aPWV compared to controls was detected. Additionally, the originally reported associations between oral use and D1SBP and D1DBP did not persist in the larger sample. There were still no associations between estrogen MHT route and AIx75.

MHT Users Only, Coefficients (Oral Usage as Reference Group).

In the original MHT user subset in Kalenga et al., there were no associations between transdermal or vaginal usage and aPWV or AIx75 relative to oral usage.⁷¹ Both transdermal ($B = -17$, 95% CI $[-32, -3]$) and vaginal use ($B = -13.6$, 95% CI $[-25, -2]$) were associated with lower D1SBP relative to oral usage. Similarly, transdermal ($B = -11$, 95% CI $[-19, -3]$) and vaginal use ($B = -6.7$, 95% CI $[-14, -0.2]$) were associated with lower D1DBP relative to oral use.

After increasing the sample size, an association between vaginal estrogen use and slower aPWV relative to oral use was detected. Vaginal estrogen usage also continued to associate with lower D1SBP but was no longer associated with D1DBP. Transdermal usage was no longer associated with any outcome. There were still no significant associations with AIx75.

Table 14. Model Fit Statistics for Regression Models Replicating Kalenga et al. (2022)

aPWV	N	R²	Adj. R²
Full model	718	0.93	0.93
MHT users only	133	0.94	0.94
AIx75			
Full model	718	0.03	0.02
MHT users only	133	0.07	0.03
D1SBP	N	R²	Adj. R²
Full model	813	0.12	0.11
MHT users only	153	0.15	0.13
D1DBP			
Full model	813	0.05	0.05
MHT users only	153	0.07	0.05

Abbreviations: aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; D1SBP, day 1 systolic blood pressure; D1DBP, day 1 diastolic blood pressure.
D1 SBP and D1 DBP adjusted for age, BMI

aPWV adjusted for age, mean arterial pressure, history of hypertension, history of vasomotor symptoms, age at menopause

AIx75 adjusted for history of hypertension, history of vasomotor symptoms, age at menopause

Table 15. Unstandardized Regression Coefficients Between Route of Unopposed Estrogen Route and CV Outcomes in Kalenga et al. and the Current Thesis

Sample	Variable	Data	
		Kalenga et al. (2022)	Thesis (2026)
Full sample	Control (reference group)		
	Oral	0.03 [-0.2, 0.3]	0.02 [-0.08, 0.13]
	Transdermal	-0.05 [-0.3, 0.2]	0.06 [-0.04, 0.16]
	Vaginal	-0.03 [-0.3, 0.3]	-0.09 [-0.17, -0.01] *
MHT users only	Oral (reference group)		
	Transdermal	-0.4 [-0.8, 0.1]	0.02 [-0.10, 0.15]
	Vaginal	-0.4 [-1, 0.2]	-0.13 [-0.25, -0.01] *
	AIx75		
Full sample	Control (reference group)		
	Oral	1.2 [-6, 9]	-0.75 [-4.07, 2.58]
	Transdermal	-5.2 [-11, 0.6]	-2.47 [-5.70, 0.77]
	Vaginal	1.7 [-4, 8]	0.17 [-2.79, 2.45]
MHT users only	Oral (reference group)		
	Transdermal	-5.3 [-0.8, 0.1]	-1.75 [-6.42, 2.91]
	Vaginal	-2 [-18, 14]	0.97 [-3.28, 5.21]
	D1 SBP	Kalenga et al. (2022)	Thesis

Full sample	Control (reference group)		
	Oral	9.4 [3, 16] *	3.31 [-0.47, 7.08]
	Transdermal	-4.5 [-10, 1]	-1.03 [-5.06, 3.00]
	Vaginal	-0.7 [-7, 5]	-2.64 [-5.84, 0.55]
MHT users only	Oral (reference group)		
	Transdermal	-17 [-32, -3] *	-4.34 [-9.95, 1.28]
	Vaginal	-13.6 [-25, -2] *	-5.91 [-10.98, -0.83] *
	D1 DBP	Kalenga et al. (2022)	Thesis
Full sample	Control (reference group)		
	Oral	5.4 [0.8, 10] *	1.36 [-1.08, 3.80]
	Transdermal	-0.5 [-5, 3]	-0.53 [-3.14, 2.07]
	Vaginal	-0.03 [-0.3, 0.3]	-0.91 [-2.97, 1.16]
MHT users only	Oral (reference group)		
	Transdermal	-11 [-19, -3] *	-1.70 [-5.36, 1.97]
	Vaginal	-6.7 [-14, -0.2] *	-1.90 [-5.21, 1.42]
Abbreviations: MHT, menopausal hormone therapy; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; D1SBP, day 1 systolic blood pressure; D1DBP, day 1 diastolic blood pressure Values displayed as unstandardized <i>B</i> [95% CI]			
* <i>p</i> < 0.05 compared to the reference group			

Objective 1A Summary.

The hypothesis for Objective 1A was that associations between estrogen MHT route and CV outcomes would persist after increasing the sample size. This hypothesis was partially supported. Several patterns were replicated after the sample size increased. In both datasets, ANOVA results indicated that oral estrogen users had faster aPWV and higher D1SBP compared to controls and vaginal estrogen users.⁷¹ Similarly, regression models in both datasets showed no associations between estrogen route and AIx75 after adjusting for covariates. Within the MHT user subgroup, the larger sample confirmed that vaginal estrogen was associated with lower D1SBP relative to oral use in this cohort.

Conversely, other findings from the original Kalenga et al. (2022) analyses were not reproduced in the expanded thesis sample. ANOVA failed to detect any group differences in AIx75 and D1DBP, and the previously observed differences between transdermal and oral users regarding aPWV and D1SBP were nullified. In the updated regression models, vaginal usage demonstrated a novel association with slower aPWV relative to both controls and oral users. In the full sample, the previously identified associations between oral usage and elevated D1SBP

and D1DBP (relative to controls) were nullified. In the MHT user subset, the associations between transdermal estrogen use and D1SBP and D1DBP, as well as the association between vaginal estrogen use and D1DBP, did not persist in the larger dataset.

3.2.2 Objective 1B

Analyses in Objective 1B parallel those of 1A with four modifications: (1) Day 2 SBP and DBP (average of trials 2 and 3) are examined alongside the Day 1 measures; (2) age was removed as a covariate in regression models predicting aPWV; (3) means and standard deviations are used to report measures of central tendency and dispersion rather than the mean and standard error; and (4) coefficients are presented for all predictors entered in each model, including covariates.

Group Comparisons.

ANOVA results for day 1 (D1SBP and D1DBP) and day 2 blood pressure variables (SBP and DBP) are presented in Table 16. As identified in Objective 1A, oral users had higher D1SBP than controls and vaginal users, while transdermal users did not differ from any other group. No significant group differences were observed for D1DBP. When using Day 2 measurements, no differences in SBP or DBP were detected between groups (Table 16).

Table 16. Day 1 and Day 2 Blood Pressure by Route of Unopposed Estrogen.

Variable	Control (N=660)	Oral (N=47)	Transdermal (N=40)	Vaginal (N=66)
D1SBP	124 (13)	130 (15) *	124 (14)	121 (12) †
D1DBP	74 (8)	75 (9)	73 (8)	72 (9)
SBP	122 (14)	125 (14)	123 (14)	119 (15)
DBP	77 (10)	77 (11)	76 (10)	78 (12)

Abbreviations: D1SBP, Day 1 systolic blood pressure; D1DBP, Day 2 diastolic blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure

SBP and DBP refer to Day 2 measurements and are reported as the average of trials 2 and 3 of 3.

* $p < 0.05$ compared to controls

† $p < 0.05$ compared to oral unopposed estrogen users

Values displayed as mean (SD)

Multiple Linear Regression Models

Model fit statistics for the updated analyses are presented in Table 17. When age was retained in the aPWV models (Objective 1A), adjusted R^2 values were 0.93 in the full sample and 0.94 among MHT users only. After removing age from aPWV models, adjusted R^2 decreased substantially to 0.20 in the full sample and 0.25 among MHT users only, indicating that age accounted for the majority of explained variance in aPWV. For blood pressure outcomes, replacing the day 1 measures with the day 2 average SBP and DBP values yielded model fit estimates that were comparably similar, albeit slightly higher for DBP compared to D1DBP. There were no changes in model specifications for AIx75 from Objective 1A.

Unstandardized regression coefficients using the updated parameters are presented in Table 18. Results are first described for the full sample (controls as the reference group), followed by those for MHT users only (oral use as the reference group).

Full Sample, Coefficients (Controls as Reference Group).

For aPWV, the inclusion of age in the model (Objective 1A) indicated no associations with oral and transdermal usage, while vaginal usage was associated with slower aPWV relative to controls. However, when age was removed from the model (Objective 1B), oral usage became associated with faster aPWV, and the previously observed association for vaginal usage was nullified.

As with Objective 1A, no route of administration was associated with AIx75. No route of administration was associated with SBP or DBP.

MHT Users Only, Coefficients (Oral Usage as Reference Group).

When age was included in models predicting aPWV (Objective 1A), vaginal use was associated with slower aPWV relative to oral use. After removing age, both transdermal and vaginal use were associated with slower aPWV relative to oral use. No estrogen routes entered into the model were independently associated with AIx75, SBP, or DBP.

Table 17. Model Fit With Updated aPWV and Blood Pressure Parameters

Sample	Original Variables				Updated Variables			
	Outcome	N	R ²	Adj. R ²	Outcome	N	R ²	Adj. R ³
Full sample MHT users only	aPWV	718	0.93	0.93	aPWV	718	0.21	0.20
		133	0.94	0.94	(age removed)	133	0.29	0.25
Full sample MHT users only	AIx75	718	0.03	0.02	AIx75	*Unchanged from the Original Variables		
		133	0.07	0.03				
Full sample MHT users only	D1SBP	812	0.12	0.11	SBP	813	0.13	0.12
		153	0.15	0.13		153	0.14	0.12
Full sample MHT users only	D1DBP	812	0.05	0.05	DBP	813	0.08	0.08
		153	0.07	0.05		153	0.13	0.10

Abbreviations: aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; D1SBP, Day 1 systolic blood pressure; D1DBP, Day 2 diastolic blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure

aPWV adjusted for age, average MAP, history of hypertension, history of VMS, age at menopause

aPWV (age removed) adjusted for average MAP, history of hypertension, history of VMS, age at menopause

AIx75 adjusted for history of hypertension, history of VMS, age at menopause

SBP and DBP adjusted for age and BMI

Table 18. Unstandardized Regression Coefficients With Updated aPWV and Blood Pressure Parameters

Sample	Predictor	Original Variable	Updated Variable
		aPWV	aPWV (age removed)
Full sample	Age	0.17 [0.16, 0.17] *	--
	Mean arterial pressure	0.04 [0.03, 0.04] *	0.04 [0.03, 0.05] *
	History of hypertension	-0.05 [-0.10, 0.01]	-0.06 [-0.24, 0.12]
	Age at menopause	0.00 [-0.01, 0.00]	0.00 [-0.02, 0.01]
	History of vasomotor symptoms	-0.03 [-0.08, 0.02]	-0.38 [-0.54, -0.21] *
	Control (reference group)		
	Oral	0.02 [-0.08, 0.13]	0.62 [0.28, 0.96] *
	Transdermal	0.06 [-0.04, 0.16]	0.12 [-0.21, 0.45]
	Vaginal	-0.09 [-0.17, -0.01] *	-0.06 [-0.33, 0.21]
MHT users only	Age	0.16 [0.16, 0.17] *	--
	Mean arterial pressure	0.04 [0.03, 0.04] *	0.04 [0.03, 0.06] *
	History of hypertension	-0.06 [-0.18, 0.06]	-0.05 [-0.47, 0.37]
	Age at menopause	0.00 [-0.01, 0.01]	0.01 [-0.01, 0.04]

	History of vasomotor symptoms	-0.03 [-0.14, 0.08]	-0.30 [-0.68, 0.09]
	Oral (reference group)		
	Transdermal	0.02 [-0.10, 0.15]	-0.56 [-1.00, -0.12] *
	Vaginal	-0.13 [-0.25, -0.01] *	-0.74 [-1.14, -0.33] *
AIx75			
Full sample	History of hypertension	2.65 [0.97, 4.34] *	
	Age at menopause	-0.10 [-0.25, 0.04]	
	History of vasomotor symptoms	-2.54 [-4.12, -0.96] *	
	Control (reference group)		
	Oral	-0.75 [-4.07, 2.58]	
	Transdermal	-2.47 [-5.70, 0.77]	
	Vaginal	0.17 [-2.79, 2.45]	
MHT users only	History of hypertension	4.98 [0.64, 9.32]	
	Age at menopause	-0.13 [-0.39, 0.13]	
	History of vasomotor symptoms	-2.25 [-6.33, 1.83]	
	Oral (reference group)		
	Transdermal	-1.75 [-6.42, 2.91]	
	Vaginal	0.97 [-3.28, 5.21]	
		D1SBP	SBP
Full sample	Age	0.58 [0.43, 0.73] *	0.36 [0.21, 0.52] *
	BMI	0.61 [0.44, 0.77] *	0.86 [0.69, 1.03] *
	Control (reference group)		
	Oral	3.31 [-0.47, 7.08]	1.40 [-2.45, 5.25]
	Transdermal	-1.03 [-5.06, 3.00]	0.31 [-3.80, 4.42]
	Vaginal	-2.64 [-5.84, 0.55]	-1.49 [-4.75, 1.77]
MHT users only	Age	0.58 [0.20, 0.97] *	0.33 [-0.07, 0.74]
	BMI	0.57 [0.18, 1.09] *	1.07 [0.59, 1.54] *
	Oral (reference group)		
	Transdermal	-4.34 [-9.95, 1.28]	-1.31 [-7.27, 4.66]
	Vaginal	-5.91 [-10.98, -0.83] *	-2.80 [-8.19, 2.60]
		D1DBP	DBP
Full sample	Age	-0.11 [-0.21, -0.02]	-0.03 [-0.15, 0.08]
	BMI	0.32 [0.22, 0.43]	0.54 [0.41, 0.67] *
	Control (reference group)		
	Oral	1.36 [-1.08, 3.80]	0.57 [-2.30, 3.45]
	Transdermal	-0.53 [-3.14, 2.07]	-1.41 [-4.48, 1.66]
	Vaginal	-0.91 [-2.97, 1.16]	1.17 [-1.27, 3.60]
MHT users only	Age	-0.04 [-0.29, 0.21]	-0.08 [-0.40, 0.23]
	BMI	0.44 [0.14, 0.73] *	0.81 [0.44, 1.18] *
	Oral (reference group)		

Transdermal	-1.70 [-5.36, 1.97]	-2.31 [-6.93, 2.31]
Vaginal	-1.90 [-5.21, 1.42]	0.69 [-3.49, 4.86]

Abbreviations: aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; D1SBP, Day 1 systolic blood pressure; D1DBP, Day 1 diastolic blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure

*p < 0.05 compared to reference group

Values displayed as unstandardized B [95% CI]

Objective 1B Summary.

The hypothesis that differences across groups and associations between estrogen MHT route and CV outcomes would persist when alternative variable operationalizations were applied was mostly unsupported by the data. Some findings persisted; for example, in the full-sample regression models, no estrogen route was associated with either Day 1 (Objective 1A) or Day 2 (Objective 1B) blood pressure relative to controls; among MHT users only, there were also no changes for either D1DBP or Day 2 DBP. It should be noted that there were also no changes to the findings for AIx75 because neither the outcome definition nor the AIx75 model specification changed from Objective 1A.

The most noticeable changes occurred in the aPWV models after removal of age as a covariate. Removing age substantially reduced model fit in both samples and fundamentally altered the independent associations between estrogen routes and aPWV. In the full sample, oral use emerged as a significant predictor of faster aPWV, an association that was not observed in the age-adjusted models. Similarly, in the subset of MHT users, both transdermal and vaginal use were associated with slower aPWV relative to oral use; these associations were likewise absent from the age-adjusted models.

Lastly, there were some inconsistencies in the blood pressure markers. Comparative analyses via ANOVA indicated that the significantly higher D1SBP among oral users (Objective 1A) was not replicated when using the day 2 SBP averages. Furthermore, regression models restricted to MHT users demonstrated that the previously observed association between vaginal usage and lower D1SBP (relative to oral usage) failed to persist when the Day 2 SBP metric was applied.

3.2.3 Objective 1C

Objective 1C extended the unopposed estrogen route-based group comparisons by testing differences in CVD risk parameters across unopposed estrogen routes in a broader set of variables, including movement behaviours (MVPA, StaB, and sleep duration) and additional outcomes (FRS, WC, HDL-C, LDL-C, TG, glucose). Results from the ANOVA and Kruskal-Wallis tests are summarized in Table 19.

Significant differences between route groups were observed for age, age at menopause, and aPWV. Oral estrogen users were older (68 [63, 72] years) than controls (63 [60, 67] years) and vaginal estrogen users (64 [59, 69] years). Age at menopause differed across groups, with controls reaching menopause at a later age (53 [51, 55] years) compared to oral estrogen users (47 [41, 51] years) and vaginal estrogen users (51 [48, 53] years). As described in Objective 1A and 1B, oral estrogen users had a faster aPWV compared to controls and vaginal users. No significant group differences were observed for BMI, mean arterial pressure, MPVA, StaB, sleep duration, AIX75, SBP, DBP, FRS, WC, HDL-C, LDL-C, TG, or glucose.

Given that only 3 of the 17 tested CVD risk variables differed across estrogen route groups, the Objective 1C hypothesis (that group differences would extend to a broader set of CV and movement variables beyond those selected in Kalenga et al. (2022)⁷¹) was not supported.

Table 19 Group Differences by Unopposed Estrogen Route of Administration.

Variable	Controls (N=660)	Oral (N=47)	Transdermal (N=40)	Vaginal (N=66)	p-value	Effect size
Age (years)	63 [60, 67]	68 [63, 72] *	64 [59, 70]	64 [59, 69] †	< 0.01	$\epsilon^2 = 0.02$
BMI (kg/m ²)	25.8 [23.2, 29.7]	25.0 [23.6, 29.7]	26.7 [23.8, 29.3]	26.1 [23.2, 29.1]	0.75	$\epsilon^2 = 0.09$
Mean arterial pressure (mmHg)	97 (11)	99 (12)	97 (11)	97 (12)	0.66	$\eta^2 = 0.00$
Age at menopause (years)	53 [51, 55]	47 [41, 51] *	50 [45, 56]	51 [48, 53] *	< 0.01	$\epsilon^2 = 0.05$
MVPA (avg. mins/day)	21.2 [9.5, 38.4]	14.4 [6.1, 24.1]	25.0 [7.7, 38.5]	22.9 [9.8, 39.9]	0.10	$\epsilon^2 = 0.00$
StaB (avg. hrs/day)	12.1 (1.6)	12.6 (1.6)	11.9 (1.4)	12.0 (1.6)	0.13	$\eta^2 = 0.01$
Sleep (avg. hrs/day)	6.5 (0.9)	6.4 (0.9)	6.5 (0.6)	6.5 (0.8)	0.91	$\eta^2 = 0.00$
aPWV (m/s)	8.8 [8.2, 9.7]	9.6 [8.8, 10.4] *	9.0 [8.3, 9.8]	8.9 [8.3, 9.6] †	< 0.01	$\epsilon^2 = 0.02$
AIx75 (%)	21.3 [13.7, 28.7]	21.7 [11.3, 30.7]	21.8 [10.6, 27.9]	22.2 [14.0, 27.3]	0.90	$\epsilon^2 = 0.00$
SBP (mmHg)	122 (14)	125 (14)	123 (14)	119 (15)	0.26	$\eta^2 = 0.00$
DBP (mmHg)	77 (10)	77 (11)	76 (10)	78 (12)	0.82	$\eta^2 = 0.01$
FRS (%)	6.3 [3.9, 8.6]	7.3 [5.3, 10.0]	6.3 [4.5, 8.6]	5.3 [3.9, 7.3]	0.06	$\epsilon^2 = 0.01$
WC (cm)	92.6 [85.0, 102.5]	92.5 [83.0, 102.3]	93.8 [86.4, 103.4]	91.5 [84.2, 101.4]	0.67	$\epsilon^2 = 0.00$
HDL-C (mmol/L)	1.67 [1.40, 2.03]	1.66 [1.47, 1.91]	1.71 [1.42, 1.99]	1.73 [1.46, 1.97]	0.97	$\epsilon^2 = 0.00$
LDL-C (mmol/L)	3.32 (0.44)	3.23 (0.70)	3.51 (0.88)	3.36 (0.80)	0.49	$\eta^2 = 0.00$
TG (mmol/L)	0.99 [0.75, 1.33]	1.24 [0.87, 1.49]	0.96 [0.86, 1.21]	1.03 [0.83, 1.36]	0.16	$\epsilon^2 = 0.00$
Glucose (mmol/L)	5.67 [5.35, 6.02]	5.71 [5.39, 6.06]	5.69 [5.29, 5.94]	5.59 [5.30, 5.83]	0.23	$\epsilon^2 = 0.00$

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Age at menopause: N = 585 (never); 37 (oral estrogen); 37 (transdermal estrogen); 59 (vaginal estrogen)

Outcomes reported as Mean (SD) or Median [Q1, Q3]

*p < 0.05 compared to controls

†p < 0.05 compared to oral users

Red bold text used to emphasize statistically significant findings.

3.2.4 Objective 1D

3.2.4.1 Objective 1D.1

In Objective 1D.1, movement behaviours were added to the model structure described in Objective 1B in a second block (see Figure 1). As such, models were constructed hierarchically as Block 1 (covariates and estrogen route) and Block 2 (covariates and estrogen route plus movement behaviours). The hypothesis that movement behaviours would better explain variance in CV outcomes than the estrogen MHT route and covariates was partially supported, as this pattern was observed in models in the full sample but not among MHT users.

Full Sample.

Adding movement behaviours in Block 2 improved model fit for aPWV, AIx75, and DBP, but not for SBP (Table 20). As an example, the baseline model (Block 1) explained 20% of the variance in aPWV (Adjusted $R^2 = 0.20$); adding movement behaviours increased this to 23% ($p < 0.01$; $\Delta AIC = -17.8$).

Unstandardized and standardized coefficients for predictors in Block 3 are detailed in Table 21. These data suggest that certain covariates may have accounted for most of the variance in the outcomes (e.g., mean arterial pressure in the model for aPWV, and BMI in the models for SBP and DBP). Adding movement behaviours did not affect the association between oral estrogen and aPWV observed in Objective 1B; oral estrogen use was associated with faster aPWV than in controls. More MVPA was associated with slower aPWV and lower AIx75. More StaB was associated with faster aPWV and lower DBP. Sleep duration was not associated with any outcome.

MHT Users Only

In the MHT users' subset, model fit did not improve significantly for any outcome when movement behaviours were added in Block 2 (Table 20). In other words, movement behaviours added nothing beyond what covariates and estrogen route could already explain. Furthermore, no individual movement behaviour was independently associated with any of the four outcomes after adjusting for covariates and MHT exposures (Table 21).

Consistent with the analyses in Objective 1B, transdermal estrogen ($\beta = -0.19$, 95% CI [-0.38, -0.01]) and vaginal estrogen ($\beta = -0.30$, 95% CI [-0.49, -0.11]) were associated with slower aPWV relative to oral administration. Furthermore, the absence of associations between estrogen route and AIx75, SBP, or DBP after covariate adjustment (as observed in Objective 1B) persisted after the inclusion of movement behaviours (Table 21).

Table 20. Objective 1D.1 Model Fit

Full Sample							
Outcome	Block	N	R ²	Adj. R ²	P Value for change in F	AIC	ΔAIC
aPWV	Block 1: Covariates + MHT	718	0.21	0.20	< 0.01	2038.7	
	Block 2: MVPA, StaB, Sleep		0.24	0.23	< 0.01	2020.9	-17.8
AIx75	Block 1: Covariates + MHT	718	0.03	0.02	< 0.01	5303.6	
	Block 2: MVPA, StaB, Sleep		0.05	0.03	0.02	5299.2	-4.4
SBP	Block 1: Covariates + MHT	813	0.13	0.12	< 0.01	6465.9	
	Block 2: MVPA, StaB, Sleep		0.13	0.12	0.37	6468.8	2.9
DBP	Block 1: Covariates + MHT	813	0.08	0.08	< 0.01	5992.1	
	Block 2: MVPA, StaB, Sleep		0.10	0.09	0.01	5986.4	-5.7
MHT users Only							
Outcome	Block	N	R ²	Adj. R ²	P Value for change in F	AIC	ΔAIC
aPWV	Block 1: Covariates + MHT	133	0.29	0.25	< 0.01	368.7	
	Block 2: MVPA, StaB, Sleep		0.32	0.27	0.16	369.0	0.4
AIx75	Block 1: Covariates + MHT	133	0.07	0.03	0.12	995.7	
	Block 2: MVPA, StaB, Sleep		0.10	0.05	0.17	996.3	0.6
SBP	Block 1: Covariates + MHT	153	0.14	0.12	< 0.01	1239.7	
	Block 2: MVPA, StaB, Sleep		0.14	0.10	0.90	1245.1	5.4
DBP	Block 1: Covariates + MHT	153	0.13	0.10	< 0.01	1161.3	
	Block 2: MVPA, StaB, Sleep		0.13	0.09	0.68	1165.7	4.4

Abbreviations: aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure

aPWV adjusted for average MAP, history of hypertension, history of VMS, age at menopause

AIx75 adjusted for history of hypertension, history of VMS, age at menopause

SBP and DBP adjusted for age and BMI

Bold text used to emphasize statistically significant change in model fit in Block 1;

Red bold text used to emphasize statistically significant changes in Block 2

Table 21. Objective 1D.1 Unstandardized and Standardized Coefficients

Outcome	Predictor	Full Sample		Sig.
		Unstandardized B [95% CI]	Standardized β [95% CI]	
aPWV	Mean arterial pressure (mmHg)	0.04 [0.03, 0.05]	0.40 [0.33, 0.47]	*
	History of hypertension	-0.07 [-0.24, 0.11]	-0.07 [-0.24, 0.11]	
	Age at menopause (years)	0.00 [-0.02, 0.01]	0.00 [-0.02, 0.01]	
	History of VMS	-0.32 [-0.48, -0.16]	-0.13 [-0.19, -0.06]	*
	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.10 [-0.18, -0.03]	*
	StaB (hours)	0.07 [0.01, 0.12]	0.07 [0.01, 0.12]	*
	Sleep duration (hours)	0.05 [-0.06, 0.15]	0.05 [-0.06, 0.15]	
	Controls (MHT reference group)			
	Oral	0.54 [0.21, 0.88]	0.11 [0.04, 0.18]	*
	Transdermal	0.12 [-0.21, 0.45]	0.12 [-0.21, 0.45]	
	Vaginal	-0.05 [-0.32, 0.21]	-0.05 [-0.32, 0.21]	
AIx75	History of hypertension	2.59 [0.90, 4.28]	0.11 [0.04, 0.18]	*
	Age at menopause (years)	-0.10 [-0.25, 0.04]	-0.05 [-0.13, 0.02]	
	History of VMS	-2.17 [-3.76, -0.59]	-0.10 [-0.17, -0.03]	*
	MVPA (mins)	-0.04 [-0.08, 0.00]	-0.08 [-0.17, 0.00]	*
	StaB (hours)	0.35 [-0.21, 0.91]	0.06 [-0.03, 0.15]	
	Sleep duration (hours)	0.09 [-0.91, 1.08]	0.01 [-0.08, 0.09]	
	Controls (MHT reference group)			
	Oral	-1.22 [-4.55, 2.10]	-0.03 [-0.10, 0.05]	
	Transdermal	-2.47 [-5.69, 0.75]	-0.06 [-0.13, 0.02]	
	Vaginal	-0.13 [-2.74, 2.47]	0.00 [-0.08, 0.07]	
SBP	Age (years)	0.38 [0.22, 0.53]	0.16 [0.10, 0.23]	*
	BMI (kg/m ²)	0.87 [0.70, 1.05]	0.34 [0.27, 0.40]	*
	MVPA (mins)	-0.02 [-0.06, 0.03]	-0.03 [-0.10, 0.05]	
	StaB (hours)	-0.49 [-1.19, 0.21]	-0.06 [-0.14, 0.02]	
	Sleep duration (hours)	0.17 [-1.04, 1.39]	0.01 [-0.06, 0.08]	
	Controls (MHT reference group)			

	Oral	1.50 [-2.36, 5.35]	0.03 [-0.04, 0.09]	
	Transdermal	0.19 [-3.91, 4.30]	0.00 [-0.06, 0.07]	
	Vaginal	-1.51 [-4.77, 1.74]	-0.03 [-0.10, 0.03]	
DBP	Age (years)	0.00 [-0.12, 0.11]	0.00 [-0.07, 0.07]	
	BMI (kg/m ²)	0.57 [0.44, 0.70]	0.30 [0.23, 0.37]	*
	MVPA (mins)	-0.02 [-0.05, 0.02]	-0.03 [-0.11, 0.04]	
	StaB (hours)	-0.79 [-1.31, -0.27]	-0.13 [-0.21, -0.04]	*
	Sleep duration (hours)	-0.03 [-0.94, 0.87]	0.00 [-0.08, 0.07]	
	Controls (MHT reference group)			
	Oral	0.77 [-2.10, 3.63]	0.02 [-0.05, 0.08]	
	Transdermal	-1.57 [-4.63, 1.48]	-0.03 [-0.10, 0.03]	
	Vaginal	1.13 [-1.29, 3.55]	0.03 [-0.04, 0.10]	
MHT Users Only				
Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	Mean arterial pressure (mmHg)	0.04 [0.03, 0.06]	0.42 [0.26, 0.57]	*
	History of hypertension	-0.12 [-0.54, 0.30]	-0.04 [-0.20, 0.11]	
	Age at menopause (years)	0.01 [-0.01, 0.04]	0.09 [-0.06, 0.24]	
	History of VMS	-0.28 [-0.66, 0.10]	-0.11 [-0.26, 0.04]	
	MVPA (mins)	-0.01 [-0.02, 0.00]	-0.11 [-0.28, 0.06]	
	StaB (hours)	0.08 [-0.06, 0.22]	0.11 [-0.09, 0.31]	
	Sleep duration (hours)	0.06 [-0.22, 0.34]	0.04 [-0.14, 0.22]	
	Oral (MHT reference group)			
	Transdermal	-0.47 [-0.91, -0.02]	-0.19 [-0.38, -0.01]	*
	Vaginal	-0.65 [-1.06, -0.24]	-0.30 [-0.49, -0.11]	*
AIx75	History of hypertension	4.18 [-0.19, 8.54]	0.17 [-0.01, 0.34]	
	Age at menopause (years)	-0.12 [-0.38, 0.14]	-0.08 [-0.26, 0.09]	
	History of VMS	-2.03 [-6.10, 2.04]	-0.08 [-0.25, 0.08]	
	MVPA (mins)	-0.08 [-0.18, 0.03]	-0.15 [-0.34, 0.05]	
	StaB (hours)	0.60 [-0.91, 2.11]	0.09 [-0.14, 0.32]	
	Sleep duration (hours)	0.28 [-2.66, 3.22]	0.02 [-0.18, 0.22]	
	Oral (MHT reference group)			

SBP	Transdermal	-0.87 [-5.59, 3.85]	-0.04 [-0.25, 0.17]	*
	Vaginal	1.82 [-2.48, 6.12]	0.09 [-0.12, 0.30]	
	Age (years)	0.30 [-0.13, 0.73]	0.12 [-0.05, 0.29]	
	BMI (kg/m ²)	1.02 [0.51, 1.53]	0.33 [0.16, 0.50]	
	MVPA (mins)	-0.03 [-0.17, 0.11]	-0.04 [-0.22, 0.15]	
	StaB (hours)	0.01 [-1.86, 1.88]	0.00 [-0.20, 0.20]	
	Sleep duration (hours)	-0.88 [-4.19, 2.44]	-0.05 [-0.23, 0.13]	
	Oral (MHT reference group)			
DBP	Transdermal	-1.10 [-7.18, 4.98]	-0.03 [-0.22, 0.15]	*
	Vaginal	-2.74 [-8.21, 2.74]	-0.09 [-0.28, 0.09]	
	Age (years)	-0.10 [-0.43, 0.23]	-0.05 [-0.22, 0.12]	
	BMI (kg/m ²)	0.79 [0.40, 1.19]	0.33 [0.17, 0.50]	
	MVPA (mins)	-0.01 [-0.12, 0.09]	-0.02 [-0.21, 0.16]	
	StaB (hours)	-0.23 [-1.67, 1.21]	-0.03 [-0.23, 0.17]	
	Sleep duration (hours)	-1.52 [-4.08, 1.04]	-0.11 [-0.29, 0.07]	
	Oral (MHT reference group)			
	Transdermal	-2.24 [-6.93, 2.46]	-0.09 [-0.28, 0.10]	
	Vaginal	0.62 [-3.60, 4.85]	0.03 [-0.16, 0.22]	

Abbreviations: Sig, significance; BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; Alx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

*denotes $p < 0.05$

3.2.4.2 Objective 1D.2

Objective 1D.2 was to construct unadjusted hierarchical regression models that examined a larger set of outcomes (primary outcomes: aPWV, AIx75, SBP, DBP, FRS; secondary outcomes: WC, HDL-C, LDL-C, TG, glucose). The unopposed estrogen MHT route was entered into Block 1, followed by movement behaviours in Block 2. No covariates were included in these models. The hypothesis that movement behaviours (collectively and individually) would explain a greater proportion of variance in the tested outcomes beyond estrogen route was supported.

Full Sample

As a group, unopposed estrogen MHT routes alone (Block 1) were poor predictors of most outcomes, providing only marginal improvements in model fit for aPWV and logTG (Table 22). However, the addition of movement behaviours (Block 2) significantly enhanced the models' explanatory ability across all outcomes except HDL-C. Notably, movement behaviours increased the explained variance from 2% to 6% for aPWV ($p < 0.01$; $\Delta AIC = -29.4$) and from 0% to 8% for logFRS ($p < 0.01$; $\Delta AIC = -62.5$).

Relative to controls, oral estrogen use was independently associated with faster aPWV and higher logTG, whereas vaginal estrogen use was associated with lower logFRS and lower logGlucose (Table 23). MVPA was independently associated with most outcomes (aPWV, AIx75, SBP, DBP, logFRS, WC, log TG, logGlucose; no independent association with LDL-C). MVPA also held the strongest associations (denoted by standardized coefficients, β) with the outcomes compared with MHT exposures, StaB, and sleep duration in all but one case (DBP, where StaB had a stronger association; Table 23). StaB was independently associated with faster aPWV, lower DBP, and lower HDL-C. Sleep duration was not associated with any outcome.

MHT Users Only

Among MHT users only, estrogen route alone continued to improve explanatory value beyond the null for aPWV (Adj. $R^2 = 0.09$, $p < 0.01$) and logTG (Adj. $R^2 = 0.04$, $p = 0.02$; Table 22). However, movement behaviours improved model fit only for aPWV, AIx75, logFRS, and logTG; unlike in the full sample, they did not improve models predicting SBP, DBP, WC, LDL-C, or logGlucose. Still, entering movement behaviours elicited notable increases in explained

variance for aPWV and logFRS; it increased from 9% to 14% for aPWV ($p = 0.01$; $\Delta AIC = -5.1$), and 0% to 12% for logFRS ($p < 0.01$; $\Delta AIC = -16.1$).

Relative to oral estrogen usage, vaginal and transdermal estrogen usage was associated with slower aPWV (Table 23). Vaginal usage was additionally associated with lower logFRS. The magnitude of association between vaginal usage and aPWV ($\beta = -0.31$, 95% CI [-0.49, -0.14]) was greater than that of MVPA and aPWV ($\beta = -0.22$, 95% CI [-0.22, -0.05]). The reverse was true for models predicting logFRS, where MVPA was more strongly associated with logFRS ($\beta = -0.25$, 95% CI [-0.43, -0.08]) than vaginal usage ($\beta = -0.23$ [-0.41, -0.04]). Of the three movement behaviours, only MVPA was independently associated with any outcomes (Table 23). Higher average daily MVPA was associated with slower aPWV, lower logFRS, smaller WC, and lower logTG.

Table 22. Objective 1D.2 Unadjusted Model Fit

Outcome	Block	N	R ²	Full Sample			
				Adj. R ²	P Value for change in F	AIC	ΔAIC
aPWV	Block 1	813	0.02	0.02	< 0.01	2468.9	
	Block 2		0.06	0.06	< 0.01	2439.4	-29.4
AIx75	Block 1	813	0.00	0.00	0.82	6041.1	
	Block 2		0.02	0.01	< 0.01	6031.9	-9.3
SBP	Block 1	813	0.00	0.00	0.26	6566.6	
	Block 2		0.02	0.01	0.02	6562.4	-4.2
DBP	Block 1	813	0.00	0.00	0.82	6057.5	
	Block 2		0.01	0.01	0.02	6053.7	-3.9
logFRS	Block 1	813	0.00	0.00	0.55	6526.2	
	Block 2		0.08	0.08	< 0.01	6463.8	-62.5
WC	Block 1	813	0.00	0.00	0.99	996.9	
	Block 2		0.04	0.03	< 0.01	969.2	-27.7
HDL-C	Block 1	813	0.00	0.00	0.49	2062.3	
	Block 2		0.01	0.00	0.27	2064.3	2.0
LDL-C	Block 1	813	0.01	0.00	0.15	946.7	
	Block 2		0.02	0.01	0.01	940.9	-5.8
logTG	Block 1	813	0.01	0.01	0.049	1243.2	
	Block 2		0.04	0.03	< 0.01	1225.4	-17.8
logGlucose	Block 1	812	0.01	0.00	0.09	-1069.2	
	Block 2		0.02	0.01	0.03	-1072.3	-3.1
Outcome	Block	N	R ²	MHT users Only			
				Adj. R ²	P Value for change in F	AIC	ΔAIC
aPWV	Block 1	153	0.10	0.09	0.00	446.4	
	Block 2		0.17	0.14	0.01	441.3	-5.1
AIx75	Block 1	153	0.00	-0.01	0.73	1140.1	
	Block 2		0.08	0.05	0.01	1133.9	-6.2
SBP	Block 1	153	0.02	0.01	0.17	1255.0	
	Block 2		0.05	0.02	0.25	1256.8	1.7

DBP	Block 1	153	0.00	-0.01	0.71	1177.2	
	Block 2		0.02	-0.01	0.41	1180.2	3.0
logFRS	Block 1	153	0.01	0.00	0.33	1217.4	
	Block 2		0.15	0.12	< 0.01	1201.2	-16.1
WC	Block 1	153	0.00	-0.01	0.96	195.7	
	Block 2		0.01	-0.02	0.58	199.7	4.0
HDL-C	Block 1	153	0.02	0.00	0.27	367.0	
	Block 2		0.05	0.02	0.17	367.8	0.8
LDL-C	Block 1	153	0.02	0.01	0.16	169.8	
	Block 2		0.07	0.04	0.06	167.9	-1.9
logTG	Block 1	153	0.05	0.04	0.02	224.1	
	Block 2		0.11	0.08	0.03	220.8	-3.2
logGlucose	Block 1	153	0.03	0.01	0.12	-148.2	
	Block 2		0.04	0.01	0.49	-144.7	3.5

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: MHT route entered (oral, transdermal, and vaginal for the full sample; transdermal and vaginal among MHT users)

Block 2: Movement behaviours entered

Bold text used to emphasize statistically significant change in model fit in Block 1;

Red bold text used to emphasize statistically significant changes in Block 2.

Table 23. Objective 1D.2 Unstandardized and Standardized Coefficients

Outcome	Predictor	Full Sample Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.15 [-0.23, -0.08]	*
	StaB (hours)	0.07 [0.01, 0.12]	0.10 [0.01, 0.18]	*
	Sleep duration (hours)	0.04 [-0.06, 0.14]	0.03 [-0.05, 0.11]	
	Controls (reference group)			
	Oral	0.59 [0.26, 0.91]	0.12 [0.06, 0.19]	*
	Transdermal	0.05 [-0.29, 0.40]	0.01 [-0.06, 0.08]	
	Vaginal	-0.11 [-0.38, 0.16]	-0.03 [-0.09, 0.04]	
AIx75	MVPA (mins)	-0.05 [-0.08, -0.01]	-0.10 [-0.18, -0.03]	*
	StaB (hours)	0.39 [-0.14, 0.92]	0.06 [-0.02, 0.15]	
	Sleep duration (hours)	0.42 [-0.51, 1.35]	0.04 [-0.04, 0.11]	
	Controls (reference group)			
	Oral	-0.78 [-3.71, 2.15]	-0.02 [-0.09, 0.05]	
	Transdermal	-1.51 [-4.66, 1.63]	-0.03 [-0.10, 0.04]	
	Vaginal	0.00 [-2.49, 2.49]	0.00 [-0.07, 0.07]	
SBP	MVPA (mins)	-0.08 [-0.13, -0.03]	-0.12 [-0.20, -0.04]	*
	StaB (hours)	-0.18 [-0.92, 0.55]	-0.02 [-0.11, 0.07]	
	Sleep duration (hours)	-0.06 [-1.35, 1.23]	0.00 [-0.08, 0.08]	
	Controls (reference group)			
	Oral	2.53 [-1.53, 6.58]	0.04 [-0.03, 0.11]	
	Transdermal	0.95 [-3.41, 5.30]	0.01 [-0.05, 0.08]	
	Vaginal	-2.17 [-5.63, 1.28]	-0.04 [-0.11, 0.03]	
DBP	MVPA (mins)	-0.05 [-0.08, -0.01]	-0.10 [-0.18, -0.02]	*
	StaB (hours)	-0.71 [-1.24, -0.17]	-0.11 [-0.20, -0.03]	*
	Sleep duration (hours)	-0.25 [-1.19, 0.69]	-0.02 [-0.10, 0.06]	
	Controls (reference group)			
	Oral	0.64 [-2.33, 3.60]	0.01 [-0.05, 0.08]	
	Transdermal	-1.09 [-4.28, 2.09]	-0.02 [-0.09, 0.05]	
	Vaginal	0.71 [-1.81, 3.24]	0.02 [-0.05, 0.09]	

logFRS	MVPA (mins)	-0.004 [-0.01, 0.00]	-0.16 [-0.24, -0.08]	*
	StaB (hours)	0.01 [-0.02, 0.03]	0.02 [-0.07, 0.11]	
	Sleep duration (hours)	0.01 [-0.03, 0.06]	0.02 [-0.06, 0.10]	
	Controls (reference group)			
	Oral	0.11 [-0.04, 0.26]	0.05 [-0.02, 0.12]	
	Transdermal	0.04 [-0.12, 0.21]	0.02 [-0.05, 0.09]	
	Vaginal	-0.13 [-0.26, 0.00]	-0.07 [-0.14, 0.00]	*
WC	MVPA (mins)	-0.17 [-0.21, -0.12]	-0.27 [-0.34, -0.19]	*
	StaB (hours)	0.14 [-0.55, 0.84]	0.02 [-0.07, 0.10]	
	Sleep duration (hours)	-0.98 [-2.19, 0.23]	-0.06 [-0.14, 0.01]	
	Controls (reference group)			
	Oral	-1.76 [-5.58, 2.05]	-0.03 [-0.10, 0.04]	
	Transdermal	2.11 [-1.99, 6.21]	0.03 [-0.03, 0.10]	
	Vaginal	-1.84 [-5.09, 1.41]	-0.04 [-0.10, 0.03]	
HDL-C	MVPA (mins)	0.00 [0.00, 0.00]	0.15 [0.07, 0.22]	*
	StaB (hours)	-0.03 [-0.05, 0.00]	-0.09 [-0.18, -0.01]	*
	Sleep duration (hours)	0.00 [-0.05, 0.04]	-0.01 [-0.09, 0.07]	
	Controls (reference group)			
	Oral	0.06 [-0.07, 0.19]	0.03 [-0.04, 0.10]	
	Transdermal	-0.01 [-0.15, 0.13]	-0.01 [-0.07, 0.06]	
	Vaginal	0.01 [-0.11, 0.12]	0.00 [-0.06, 0.07]	
LDL-C	MVPA (mins)	0.00 [0.00, 0.01]	0.07 [-0.01, 0.14]	
	StaB (hours)	0.00 [-0.04, 0.05]	0.01 [-0.08, 0.09]	
	Sleep duration (hours)	0.03 [-0.05, 0.11]	0.03 [-0.05, 0.11]	
	Controls (reference group)			
	Oral	-0.08 [-0.33, 0.18]	-0.02 [-0.09, 0.05]	
	Transdermal	0.18 [-0.09, 0.45]	0.05 [-0.02, 0.11]	
	Vaginal	0.04 [-0.18, 0.25]	0.01 [-0.06, 0.08]	
logTG	MVPA (mins)	0.00 [0.00, 0.00]	-0.11 [-0.19, -0.04]	*
	StaB (hours)	0.00 [-0.02, 0.03]	0.01 [-0.07, 0.10]	
	Sleep duration (hours)	0.01 [-0.03, 0.06]	0.03 [-0.05, 0.11]	
	Controls (reference group)			

	Oral	0.13 [0.00, 0.26]	0.07 [0.00, 0.14]	*
	Transdermal	-0.01 [-0.15, 0.13]	-0.01 [-0.07, 0.06]	
	Vaginal	0.02 [-0.08, 0.13]	0.02 [-0.05, 0.08]	
logGlucose	MVPA (mins)	0.00 [0.00, 0.00]	-0.10 [-0.18, -0.02]	*
	StaB (hours)	0.00 [-0.01, 0.01]	0.01 [-0.08, 0.10]	
	Sleep duration (hours)	0.00 [-0.01, 0.01]	0.00 [-0.08, 0.08]	
	Controls (reference group)			
	Oral	0.01 [-0.02, 0.05]	0.03 [-0.04, 0.10]	
	Transdermal	0.00 [-0.04, 0.04]	0.01 [-0.06, 0.08]	
	Vaginal	-0.04 [-0.07, 0.00]	-0.08 [-0.15, -0.01]	*
MHT Users Only				
Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	MVPA (mins)	-0.01 [-0.02, 0.00]	-0.22 [-0.39, -0.05]	*
	StaB (hours)	0.05 [-0.09, 0.18]	0.07 [-0.13, 0.26]	
	Sleep duration (hours)	-0.03 [-0.27, 0.21]	-0.02 [-0.20, 0.16]	
	Oral (MHT reference group)			
	Transdermal	-0.51 [-0.94, -0.08]	-0.21 [-0.39, -0.03]	*
	Vaginal	-0.68 [-1.06, -0.29]	-0.31 [-0.49, -0.14]	*
AIx75	MVPA (mins)	-0.09 [-0.18, 0.00]	-0.17 [-0.35, 0.01]	
	StaB (hours)	1.18 [-0.13, 2.49]	0.18 [-0.02, 0.39]	
	Sleep duration (hours)	1.31 [-1.01, 3.63]	0.10 [-0.08, 0.29]	
	Oral (MHT reference group)			
	Transdermal	0.00 [-4.15, 4.16]	0.00 [-0.19, 0.19]	
	Vaginal	1.50 [-2.19, 5.19]	0.08 [-0.11, 0.26]	
SBP	MVPA (mins)	-0.11 [-0.25, 0.03]	-0.14 [-0.32, 0.04]	
	StaB (hours)	0.15 [-1.80, 2.10]	0.02 [-0.19, 0.22]	
	Sleep duration (hours)	-1.03 [-4.49, 2.44]	-0.06 [-0.24, 0.13]	
	Oral (MHT reference group)			
	Transdermal	-0.98 [-7.19, 5.22]	-0.03 [-0.22, 0.16]	
	Vaginal	-4.23 [-9.75, 1.28]	-0.15 [-0.33, 0.04]	
DBP	MVPA (mins)	-0.06 [-0.17, 0.05]	-0.10 [-0.29, 0.08]	
	StaB (hours)	-0.18 [-1.70, 1.34]	-0.03 [-0.24, 0.19]	

	Sleep duration (hours)	-1.55 [-4.25, 1.14]	-0.11 [-0.30, 0.08]	
	Oral (MHT reference group)			
	Transdermal	-1.10 [-5.93, 3.74]	-0.04 [-0.24, 0.15]	
	Vaginal	0.53 [-3.76, 4.82]	0.02 [-0.17, 0.22]	
logFRS	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.25 [-0.43, -0.08]	*
	StaB (hours)	-0.01 [-0.08, 0.05]	-0.04 [-0.24, 0.16]	
	Sleep duration (hours)	-0.01 [-0.13, 0.10]	-0.02 [-0.20, 0.16]	
	Oral (MHT reference group)			
	Transdermal	-0.05 [-0.26, 0.16]	-0.05 [-0.23, 0.14]	
	Vaginal	-0.23 [-0.42, -0.04]	-0.23 [-0.41, -0.04]	*
WC	MVPA (mins)	-0.24 [-0.35, -0.12]	-0.35 [-0.52, -0.18]	*
	StaB (hours)	0.38 [-1.25, 2.01]	0.05 [-0.15, 0.24]	
	Sleep duration (hours)	0.35 [-2.54, 3.24]	0.02 [-0.16, 0.20]	
	Oral (MHT reference group)			
	Transdermal	4.37 [-0.81, 9.54]	0.15 [-0.03, 0.33]	
	Vaginal	0.49 [-4.11, 5.09]	0.02 [-0.16, 0.20]	
HDL-C	MVPA (mins)	0.00 [0.00, 0.01]	0.12 [-0.06, 0.30]	
	StaB (hours)	0.00 [-0.06, 0.06]	0.01 [-0.21, 0.22]	
	Sleep duration (hours)	0.01 [-0.10, 0.11]	0.01 [-0.18, 0.20]	
	Oral (MHT reference group)			
	Transdermal	-0.05 [-0.24, 0.15]	-0.05 [-0.24, 0.15]	
	Vaginal	-0.03 [-0.21, 0.14]	-0.04 [-0.23, 0.16]	
LDL-C	MVPA (mins)	0.00 [-0.01, 0.01]	0.05 [-0.13, 0.23]	
	StaB (hours)	-0.07 [-0.18, 0.04]	-0.14 [-0.35, 0.07]	
	Sleep duration (hours)	0.04 [-0.15, 0.23]	0.04 [-0.15, 0.22]	
	Oral (MHT reference group)			
	Transdermal	0.21 [-0.13, 0.55]	0.12 [-0.07, 0.30]	
	Vaginal	0.07 [-0.23, 0.37]	0.04 [-0.14, 0.23]	
logTG	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.25 [-0.43, -0.07]	*
	StaB (hours)	-0.04 [-0.10, 0.02]	-0.15 [-0.35, 0.06]	
	Sleep duration (hours)	-0.03 [-0.13, 0.07]	-0.05 [-0.24, 0.13]	
	Oral (MHT reference group)			

	Transdermal	-0.14 [-0.32, 0.03]	-0.15 [-0.34, 0.04]
	Vaginal	-0.11 [-0.26, 0.05]	-0.13 [-0.32, 0.06]
logGlucose	MVPA (mins)	0.00 [0.00, 0.00]	-0.10 [-0.28, 0.08]
	StaB (hours)	0.00 [-0.02, 0.02]	-0.04 [-0.25, 0.17]
	Sleep duration (hours)	0.01 [-0.02, 0.05]	0.07 [-0.12, 0.26]
	Oral (MHT reference group)		
	Transdermal	-0.01 [-0.08, 0.05]	-0.04 [-0.23, 0.15]
	Vaginal	-0.05 [-0.11, 0.00]	-0.18 [-0.37, 0.01]

Abbreviations: Sig, significance; MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

*denotes $p < 0.05$

3.2.4.3 Objective 1D.3

Objective 1D.3 was to build on Objective 1D.2 by creating fully adjusted hierarchical models structured in three blocks: Covariates in Block 1, MHT exposures in Block 2, and movement behaviours in Block 3. Furthermore, an alternative set of covariates from Kalenga et al. and Objective 1A and 1B was used, as outlined in previous chapters.⁷¹ These covariates were age, age at menopause, spontaneous menopause, history of vasomotor symptoms, postsecondary education, and primary earner status. However, age was not included in models predicting aPWV, AIx75, or logFRS. The hypothesis that movement behaviours (collectively and individually) would explain a greater proportion of outcomes using the new hierarchical model structure was broadly supported.

Full Sample

Table 24 presents the model fit statistics for the regression models estimated in the full sample and among MHT users only. Covariates alone (Block 1) improved the models better than the null for all outcomes except DBP (change in F statistic $p < 0.05$; $p = 0.18$ for DBP). Adding unopposed estrogen route (Block 2), after the covariates (Block 1) improved the model's prediction of aPWV. However, these MHT exposures did not improve models beyond the covariates for any other outcome. Adding movement behaviours (Block 3) after covariates and MHT (Block 2) improved model fit for aPWV, AIx75, logFRS, WC, and HDL-C.

Once covariates and movement behaviours were accounted for, MHT exposures were associated with aPWV and logFRS. Relative to controls, oral usage was associated with faster aPWV ($\beta = 0.13$, 95% CI [0.06, 0.21]), and vaginal usage was associated with lower logFRS ($\beta = -0.08$, 95% CI [-0.16, -0.01]).

MVPA consistently contributed to these improvements in model fit and was independently associated with all outcomes except for LDL-C, even when movement behaviours as a whole did not add significant explanatory value (Table 24; Table 25). Higher average daily MVPA was associated with slower aPWV, lower AIx75, lower SBP, lower DBP, lower logFRS, smaller WC, higher HDL-C, lower logTG, and lower logGlucose. Additionally, greater amounts of StaB were independently associated with lower DBP and lower HDL-C. Sleep duration was not associated with any outcome.

Each covariate was also independently associated with at least one outcome (Table 25). Older age was associated with higher SBP, but also smaller WC, higher HDL-C, lower LDL-C, and lower logTG. Older age at menopause was associated with higher logGlucose. Experiencing spontaneous menopause was associated with a smaller WC, higher HDL-C, and lower logGlucose. Interestingly, a history of experiencing vasomotor symptoms (regardless of duration, frequency, or severity) was associated with slower aPWV and lower AIx75. Postsecondary education was associated with lower logFRS, smaller WC, and higher HDL-C, while being the primary household earner was associated with larger WC. None of these covariates were associated with DBP.

MHT Users Only

In contrast to the models created within the full sample, covariates alone did not improve models beyond the null for any outcome in this sample (Table 24). Adding unopposed estrogen MHT, route (Block 2), after the covariates (Block 1) improved the models' predictive performance for aPWV and logFRS. Block 2 did not improve models beyond the covariates or the null for any other outcome. Adding movement behaviours (Block 3) after covariates and MHT (Block 2) improved model fit for logFRS, WC, and logTG. Notably, Block 3 increased the amount of explained variance from 1% to 5% for logFRS ($p = 0.04$; $\Delta AIC = -3.0$), 4% to 15% for WC ($p = < 0.01$; $\Delta AIC = -13.8$), and 5% to 9% for logTG ($p = 0.046$, $\Delta AIC = -2.8$).

As with the models in the full sample, individual MHT exposures were associated with aPWV and logFRS (Table 25). Relative to oral estrogen usage, transdermal and vaginal estrogen usage were associated with slower aPWV, and vaginal estrogen usage was associated with lower logFRS. MVPA continued to be the predictor most often independently associated with outcomes (Table 25). Higher average daily MVPA was significantly and independently associated with slower aPWV, lower AIx75, lower SBP, lower logFRS, smaller WC, and lower logTG. Neither StaB nor sleep duration was associated with any outcome in these models. Compared with the full-sample models, covariates played a smaller role in predicting outcomes. Older age was associated with smaller WC and higher logGlucose. Postsecondary education was associated with higher HDL-C and lower logTG. No other covariate showed a significant association.

Table 24. Objective 1D.3 Covariate-Adjusted Model Fit

Outcome	Block	N	R ²	Full Sample		AIC	ΔAIC
				Adj. R ²	P Value for change in F		
aPWV	Block 1	692	0.03	0.03	< 0.01	2059.2	
	Block 2		0.06	0.04	< 0.01	2049.5	-9.7
	Block 3		0.08	0.07	< 0.01	2033.8	-15.7
AIx75	Block 1	692	0.02	0.01	0.04	5116.7	
	Block 2		0.02	0.01	0.49	5120.3	3.5
	Block 3		0.03	0.02	0.02	5116.2	-4.0
SBP	Block 1	692	0.02	0.02	0.01	5583.6	
	Block 2		0.03	0.02	0.28	5585.7	2.1
	Block 3		0.04	0.02	0.13	5585.9	0.2
DBP	Block 1	692	0.01	0.00	0.18	5154.8	
	Block 2		0.01	0.00	0.80	5159.8	5.0
	Block 3		0.02	0.01	0.06	5158.3	-1.5
logFRS	Block 1	692	0.02	0.02	< 0.01	1058.0	
	Block 2		0.03	0.02	0.07	1056.7	-1.2
	Block 3		0.05	0.04	0.01	1050.2	-6.6
WC	Block 1	692	0.06	0.05	< 0.01	5516.3	
	Block 2		0.06	0.05	0.52	5520.0	3.7
	Block 3		0.12	0.11	< 0.01	5478.9	-41.1
HDL-C	Block 1	692	0.04	0.04	< 0.01	827.5	
	Block 2		0.05	0.03	0.87	832.8	5.3
	Block 3		0.08	0.07	< 0.01	811.9	-20.9
LDL-C	Block 1	692	0.02	0.01	0.03	1761.6	
	Block 2		0.02	0.01	0.76	1766.4	4.8
	Block 3		0.02	0.01	0.55	1770.3	3.9
logTG	Block 1	692	0.03	0.02	< 0.01	767.0	
	Block 2		0.04	0.02	0.36	769.7	2.7
	Block 3		0.04	0.03	0.09	769.1	-0.6
logGlucose	Block 1	691	0.03	0.02	< 0.01	-903.0	

	Block 2		0.04	0.02	0.26	-901.1	2.0
	Block 3		0.04	0.03	0.23	-899.5	1.6
MHT users Only							
Outcome	Block	N	R²	Adj. R²	P Value for change in F	AIC	ΔAIC
aPWV	Block 1	132	0.01	-0.03	0.95	405.8	
	Block 2		0.11	0.06	< 0.01	395.5	-10.3
	Block 3		0.16	0.09	0.09	394.4	-1.1
AIx75	Block 1	132	0.03	-0.01	0.50	993.8	
	Block 2		0.04	-0.02	0.70	997.0	3.2
	Block 3		0.08	0.01	0.13	997.0	-0.1
SBP	Block 1	132	0.03	-0.01	0.61	1081.5	
	Block 2		0.05	-0.01	0.28	1082.8	1.3
	Block 3		0.10	0.01	0.13	1082.6	-0.2
DBP	Block 1	132	0.02	-0.02	0.83	1012.4	
	Block 2		0.02	-0.04	0.99	1016.4	4.0
	Block 3		0.04	-0.05	0.56	1020.1	3.7
logFRS	Block 1	132	0.01	-0.03	0.88	215.3	
	Block 2		0.06	0.01	0.04	212.4	-2.9
	Block 3		0.13	0.05	0.04	209.4	-3.0
WC	Block 1	132	0.07	0.03	0.15	1057.3	
	Block 2		0.10	0.04	0.18	1057.5	0.3
	Block 3		0.22	0.15	< 0.01	1043.7	-13.8
HDL-C	Block 1	132	0.07	0.03	0.13	167.1	
	Block 2		0.08	0.02	0.62	170.1	3.0
	Block 3		0.10	0.02	0.50	173.5	3.4
LDL-C	Block 1	132	0.06	0.02	0.24	322.2	
	Block 2		0.07	0.01	0.44	324.4	2.2
	Block 3		0.10	0.02	0.31	326.5	2.1
logTG	Block 1	132	0.09	0.05	0.05	147.2	
	Block 2		0.11	0.05	0.39	149.2	2.0
	Block 3		0.17	0.09	0.046	146.4	-2.8
logGlucose	Block 1	132	0.08	0.04	0.08	-112.8	

Block 2	0.10	0.04	0.33	-111.2	1.6
Block 3	0.13	0.05	0.28	-109.4	1.8

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: MHT route entered

Block 3: Movement behaviours entered

Bold text used to emphasize statistically significant change in model fit in Block 1 or Block 2;

Red bold text used to emphasize statistically significant changes in Block 3.

Table 25. Objective 1D.3 Unstandardized and Standardized Coefficients in Adjusted Models

Outcome	Predictor	Full Sample Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	-0.01 [-0.03, 0.01]	-0.04 [-0.12, 0.04]	
	Spontaneous menopause	0.19 [-0.03, 0.42]	0.07 [-0.01, 0.15]	
	History of VMS	-0.36 [-0.53, -0.18]	-0.15 [-0.22, -0.07]	*
	Postsecondary education	-0.06 [-0.25, 0.13]	-0.02 [-0.09, 0.05]	
	Primary earner status	0.03 [-0.13, 0.20]	0.02 [-0.06, 0.09]	
	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.14 [-0.22, -0.06]	*
	StaB (hours)	0.04 [-0.02, 0.11]	0.07 [-0.03, 0.16]	
	Sleep duration (hours)	0.05 [-0.06, 0.16]	0.04 [-0.04, 0.12]	
	Controls (MHT reference group)			
	Oral	0.63 [0.27, 1.00]	0.13 [0.06, 0.21]	*
	Transdermal	0.15 [-0.21, 0.51]	0.03 [-0.04, 0.11]	
	Vaginal	-0.10 [-0.39, 0.18]	-0.03 [-0.10, 0.05]	
AIx75	Age at menopause (years)	-0.11 [-0.27, 0.04]	-0.06 [-0.14, 0.02]	
	Spontaneous menopause	-0.02 [-2.11, 2.07]	0.00 [-0.08, 0.08]	
	History of VMS	-2.22 [-3.86, -0.58]	-0.10 [-0.18, -0.03]	*
	Postsecondary education	0.12 [-1.66, 1.91]	0.01 [-0.07, 0.08]	
	Primary earner status	-0.74 [-2.24, 0.75]	-0.04 [-0.11, 0.04]	
	MVPA (mins)	-0.04 [-0.08, 0.00]	-0.09 [-0.17, 0.00]	*
	StaB (hours)	0.36 [-0.21, 0.93]	0.06 [-0.03, 0.15]	
	Sleep duration (hours)	0.19 [-0.84, 1.22]	0.02 [-0.07, 0.10]	
	Controls (MHT reference group)			
	Oral	-1.36 [-4.75, 2.03]	-0.03 [-0.11, 0.05]	
	Transdermal	-2.60 [-5.96, 0.76]	-0.06 [-0.14, 0.02]	
	Vaginal	-0.51 [-3.14, 2.11]	-0.01 [-0.09, 0.06]	
SBP	Age (years)	0.25 [0.06, 0.43]	0.10 [0.03, 0.18]	*
	Age at menopause (years)	0.01 [-0.22, 0.23]	0.00 [-0.08, 0.08]	
	Spontaneous menopause	-0.44 [-3.38, 2.50]	-0.01 [-0.10, 0.07]	
	History of VMS	-1.71 [-4.03, 0.62]	-0.06 [-0.13, 0.02]	

	Postsecondary education	-1.76 [-4.26, 0.74]	-0.05 [-0.13, 0.02]	
	Primary earner status	0.84 [-1.26, 2.93]	0.03 [-0.05, 0.11]	
	MVPA (mins)	-0.06 [-0.12, -0.01]	-0.10 [-0.18, -0.01]	*
	StaB (hours)	-0.50 [-1.31, 0.30]	-0.06 [-0.15, 0.04]	
	Sleep duration (hours)	0.00 [-1.45, 1.45]	0.00 [-0.08, 0.09]	
	Controls (MHT reference group)			
	Oral	1.38 [-3.42, 6.19]	0.02 [-0.06, 0.10]	
	Transdermal	1.16 [-3.55, 5.88]	0.02 [-0.06, 0.10]	
	Vaginal	-3.23 [-6.90, 0.45]	-0.07 [-0.14, 0.01]	
DBP	Age (years)	-0.07 [-0.20, 0.07]	-0.04 [-0.12, 0.04]	
	Age at menopause (years)	-0.09 [-0.25, 0.07]	-0.04 [-0.13, 0.04]	
	Spontaneous menopause	-0.16 [-2.32, 2.00]	-0.01 [-0.09, 0.08]	
	History of VMS	-0.17 [-1.88, 1.53]	-0.01 [-0.08, 0.07]	
	Postsecondary education	-1.84 [-3.67, 0.00]	-0.08 [-0.15, 0.00]	
	Primary earner status	0.98 [-0.56, 2.52]	0.05 [-0.03, 0.12]	
	MVPA (mins)	-0.04 [-0.08, 0.00]	-0.09 [-0.18, -0.01]	*
	StaB (hours)	-0.69 [-1.28, -0.10]	-0.11 [-0.21, -0.02]	*
	Sleep duration (hours)	-0.20 [-1.26, 0.87]	-0.02 [-0.10, 0.07]	
	Controls (MHT reference group)			
	Oral	-1.11 [-4.64, 2.42]	-0.02 [-0.10, 0.05]	
	Transdermal	-1.31 [-4.78, 2.15]	-0.03 [-0.11, 0.05]	
	Vaginal	-0.62 [-3.33, 2.08]	-0.02 [-0.09, 0.06]	
logFRS	Age at menopause (years)	0.00 [-0.01, 0.01]	0.00 [-0.08, 0.08]	
	Spontaneous menopause	-0.02 [-0.13, 0.09]	-0.01 [-0.10, 0.07]	
	History of VMS	-0.08 [-0.16, 0.01]	-0.07 [-0.14, 0.01]	
	Postsecondary education	-0.12 [-0.22, -0.03]	-0.10 [-0.17, -0.02]	*
	Primary earner status	0.04 [-0.04, 0.12]	0.04 [-0.03, 0.12]	
	MVPA (mins)	0.00 [-0.01, 0.00]	-0.13 [-0.22, -0.05]	*
	StaB (hours)	0.00 [-0.03, 0.03]	0.00 [-0.09, 0.09]	
	Sleep duration (hours)	0.01 [-0.04, 0.07]	0.02 [-0.07, 0.10]	
	Controls (MHT reference group)			
	Oral	0.09 [-0.09, 0.27]	0.04 [-0.04, 0.12]	

WC	Transdermal	0.05 [-0.12, 0.23]	0.02 [-0.05, 0.10]	
	Vaginal	-0.15 [-0.29, -0.02]	-0.08 [-0.16, -0.01]	*
	Age (years)	-0.30 [-0.47, -0.12]	-0.13 [-0.20, -0.05]	*
	Age at menopause (years)	0.09 [-0.12, 0.29]	0.03 [-0.05, 0.11]	
	Spontaneous menopause	-3.72 [-6.44, -1.00]	-0.11 [-0.19, -0.03]	*
	History of VMS	-1.48 [-3.63, 0.67]	-0.05 [-0.12, 0.02]	
	Postsecondary education	-2.32 [-4.64, -0.01]	-0.07 [-0.14, 0.00]	*
	Primary earner status	3.19 [1.25, 5.13]	0.12 [0.05, 0.19]	*
	MVPA (mins)	-0.15 [-0.20, -0.10]	-0.24 [-0.33, -0.16]	*
	StaB (hours)	0.03 [-0.72, 0.77]	0.00 [-0.09, 0.09]	
	Sleep duration (hours)	-0.98 [-2.32, 0.36]	-0.06 [-0.14, 0.02]	
	Controls (MHT reference group)			
	Oral	-1.04 [-5.48, 3.41]	-0.02 [-0.09, 0.06]	
	Transdermal	2.52 [-1.84, 6.88]	0.04 [-0.03, 0.12]	
	Vaginal	-1.68 [-5.09, 1.72]	-0.04 [-0.11, 0.04]	
HDL-C	Age (years)	0.01 [0.01, 0.02]	0.15 [0.07, 0.22]	*
	Age at menopause (years)	0.00 [-0.01, 0.00]	-0.05 [-0.13, 0.03]	
	Spontaneous menopause	0.13 [0.03, 0.22]	0.11 [0.03, 0.19]	*
	History of VMS	0.03 [-0.04, 0.10]	0.03 [-0.04, 0.11]	
	Postsecondary education	0.10 [0.02, 0.18]	0.09 [0.02, 0.17]	*
	Primary earner status	-0.06 [-0.13, 0.00]	-0.07 [-0.14, 0.00]	
	MVPA (mins)	0.00 [0.00, 0.00]	0.12 [0.04, 0.21]	*
	StaB (hours)	-0.03 [-0.06, -0.01]	-0.12 [-0.21, -0.02]	*
	Sleep duration (hours)	-0.01 [-0.06, 0.04]	-0.02 [-0.10, 0.07]	
	Controls (MHT reference group)			
	Oral	-0.01 [-0.16, 0.14]	0.00 [-0.08, 0.07]	
	Transdermal	0.00 [-0.15, 0.15]	0.00 [-0.07, 0.07]	
	Vaginal	-0.05 [-0.16, 0.07]	-0.03 [-0.10, 0.04]	
	Age (years)	-0.02 [-0.03, 0.00]	-0.10 [-0.18, -0.03]	*
LDL-C	Age at menopause (years)	0.00 [-0.02, 0.01]	-0.01 [-0.10, 0.07]	
	Spontaneous menopause	0.01 [-0.18, 0.19]	0.00 [-0.08, 0.09]	
	History of VMS	-0.05 [-0.19, 0.10]	-0.02 [-0.10, 0.05]	

logTG	Postsecondary education	0.05 [-0.11, 0.21]	0.02 [-0.05, 0.10]	
	Primary earner status	-0.13 [-0.26, 0.01]	-0.07 [-0.15, 0.00]	
	MVPA (mins)	0.00 [0.00, 0.01]	0.06 [-0.02, 0.15]	
	StaB (hours)	0.02 [-0.03, 0.07]	0.03 [-0.06, 0.13]	
	Sleep duration (hours)	0.03 [-0.06, 0.12]	0.03 [-0.06, 0.11]	
	Controls (MHT reference group)			
	Oral	-0.09 [-0.39, 0.22]	-0.02 [-0.10, 0.06]	
	Transdermal	0.13 [-0.17, 0.43]	0.03 [-0.04, 0.11]	
	Vaginal	0.02 [-0.22, 0.25]	0.01 [-0.07, 0.08]	
	Age (years)	-0.01 [-0.01, 0.00]	-0.12 [-0.20, -0.05]	*
	Age at menopause (years)	0.00 [-0.01, 0.00]	-0.03 [-0.11, 0.06]	
	Spontaneous menopause	-0.09 [-0.18, 0.00]	-0.08 [-0.16, 0.00]	
	History of VMS	-0.06 [-0.13, 0.02]	-0.06 [-0.13, 0.02]	
	Postsecondary education	-0.05 [-0.13, 0.03]	-0.05 [-0.12, 0.03]	
	Primary earner status	0.05 [-0.02, 0.11]	0.05 [-0.02, 0.13]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.09 [-0.17, 0.00]	*
	StaB (hours)	0.01 [-0.02, 0.03]	0.03 [-0.07, 0.12]	
	Sleep duration (hours)	0.01 [-0.03, 0.06]	0.02 [-0.06, 0.11]	
	Controls (MHT reference group)			
logGlucose	Oral	0.10 [-0.04, 0.25]	0.06 [-0.02, 0.13]	
	Transdermal	-0.04 [-0.19, 0.10]	-0.02 [-0.10, 0.05]	
	Vaginal	0.04 [-0.07, 0.15]	0.03 [-0.05, 0.10]	
	Age (years)	0.00 [0.00, 0.00]	0.04 [-0.04, 0.12]	
	Age at menopause (years)	0.00 [0.00, 0.00]	0.12 [0.03, 0.20]	*
	Spontaneous menopause	-0.04 [-0.07, -0.01]	-0.12 [-0.20, -0.04]	*
	History of VMS	-0.02 [-0.04, 0.01]	-0.06 [-0.13, 0.02]	
	Postsecondary education	-0.01 [-0.04, 0.01]	-0.05 [-0.12, 0.03]	
	Primary earner status	0.01 [-0.01, 0.03]	0.05 [-0.03, 0.12]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.09 [-0.17, 0.00]	*
	StaB (hours)	0.00 [-0.01, 0.01]	-0.03 [-0.12, 0.07]	
	Sleep duration (hours)	0.00 [-0.01, 0.01]	0.01 [-0.08, 0.09]	
	Controls (MHT reference group)			

	Oral	0.03 [-0.02, 0.07]	0.05 [-0.03, 0.13]	
	Transdermal	0.00 [-0.04, 0.04]	0.00 [-0.07, 0.08]	
	Vaginal	-0.03 [-0.06, 0.01]	-0.06 [-0.13, 0.02]	
	MHT Users Only			
Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	0.01 [-0.02, 0.04]	0.04 [-0.15, 0.23]	
	Spontaneous menopause	0.20 [-0.24, 0.64]	0.09 [-0.11, 0.28]	
	History of VMS	-0.25 [-0.69, 0.19]	-0.10 [-0.27, 0.07]	
	Postsecondary education	0.09 [-0.36, 0.55]	0.04 [-0.14, 0.21]	
	Primary earner status	-0.12 [-0.51, 0.28]	-0.05 [-0.22, 0.12]	
	MVPA (mins)	-0.01 [-0.02, 0.00]	-0.19 [-0.38, 0.00]	*
	StaB (hours)	0.05 [-0.11, 0.20]	0.06 [-0.16, 0.29]	
	Sleep duration (hours)	0.06 [-0.25, 0.37]	0.04 [-0.16, 0.24]	
	Oral (MHT reference group)			
	Transdermal	-0.53 [-1.03, -0.03]	-0.22 [-0.43, -0.01]	*
AIx75	Vaginal	-0.76 [-1.23, -0.30]	-0.35 [-0.57, -0.14]	*
	Age at menopause (years)	-0.13 [-0.42, 0.17]	-0.08 [-0.28, 0.11]	
	Spontaneous menopause	-0.99 [-5.27, 3.29]	-0.05 [-0.25, 0.16]	
	History of VMS	-2.00 [-6.29, 2.29]	-0.08 [-0.26, 0.09]	
	Postsecondary education	0.52 [-3.94, 4.99]	0.02 [-0.16, 0.20]	
	Primary earner status	1.46 [-2.41, 5.33]	0.07 [-0.11, 0.25]	
	MVPA (mins)	-0.08 [-0.19, 0.03]	-0.15 [-0.35, 0.05]	*
	StaB (hours)	0.73 [-0.83, 2.28]	0.11 [-0.12, 0.34]	
	Sleep duration (hours)	0.42 [-2.62, 3.46]	0.03 [-0.18, 0.24]	
	Oral (MHT reference group)			
SBP	Transdermal	-0.33 [-5.20, 4.54]	-0.01 [-0.23, 0.20]	
	Vaginal	1.67 [-2.88, 6.21]	0.08 [-0.14, 0.31]	
	Age (years)	0.30 [-0.16, 0.75]	0.12 [-0.07, 0.30]	
	Age at menopause (years)	0.02 [-0.39, 0.43]	0.01 [-0.19, 0.21]	
	Spontaneous menopause	-0.76 [-6.71, 5.18]	-0.03 [-0.23, 0.18]	
	History of VMS	0.64 [-5.32, 6.60]	0.02 [-0.16, 0.20]	
	Postsecondary education	2.07 [-4.09, 8.23]	0.06 [-0.12, 0.24]	

	Primary earner status	-0.45 [-5.79, 4.89]	-0.02 [-0.19, 0.16]	
	MVPA (mins)	-0.17 [-0.31, -0.02]	-0.22 [-0.42, -0.02]	*
	StaB (hours)	-1.06 [-3.21, 1.09]	-0.11 [-0.35, 0.12]	
	Sleep duration (hours)	0.71 [-3.49, 4.90]	0.04 [-0.17, 0.24]	
	Oral (MHT reference group)			
	Transdermal	-0.18 [-7.06, 6.70]	-0.01 [-0.23, 0.21]	
	Vaginal	-4.14 [-10.63, 2.34]	-0.15 [-0.38, 0.08]	
DBP	Age (years)	-0.12 [-0.49, 0.24]	-0.07 [-0.26, 0.13]	
	Age at menopause (years)	-0.09 [-0.41, 0.23]	-0.06 [-0.26, 0.15]	
	Spontaneous menopause	1.62 [-3.07, 6.31]	0.07 [-0.14, 0.28]	
	History of VMS	0.46 [-4.24, 5.17]	0.02 [-0.16, 0.20]	
	Postsecondary education	0.38 [-4.48, 5.25]	0.01 [-0.17, 0.20]	
	Primary earner status	2.28 [-1.94, 6.50]	0.10 [-0.09, 0.29]	
	MVPA (mins)	-0.08 [-0.20, 0.03]	-0.15 [-0.36, 0.06]	
	StaB (hours)	-0.70 [-2.39, 1.00]	-0.10 [-0.34, 0.14]	
	Sleep duration (hours)	-0.67 [-3.98, 2.64]	-0.04 [-0.26, 0.17]	
	Oral (MHT reference group)			
	Transdermal	-0.24 [-5.36, 4.88]	-0.01 [-0.25, 0.23]	
	Vaginal	-0.01 [-5.44, 5.42]	0.00 [-0.23, 0.23]	
logFRS	Age at menopause (years)	0.00 [-0.02, 0.01]	-0.06 [-0.25, 0.13]	
	Spontaneous menopause	0.07 [-0.15, 0.28]	0.06 [-0.14, 0.26]	
	History of VMS	0.00 [-0.22, 0.21]	0.00 [-0.17, 0.17]	
	Postsecondary education	0.01 [-0.22, 0.23]	0.01 [-0.17, 0.18]	
	Primary earner status	-0.06 [-0.26, 0.13]	-0.06 [-0.23, 0.12]	
	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.27 [-0.47, -0.08]	*
	StaB (hours)	-0.03 [-0.10, 0.05]	-0.07 [-0.30, 0.15]	
	Sleep duration (hours)	0.02 [-0.13, 0.17]	0.03 [-0.18, 0.23]	
	Oral (MHT reference group)			
	Transdermal	-0.04 [-0.28, 0.21]	-0.03 [-0.24, 0.18]	
	Vaginal	-0.25 [-0.48, -0.02]	-0.24 [-0.45, -0.02]	*
WC	Age (years)	-0.50 [-0.89, -0.10]	-0.21 [-0.39, -0.04]	*
	Age at menopause (years)	-0.15 [-0.50, 0.20]	-0.08 [-0.26, 0.10]	

HDL-C	Spontaneous menopause	1.38 [-3.75, 6.51]	0.05 [-0.14, 0.24]	*
	History of VMS	1.71 [-3.44, 6.85]	0.05 [-0.11, 0.22]	
	Postsecondary education	-3.17 [-8.49, 2.15]	-0.10 [-0.26, 0.07]	
	Primary earner status	2.42 [-2.19, 7.03]	0.09 [-0.08, 0.25]	
	MVPA (mins)	-0.27 [-0.39, -0.14]	-0.39 [-0.57, -0.20]	
	StaB (hours)	-0.52 [-2.37, 1.34]	-0.06 [-0.28, 0.16]	
	Sleep duration (hours)	-1.33 [-4.95, 2.29]	-0.07 [-0.26, 0.12]	
	Oral (MHT reference group)			
	Transdermal	3.70 [-2.24, 9.63]	0.13 [-0.08, 0.33]	
	Vaginal	-1.61 [-7.21, 3.99]	-0.06 [-0.28, 0.15]	
	Age (years)	0.00 [-0.01, 0.02]	0.03 [-0.15, 0.22]	
	Age at menopause (years)	0.00 [-0.01, 0.01]	0.01 [-0.18, 0.21]	
	Spontaneous menopause	0.17 [-0.02, 0.36]	0.18 [-0.02, 0.39]	
	History of VMS	0.00 [-0.19, 0.19]	0.00 [-0.18, 0.18]	
LDL-C	Postsecondary education	0.21 [0.02, 0.41]	0.19 [0.02, 0.37]	*
	Primary earner status	-0.02 [-0.19, 0.15]	-0.03 [-0.20, 0.15]	
	MVPA (mins)	0.00 [0.00, 0.01]	0.15 [-0.05, 0.35]	
	StaB (hours)	0.01 [-0.06, 0.08]	0.03 [-0.21, 0.26]	
	Sleep duration (hours)	0.02 [-0.11, 0.16]	0.03 [-0.17, 0.24]	
	Oral (MHT reference group)			
	Transdermal	-0.01 [-0.23, 0.21]	-0.01 [-0.23, 0.21]	
	Vaginal	-0.09 [-0.30, 0.11]	-0.10 [-0.33, 0.13]	
	Age (years)	-0.02 [-0.05, 0.01]	-0.14 [-0.33, 0.04]	
	Age at menopause (years)	-0.02 [-0.04, 0.01]	-0.14 [-0.33, 0.06]	
	Spontaneous menopause	0.17 [-0.17, 0.51]	0.10 [-0.10, 0.31]	
	History of VMS	-0.08 [-0.42, 0.26]	-0.04 [-0.22, 0.14]	
	Postsecondary education	0.20 [-0.16, 0.55]	0.10 [-0.08, 0.28]	
	Primary earner status	-0.06 [-0.37, 0.24]	-0.04 [-0.21, 0.14]	
	MVPA (mins)	0.00 [-0.01, 0.01]	0.03 [-0.17, 0.23]	
	StaB (hours)	-0.08 [-0.20, 0.04]	-0.15 [-0.39, 0.08]	
	Sleep duration (hours)	0.01 [-0.23, 0.25]	0.01 [-0.20, 0.22]	
	Oral (MHT reference group)			

logTG	Transdermal	0.19 [-0.20, 0.58]	0.11 [-0.11, 0.32]	
	Vaginal	0.02 [-0.35, 0.39]	0.01 [-0.22, 0.24]	
	Age (years)	-0.01 [-0.02, 0.00]	-0.13 [-0.31, 0.05]	
	Age at menopause (years)	-0.01 [-0.02, 0.00]	-0.15 [-0.34, 0.04]	
	Spontaneous menopause	0.00 [-0.17, 0.17]	0.00 [-0.20, 0.19]	
	History of VMS	-0.02 [-0.20, 0.15]	-0.02 [-0.19, 0.15]	
	Postsecondary education	-0.18 [-0.36, 0.00]	-0.17 [-0.34, 0.00]	*
	Primary earner status	-0.01 [-0.17, 0.14]	-0.01 [-0.19, 0.16]	
	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.27 [-0.46, -0.08]	*
	StaB (hours)	-0.04 [-0.10, 0.02]	-0.15 [-0.38, 0.07]	
	Sleep duration (hours)	-0.01 [-0.13, 0.12]	-0.01 [-0.21, 0.19]	
logGlucose	Oral (MHT reference group)			
	Transdermal	-0.14 [-0.34, 0.05]	-0.15 [-0.36, 0.06]	
	Vaginal	-0.06 [-0.25, 0.13]	-0.07 [-0.29, 0.15]	
	Age (years)	0.01 [0.00, 0.01]	0.19 [0.01, 0.38]	*
	Age at menopause (years)	0.00 [0.00, 0.01]	0.18 [-0.01, 0.38]	
	Spontaneous menopause	-0.02 [-0.09, 0.04]	-0.07 [-0.27, 0.13]	
	History of VMS	-0.02 [-0.08, 0.05]	-0.05 [-0.22, 0.12]	
	Postsecondary education	0.03 [-0.04, 0.10]	0.08 [-0.10, 0.25]	
	Primary earner status	0.00 [-0.06, 0.06]	-0.01 [-0.18, 0.17]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.10 [-0.29, 0.10]	
	StaB (hours)	-0.01 [-0.03, 0.02]	-0.05 [-0.28, 0.18]	
	Sleep duration (hours)	0.03 [-0.02, 0.07]	0.13 [-0.08, 0.33]	
	Oral (MHT reference group)			
	Transdermal	-0.02 [-0.09, 0.06]	-0.05 [-0.27, 0.16]	
	Vaginal	-0.05 [-0.12, 0.02]	-0.15 [-0.38, 0.08]	

Abbreviations: Sig, significance; MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

*denotes $p < 0.05$

Objective 1D Summary

The overall hypothesis for Objective 1D was that movement behaviours would account for greater variance in CV outcomes compared to the estrogen route, which was generally supported.

Interpretation of the regression models evolved as their structure changed from adding movement to the original structure used by Kalenga et al. (Objective 1D.1), to unadjusted hierarchical models with a larger set of outcomes (1D.2), and finally to fully adjusted models with an alternate set of covariates (1D.3). In 1D.1, adding movement behaviours to the original model structure produced a statistically significant improvement in fit for aPWV (+ 3% explanatory value), AIx75 (+1% explanatory value), and DBP (+1% explanatory value) in the full sample (Table 20), but did not change the overall pattern of independent estrogen route associations. That is, oral use remained associated with faster aPWV, with only slight attenuation in magnitude (Table 21). In the MHT user subset, movement behaviours did not improve model fit for any outcome, and route associations were again limited to aPWV (Table 21). In contrast, in the unadjusted models of 1D.2, the estrogen routes alone explained very little variance across outcomes, whereas adding movement behaviours substantially increased explanatory value for most primary and secondary outcomes in the full sample (Table 22). Under this specification, MVPA was independently associated with multiple outcomes and often demonstrated larger standardized effects than MHT exposures (Table 23).

In the fully adjusted models of Objective 1D.3, covariates accounted for much of the variance in outcomes, and adding MHT route improved model fit only for aPWV (and logFRS among MHT users; Table 24). Once movement behaviours were entered, model fit improved for aPWV, AIx75, logFRS, WC, and HDL-C in the full sample, with MVPA independently associated with nearly all CV outcomes except for LDL-C. Furthermore, after accounting for both covariates and movement behaviours, MHT exposures were no longer independently associated with most outcomes, and remained significant only for aPWV and logFRS; this trend persisted when the sample was restricted to MHT users only (Table 25). MVPA continued to be an influential predictor in the MHT user subset, and was favourably associated with logFRS, WC, and logTG.

3.2.5 Summary of Objective 1 Results

The overall hypothesis for Objective 1 was that estrogen MHT routes would be associated with CV outcomes, but movement behaviours would contribute more substantially to the explanation of variance in these outcomes, regardless of sample size or variable operationalization. This hypothesis was partially supported.

Progressively altering the framing of the research question, the structure of the statistical models, and the variables analyzed (see Table 11) shifted the interpretation away from estrogen MHT route and toward movement behaviours and covariates as the predominant explanatory factors of CV outcomes. Some of the route-based differences reported by Kalenga et al. (2022), particularly for aPWV and D1SBP, were replicated. However, other findings were attenuated or nullified after increasing the sample size, modifying the definitions of the blood pressure variable (Day 2 averages rather than Day 1 single measurements), and/or altering the covariate structure. It should be noted that associations between MHT route and outcomes, such as aPWV (and, to a lesser extent, logFRS), paralleled age differences between groups, and the removal or inclusion of age substantially altered model fit and route estimates for aPWV. This pattern raises questions about the role of age in interpreting findings on MHT use more generally.

When models were expanded to include movement behaviours and broader covariate adjustment, routes of estrogen administration explained little additional variance in most CV outcomes, and individual routes (e.g., oral and vaginal estrogen) were independently associated with aPWV and logFRS. In contrast, movement behaviours (particularly MVPA and, in some models, StaB) frequently improved model fit and demonstrated independent associations across multiple outcomes, whereas sleep duration was not associated with any outcome. Overall, within the WARM Hearts cohort, CV health was more consistently and broadly explained by movement behaviours than by route of unopposed estrogen administration. These findings contextualize and qualify the original route-based interpretations reported by Kalenga et al. (2022).

3.3 Objective 2 Results

Objective 2 is to extend the Objective 1 analyses by using alternative MHT exposure definitions: (1) MHT usage history (controls, former users, current users); (2) MHT type, irrespective of route of administration (controls, combined estrogen-progestogen, unopposed

estrogen); and (3) MHT route of administration, irrespective of type of hormone(s) (controls, oral, transdermal, vaginal).

3.3.1 Objective 2A

Analyses in Objective 1A examine group differences in demographic variables, movement behaviours, and CV outcomes by MHT usage history (2A.1), MHT type (2A.2), and MHT route of administration (2A.3) using ANOVA and Kruskal-Wallis tests. The following variables were tested: Age, BMI, mean arterial pressure, age at menopause, MVPA, StaB, sleep duration, aPWV, AIx75, SBP, DBP, FRS, WC, HDL-C, LDL-C, TG, and glucose. Results for variables following a normal distribution are presented as mean $\pm$ SD, and results for non-normal variables are presented as median [Q1, Q3].

3.3.1.1 Objective 2A.1

Differences in continuous variables by MHT usage history are summarized in Table 26. The hypothesis that the tested variables would differ across groups defined by MHT usage history (controls vs. former usage vs. current usage) was generally not supported, as differences were observed for just 6 of the 17 variables.

Significant differences were observed between usage history groups in age, age at menopause, MVPA, aPWV, FRS, and glucose. Former MHT users were older (67 [62, 72] years) than controls (63 [60, 67] years) and current MHT users (63 [59, 67] years). Controls were older at the time of menopause (53 [51, 55] years) than both former (51 [46, 54] years) and current users (51 [48, 53] years). Controls also averaged higher daily MVPA (21.2 [9.7, 38.4] mins/day) than former MHT users (17.2 [6.8, 30.8] mins/day). Extrapolating these values and multiplying the average daily minutes by 7 to get the average weekly minutes suggests that controls were nearly meeting the Canadian 24-hour movement guidelines of 150 mins/week (at 148.4 [67.9, 268.8] mins/week), while former users were further away from the target (120.4 [47.6, 215.6] mins/week).⁷⁶ However, as mentioned previously, extrapolation can introduce bias. Most participants (N=635; 68.4%) recorded 7 valid days of accelerometer wear time. The remainder (N=294, 31.6%) had 4 to 6 days of valid wear time, and so a weekly total would be extrapolated. Therefore, this “weekly MVPA” framing of the data should be interpreted cautiously.

Former users had faster aPWV (9.5 [8.7, 10.3] m/s) than current users (8.8 m/s [8.2, 9.5] m/s) and controls (8.8 m/s [8.2, 9.7] m/s). Former users also had higher FRS (6.3% [4.5, 8.6]) than current users (5.5% [5.3, 5.8]). Lastly, current users had lower fasting glucose (5.53 [5.30, 5.79] mmol/L) than controls (5.67 [5.35, 6.02] mmol/L). There were no significant differences between groups for any other variable. Although former users have a relatively more unfavourable CV risk profile compared to controls and current users in these outcomes, all of the values are within healthy ranges (Table 9).

The chi-square tests of independence indicated significant associations between MHT usage history and spontaneous menopause, experience of vasomotor symptoms, severity of vasomotor symptoms, and primary earner status Table 27. The prevalence of spontaneous menopause was significantly higher among controls (86.4%) than former users (70.5%) and current users (68.8%). A significant association between MHT status and a history of experiencing vasomotor symptoms was detected, but post-hoc tests revealed no statistically significant differences between specific groups. That said, the proportion of individuals reporting a history of vasomotor symptoms was nominally higher among former users (76.9%) and current users (79.2%) compared to controls (69.2%). Former MHT users reported a significantly higher proportion of moderate-to-severe symptoms (49.7%) compared to the control group (36.1%). The proportion of current MHT users reporting moderate-to-severe symptoms (45.8%) did not differ significantly from either the control group or the former users. Lastly, former users were significantly less likely to report being the primary household earner (32.4%) compared to controls (42.9%).

Table 26. Group Differences in Continuous Variables by MHT Usage History.

Variable	Controls (N=660)	Former MHT Usage (N=173)	Current MHT Usage (N=96)	Omnibus p-value	Effect size
Age (years)	63 [60, 67]	67 [62, 72] *	63 [59, 67] †	< 0.01	$\epsilon^2=0.05$
BMI (kg/m ²)	25.8 [23.2, 29.7]	25.8 [23.4, 29.0]	25.5 [22.8, 28.5]	0.63	$\epsilon^2=0.00$
Mean arterial pressure (mmHg)	97 (11)	98 (11)	96 (13)	0.26	$\eta^2=0.00$
Age at menopause (years)	53 [51, 55]	51 [46, 54] *	51 [47.5, 53] *	< 0.01	$\epsilon^2=0.03$
MVPA (avg. mins/day)	21.2 [9.7, 38.4]	17.2 [6.8, 30.8] *	20.8 [9.3, 39.0]	0.04	$\epsilon^2=0.00$
StaB (avg. hours/day)	12.1 (1.6)	12.2 (1.6)	12.0 (1.7)	0.68	$\eta^2=0.00$
Sleep (avg. hours/day)	6.5 (0.9)	6.5 [0.9]	6.5 (0.9)	0.67	$\eta^2=0.00$
aPWV (m/s)	8.8 [8.2, 9.7]	9.5 [8.7, 10.3] *	8.8 [8.2, 9.5] †	< 0.01	$\epsilon^2=0.04$
AIx75 (%)	21.3 [13.7, 28.7]	21.0 [13.3, 30.3]	21.5 [13.3, 27.1]	0.40	$\epsilon^2=0.00$
SBP (mmHg)	122 (14)	123 (14)	119 (16)	0.08	$\eta^2=0.01$
DBP (mmHg)	77 (10)	77 (11)	76 (12)	0.69	$\eta^2=0.00$
FRS (%)	6.3 [3.9, 8.6]	6.3 [4.5, 8.6]	5.5 [5.3, 5.8] †	0.01	$\epsilon^2=0.01$
WC (cm)	92.6 [85, 102.5]	94 [84, 102]	91.5 [85.0, 99.8]	0.62	$\epsilon^2=0.00$
HDL-C (mmol/L)	1.67 [1.40, 2.03]	1.71 [1.50, 2.03]	1.73 [1.43, 1.95]	0.47	$\epsilon^2=0.00$
LDL-C (mmol/L)	3.30 [2.69, 3.91]	3.34 [2.69, 3.91]	3.26 [2.71, 3.92]	0.88	$\epsilon^2=0.00$
TG (mmol/L)	0.99 [0.75, 1.33]	0.96 [0.80, 1.33]	0.98 [0.74, 1.33]	0.98	$\epsilon^2=0.00$
Glucose (mmol/L)	5.67 [5.35, 6.02]	5.67 [5.37, 6.02]	5.53 [5.30, 5.79] *	0.04	$\epsilon^2=0.00$

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Age at menopause: N = 585 (never); 156 (former); 83 (current)

Glucose: N=659 (controls)

Outcomes reported as Mean (SD) or Median [Q1, Q3]

*p < 0.05 compared to controls

†p < 0.05 compared to former users

Red bold text used to emphasize statistically significant findings.

Table 27. Group Differences in Categorical Variables by MHT Usage History.

Variable	Controls (N=660)		Former MHT Usage (N=173)		Current MHT Usage (N=96)		P-Value
	Freq.	%	Freq.	%	Freq.	%	
History of Hypertension							NS
No	503	76.2%	137	79.2%	77	80.2%	
Yes	157	23.8%	36	20.8%	19	19.8%	
Sleep Apnea							NS
No	618	93.6%	166	96.0%	93	96.9%	
Yes	42	6.4%	7	4.0%	3	3.1%	
Type 1 Diabetes							NS
No	660	100.0%	173	100.0%	96	100.0%	
Yes	0	0.0%	0	0.0%	0	0.0%	
Type 2 Diabetes							NS
No	639	96.8%	170	98.3%	96	100.0%	
Yes	21	3.2%	3	1.7%	0	0.0%	
Ever APO							NS
No	358	54.2%	88	50.9%	47	49.0%	
Yes	302	45.8%	85	49.1%	49	51.0%	
Spontaneous Menopause							< 0.01
No	90	13.6%	51	29.5% *	30	31.3% *	
Yes	570	86.4%	122	70.5% *	66	68.8% *	
Ever VMS							0.03
No	203	30.8% ^a	40	23.1%	20	20.8%	
Yes	457	69.2% ^a	133	76.9%	76	79.2%	
Severity of VMS^b							0.02
None	203	30.8%	40	23.1%	20	20.8%	
Mild	214	32.4%	47	27.2%	32	33.3%	
Moderate-Severe	238	36.1%	86	49.7% *	44	45.8%	
Education							NS
Less than postsecondary	141	21.4%	31	17.9%	21	21.9%	
Postsecondary	519	78.6%	142	82.1%	75	78.1%	

Primary Earner ^c							0.03
No	360	57.1%	115	67.6% *	60	63.2%	
Yes	271	42.9%	55	32.4% *	35	36.8%	

Abbreviations: MHT, menopausal hormone therapy; NS, non-significant; APO, adverse pregnancy outcomes; VMS, vasomotor symptoms

* differs from controls

^a Denotes a proportion significantly different from expected, but pairwise differences are non-significant after Bonferroni adjustment.

^b N=655 for controls

^c N=631 controls, N=170 former, N=95 current

Red bold text used to emphasize statistically significant findings.

3.3.1.2 Objective 2A.2

Results from the ANOVA and Kruskal-Wallis tests examining differences in continuous variables by MHT type are summarized in Table 28. The hypothesis that the tested variables would differ across groups defined by MHT type (controls vs. combined estrogen-progestogen vs. unopposed estrogen usage) was generally not supported, as differences were observed for just 3 of the 17 variables.

Significant differences were observed among MHT type groups in age, age at menopause, and aPWV. Combined estrogen-progestogen users were older (67 [62, 72] years) than controls (63 [60, 67] years). Unopposed estrogen users were younger at the time of menopause (50 [44, 53] years) than controls (53 [51, 55] years). Lastly, the median aPWV was faster among combined estrogen-progestogen users (9.4 [8.6, 10.6] m/s) than in controls (8.8 [8.2, 9.7] m/s). However, these values are still under the 10 m/s threshold identified earlier in this thesis (Table 9). There were no significant differences between groups for any other continuous variable.

The chi-square tests of independence indicated significant associations between MHT type and usage status, spontaneous menopause, history of vasomotor symptoms, severity of vasomotor symptoms, and primary household earner status (Table 29). Combined estrogen-progestogen users were significantly more likely to be former users (90.0%) and less likely to be current users (10.0%) compared to unopposed estrogen users (57.4% former users, 42.6% current users; Figure 5). The prevalence of spontaneous menopause was significantly lower among unopposed estrogen users (53.5%) compared to controls (86.4%), but there was no statistically significant difference from combined estrogen-progestogen users (84.3%) (Figure 6). A history of vasomotor symptoms was significantly more prevalent among combined estrogen-progestogen users (84.3%) compared to controls (69.2%), and they also reported a significantly higher proportion of moderate-to-severe symptoms (60.0%) compared to controls (36.1%). Lastly, there was a significantly lower proportion of unopposed estrogen users who reported being the primary household earner (28.7%) compared to controls (42.9%).

Table 28. Group Differences in Continuous Variables by MHT Type.

Variable	Controls N=660	Combined Estrogen- Progestogen N=70	Unopposed Estrogen N=101	Omnibus p- value	Effect size
Age (years)	63 [60, 67]	67 [62, 72] *	64 [60, 69]	< 0.01	$\varepsilon^2=0.02$
BMI (kg/m ²)	25.8 [23.2, 29.7]	25.8 [22.9, 28.3]	26.7 [23.8, 29.3]	0.40	$\varepsilon^2=0.00$
Mean arterial pressure (mmHg)	97 (11)	98 (11)	97 (11)	0.71	$\eta^2=0.00$
Age at menopause (years)	53 [51, 55]	52 [47, 54]	50 [44, 53] *	< 0.01	$\varepsilon^2=0.04$
MVPA (avg. mins/day)	21.2 [9.7, 38.4]	16.8 [7.4, 33.3]	17.7 [8.0, 30.8]	0.09	$\varepsilon^2=0.00$
StaB (avg. hours/day)	12.1 (1.6)	12.0 (1.8)	12.2 (1.5)	0.74	$\eta^2=0.00$
Sleep (avg. hours/day)	6.5 (0.9)	6.6 (1.0)	6.4 (0.8)	0.50	$\eta^2=0.00$
aPWV (m/s)	8.8 [8.2, 9.7]	9.4 [8.6, 10.6] *	8.9 [8.3, 9.8]	< 0.01	$\varepsilon^2=0.01$
AIx75 (%)	21.3 [13.7, 28.7]	24.2 [13.0, 30.2]	22.3 [13.3, 28.0]	0.58	$\varepsilon^2=0.00$
SBP (mmHg)	122 (14)	123 (15)	121 (15)	0.53	$\eta^2=0.00$
DBP (mmHg)	77 (10)	77 [70, 83]	77 [68, 83]	0.78	$\eta^2=0.00$
FRS (%)	6.3 [3.9, 8.6]	6.3 [3.9, 8.6]	5.3 [3.9, 8.6]	0.73	$\varepsilon^2=0.00$
WC (cm)	92.6 [85, 102.5]	92.3 [86.0, 99.9]	94.5 [85.3, 101.8]	0.56	$\varepsilon^2=0.00$
HDL-C (mmol/L)	1.67 [1.40, 2.03]	1.68 [1.40, 1.91]	1.79 [1.54, 2.14]	0.06	$\varepsilon^2=0.00$
LDL-C (mmol/L)	3.32 (0.87)	3.28 (0.76)	3.14 (0.77)	0.16	$\eta^2=0.00$
TG (mmol/L)	0.99 [0.75, 1.33]	1.05 [0.86, 1.41]	0.88 [0.74, 1.28]	0.05	$\varepsilon^2=0.00$
Glucose (mmol/L)	5.67 [5.35, 6.02]	5.64 [5.39, 5.92]	5.55 [5.33, 5.90]	0.67	$\varepsilon^2=0.00$

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Age at menopause: N = 585 (never); 65 (combined); 90 (unopposed estrogen)

Glucose: N=659 (controls)

Outcomes reported as Mean (SD) or Median [Q1, Q3]

*p < 0.05 compared to controls

†p < 0.05 compared to combined estrogen-progestogen users

Red bold text used to emphasize statistically significant findings.

Table 29. Group Differences in Categorical Variables by MHT Type.

Variable	Controls (N=660)		Combined Estrogen-Progestogen (N=70)		Unopposed Estrogen (N=101)		P-Value
	Freq.	%	Freq.	%	Freq.	%	
MHT Usage							< 0.01
Former	--	--	63	90.0%	58	57.4% †	
Current	--	--	7	10.0%	43	42.6% †	
History of Hypertension							NS
No	503	76.2%	57	81.4%	79	78.2%	
Yes	157	23.8%	13	18.6%	22	18.6%	
Sleep Apnea							NS
No	618	93.6%	68	97.1%	97	96.0%	
Yes	42	6.4%	2	2.9%	4	4.0%	
Type 1 Diabetes							NS
No	660	100.0%	70	100.0%	101	100.0%	
Yes	0	0.0%	0	0.0%	0	0.0%	
Type 2 Diabetes							NS
No	639	96.8%	69	98.6%	100	99.0%	
Yes	21	3.2%	1	1.4%	1	1.0%	
Ever APO							NS
No	358	54.2%	34	48.6%	52	51.5%	
Yes	302	45.8%	36	51.4%	49	48.5%	
Spontaneous Menopause							< 0.01
No	90	13.6%	11	15.7%	47	46.5% *	
Yes	570	86.4%	59	84.3%	54	53.5% *	
Ever VMS							0.02
No	203	30.8%	11	15.7% *	25	24.8%	
Yes	457	69.2%	59	84.3% *	76	75.2%	
Severity of VMS^a							< 0.01
None	203	30.8%	11	15.7% *	25	24.8%	
Mild	214	32.4%	17	24.3%	32	31.7%	

Moderate-Severe	238	36.1%	42	60.0% *	44	43.6%	NS
Education							
Less than postsecondary	141	21.4%	13	18.6%	23	22.8%	
Postsecondary	519	78.6%	57	81.4%	78	77.2%	
Primary Earner ^b							0.02
No	360	57.1%	45	65.2%	71	70.3%	
Yes	271	42.9%	24	34.8%	29	28.7%	

Abbreviations: MHT, menopausal hormone therapy; NS, non-significant; APO, adverse pregnancy outcomes; VMS, vasomotor symptoms

* Differs from controls

† Differs from combined estrogen-progestogen users

^a N=655 for controls

^b N=631 controls, N=69 combined, N=100 former

Red bold text used to emphasize statistically significant findings.

Figure 5. MHT Type by Usage History Status

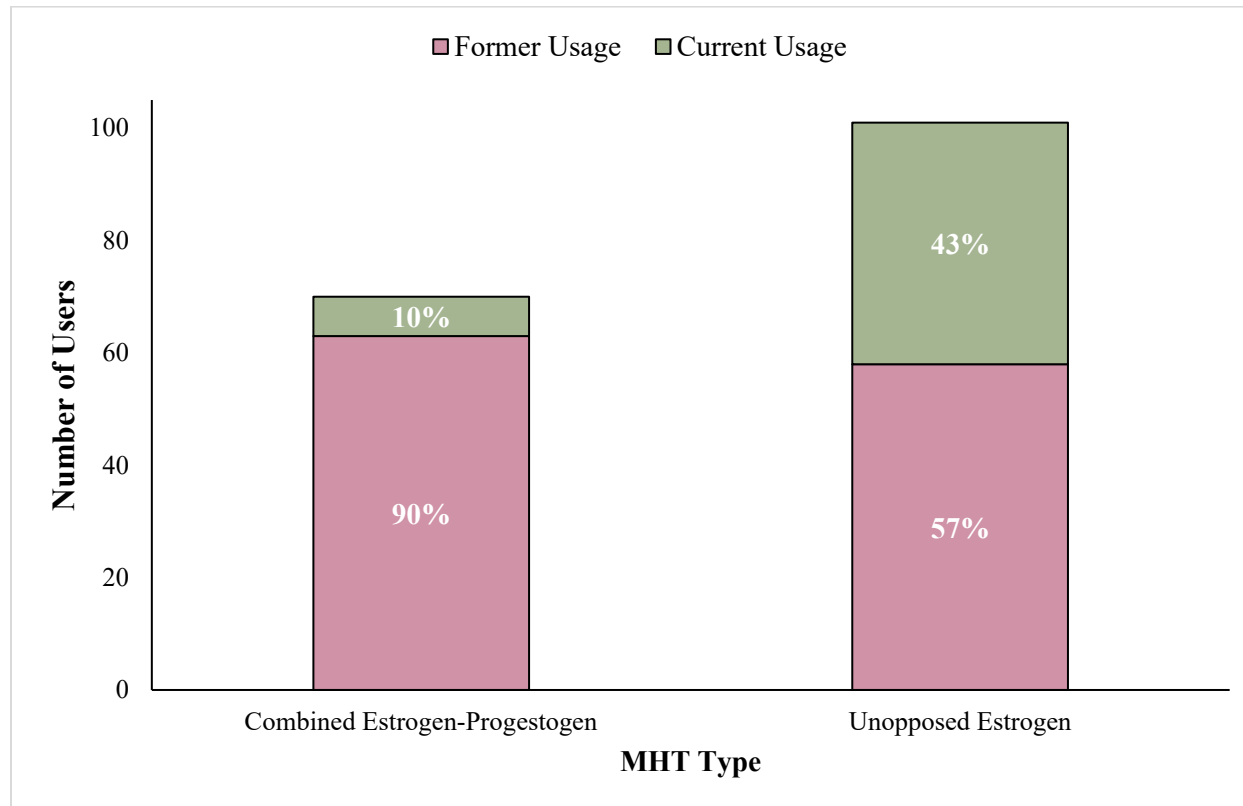
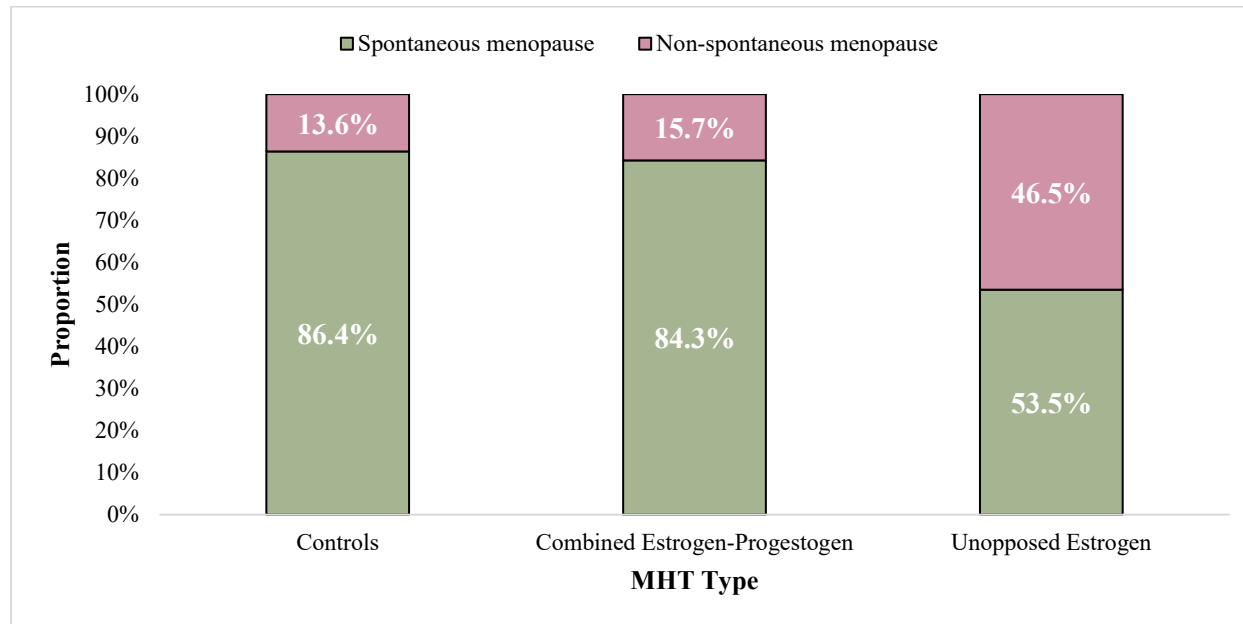


Figure 6. Type of Menopause by Type of MHT.



3.3.1.3 Objective 2A.3

Results from the ANOVA and Kruskal-Wallis tests examining differences in continuous variables by MHT route of administration are summarized in Table 30. The hypothesis that the tested variables would differ across groups defined by MHT route of administration (controls vs. oral vs. transdermal vs. vaginal) was generally not supported, as differences were observed for only 5 of the 17 variables.

Significant differences between groups defined by route of MHT administration were observed for age, age at menopause, MVPA, aPWV, and FRS. Oral users were older (67 [62, 72] years) than controls (63 [60, 67] years) and vaginal users (64 [60, 66] years). Controls were older at the time of menopause (53 [51, 55] years) compared to oral users (51 [46, 54] years) and transdermal users (50 [45, 54] years). Similar to Objective 2A.1, controls averaged higher daily MVPA (21.2 [9.7, 38.4] mins/day) than oral users (16.0 [6.8, 25.6] mins/day). These values correspond to 148.4 [67.9, 268.8] mins/week for controls, and 112.0 [47.6, 179.2] mins/week for oral users.

The median aPWV was faster among oral users (9.6 [8.6, 10.6] m/s) than vaginal users (8.8 [8.3, 9.3] m/s) and controls (8.8 m/s [8.2, 9.7] m/s); all values are within the suggested normal range (Table 9). Lastly, although the omnibus Kruskal-Wallis test suggested significant differences in FRS across groups, the post-hoc tests did not reach statistical significance. There were no significant differences between groups for any other continuous variable.

The chi-square tests of independence indicated significant associations between MHT route and ever-usage status and spontaneous menopause (Table 31). Among the vaginal MHT users, there was a significantly higher prevalence of current users (68.9%) and lower prevalence of former users (31.1%) compared to both oral MHT users (16.5% current, 83.5% former) and transdermal MHT users (25.5% current, 74.5% former) (Figure 7a; Figure 7b). Compared to controls, experiencing spontaneous menopause was significantly less prevalent among oral MHT users (69.1%) and transdermal MHT users (53.2%) compared to controls (86.4%). The proportion of vaginal MHT users who experienced spontaneous menopause (75.4%) did not differ statistically from any of the other three groups. Lastly, the omnibus test for vasomotor symptom severity was non-significant, but post-hoc comparisons indicated a difference: oral

users reported a significantly higher prevalence of moderate-to-severe symptoms (51.5%) compared to the control group (36.1%).

Table 30. Group Differences by MHT Route.

Variable	Controls (N=660)	Oral (N=97)	Transdermal (N=47)	Vaginal (N=61)	Omnibus p-value	Effect size
Age (years)	63 [60, 67]	67 [62, 72] *	65 [60.5, 70]	64 [60, 66] †	< 0.01	$\epsilon^2=0.03$
BMI (kg/m ²)	25.8 [23.2, 29.7]	25.2 [23.2, 28.9]	26.6 [23.6, 28.8]	26.1 [23.1, 28.7]	0.72	$\epsilon^2=0.00$
Mean arterial pressure (mmHg)	97 (11)	97.7 (11.9)	98 (10)	96.7 (12.9)	0.92	$\eta^2=0.00$
Age at menopause (years)	53 [51, 55]	51 [45.5, 53.5] *	50 [44.5, 53.5] *	52 [48, 54]	< 0.01	$\epsilon^2=0.03$
MVPA (avg. mins/day)	21.2 [9.7, 38.4]	16.0 [6.8, 25.6] *	17.5 [5.8, 34.5]	20.6 [10.5, 39.1]	0.02	$\epsilon^2=0.01$
StaB (avg. hours/day)	12.1 (1.6)	12.3 (1.6)	12.1 (1.8)	12.0 (1.6)	0.73	$\eta^2=0.00$
Sleep (avg. hours/day)	6.5 (0.9)	6.5 (0.9)	6.5 (0.7)	6.5 (0.8)	0.87	$\eta^2=0.00$
aPWV (m/s)	8.8 [8.2, 9.7]	9.6 [8.6, 10.6] *	9.2 [8.4, 9.8]	8.8 [8.3, 9.3] †	< 0.01	$\epsilon^2=0.03$
AIx75 (%)	21.3 [13.7, 28.7]	21.3 [12.0, 30.3]	23.7 [13.2, 29.8]	22.3 [14.3, 28.0]	0.97	$\epsilon^2=0.00$
SBP (mmHg)	122 (14)	123 (15)	124 (13)	119 (16)	0.32	$\eta^2=0.00$
DBP (mmHg)	77 (10)	76 [70, 83]	76 [70, 81]	78 [67, 84]	0.91	$\eta^2=0.00$
FRS (%)	6.3 [3.9, 8.6]	6.3 [4.5, 8.6]	6.3 [4.5, 8.6]	5.3 [3.9, 6.3]	0.04	$\epsilon^2=0.01$
WC (cm)	92.6 [85, 102.5]	90.5 [83.3, 100.1]	95.5 [88.0, 103.4]	92.8 [84.8, 100.0]	0.42	$\epsilon^2=0.00$
HDL-C (mmol/L)	1.67 [1.40, 2.03]	1.69 [1.50, 2.06]	1.77 [1.44, 2.01]	1.73 [1.47, 1.94]	0.69	$\epsilon^2=0.00$
LDL-C (mmol/L)	3.32 (0.87)	3.20 (0.75)	3.31 (0.81)	3.33 (0.89)	0.51	$\eta^2=0.00$
TG (mmol/L)	0.99 [0.75, 1.33]	0.97 [0.76, 1.35]	0.96 [0.79, 1.30]	0.94 [0.78, 1.28]	1.00	$\epsilon^2=0.00$
Glucose (mmol/L)	5.67 [5.35, 6.02]	5.65 [5.38, 6.06]	5.70 [5.45, 5.95]	5.59 [5.39, 5.79]	0.56	$\epsilon^2=0.00$

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Age at menopause: N = 585 (never); 37 (oral estrogen); 37 (transdermal estrogen); 59 (vaginal estrogen)

Glucose: N=659 (controls)

Outcomes reported as Mean (SD) or Median [IQR]

*p < 0.05 compared to controls

†p < 0.05 compared to oral users

Red bold text used to emphasize statistically significant findings.

Table 31. Group Differences in Categorical Variables by MHT Route.

Variable	Controls (N=660)		Oral (N=97)		Transdermal (N=47)		Vaginal (N=61)		P-Value
	Freq.	%	Freq.	%	Freq.	%	Freq.	%	
Usage									< 0.01
Former	--	--	81	83.5%	35	74.5%	19	31.1% ††	
Current	--	--	16	16.5%	12	25.5%	42	68.9% ††	
History of Hypertension									NS
No	503	76.2%	78	80.4%	34	72.3%	52	85.2%	
Yes	157	23.8%	19	19.6%	13	27.7%	9	14.8%	
Sleep Apnea									NS
No	618	93.6%	92	94.8%	46	97.9%	60	98.4%	
Yes	42	6.4%	5	5.2%	1	2.1%	1	1.6%	
Type 1 Diabetes									NS
No	660	100.0%	97	100.0%	47	100.0%	61	100.0%	
Yes	0	0.0%	0	0.0%	0	0.0%	0	0.0%	
Type 2 Diabetes									NS
No	639	96.8%	95	97.9%	46	97.9%	61	100.0%	
Yes	21	3.2%	2	2.1%	1	2.1%	0	0.0%	
Ever APO									NS
No	358	54.2%	53	54.6%	23	48.9%	33	54.1%	
Yes	302	45.8%	44	45.4%	24	51.1%	28	45.9%	
Spontaneous Menopause									< 0.01
No	90	13.6%	30	30.9% *	22	46.8% *	15	24.6%	
Yes	570	86.4%	67	69.1% *	25	53.2% *	46	75.4%	
Ever VMS									NS
No	203	30.8%	21	21.6%	10	21.3%	16	26.2%	
Yes	457	69.2%	76	78.4%	37	78.7%	45	73.8%	
Severity of VMS ^a									NS ^b
None	203	30.8%	21	21.6%	10	21.3%	16	26.2%	
Mild	214	32.4%	26	26.8%	14	29.8%	21	34.4%	
Moderate-Severe	238	36.1%	50	51.5% *	23	48.9%	24	39.3%	

Education									NS
Less than postsecondary	141	21.4%	25	25.8%	11	23.4%	8	13.1%	
Postsecondary	519	78.6%	72	74.2%	36	76.6%	53	86.9%	
Primary Earner ^c									NS
No	360	57.1%	63	66.3%	32	69.6%	42	68.9%	
Yes	271	42.9%	32	33.7%	14	30.4%	19	31.1%	

Abbreviations: MHT, menopausal hormone therapy; NS, non-significant; APO, adverse pregnancy outcomes; VMS, vasomotor symptoms

* differs from controls

[†] differs from oral users

[‡] differs from transdermal users

^a N=655 for controls

^b Pearson chi-square NS, but significant differences in column proportions indicated

^c N=631 controls, N=95 oral, N=46 transdermal

Red bold text used to emphasize statistically significant findings.

Figure 7a. Usage History Status of MHT Routes.

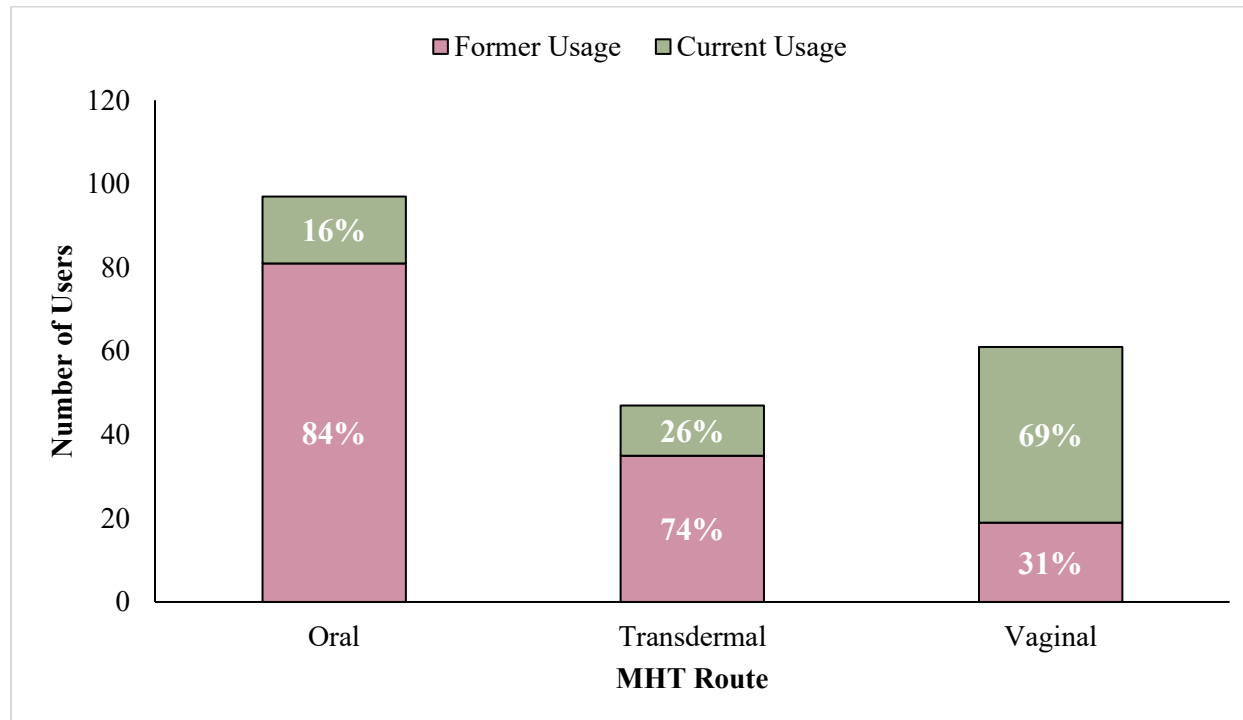
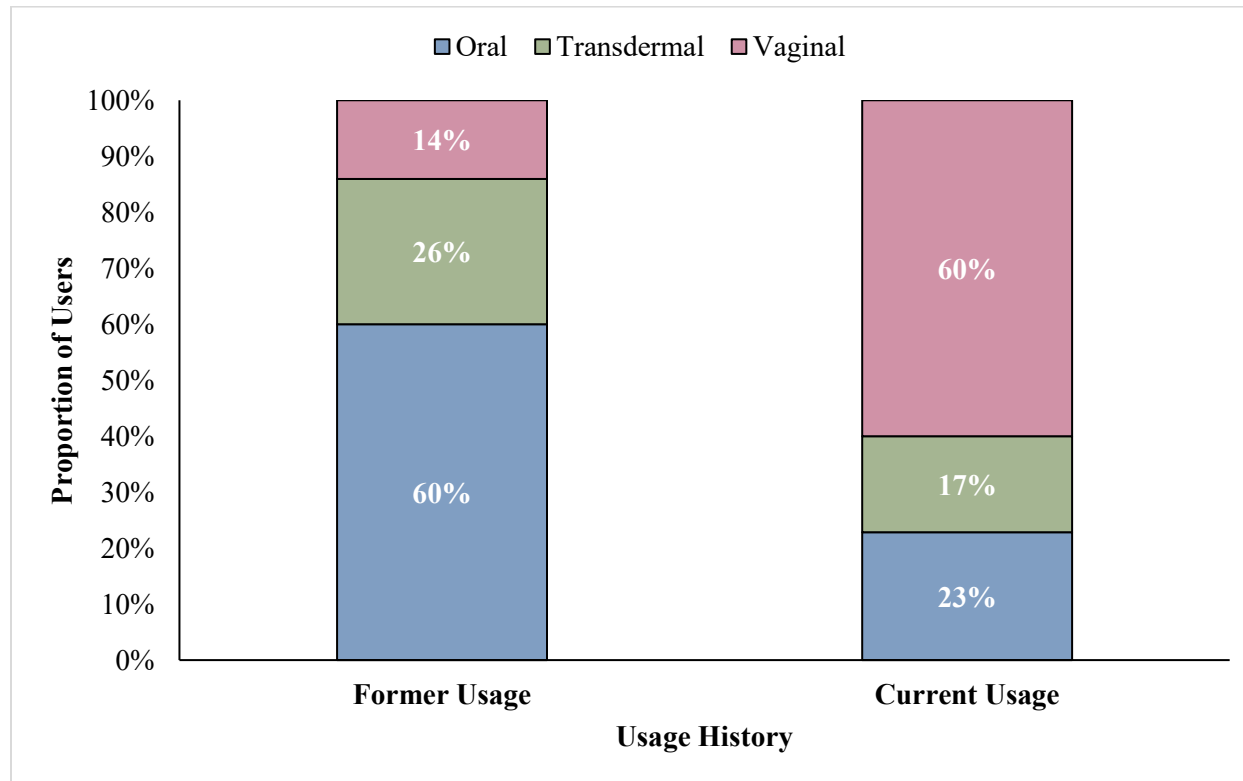


Figure 7b. Proportion of MHT Route by Former and Current Users



3.3.1.4 Summary of Objective 2A.

The hypothesis that demographic characteristics, movement behaviours, and CV outcomes would differ across groups defined by various MHT exposure definitions was not supported, as only 3 to 6 of the tested variables differed across groups.

Across the three MHT exposure definitions, age was a consistent differentiating factor between groups. In each categorization, controls were significantly younger than one MHT group (former users for 2A.1, combined estrogen-progestogen users for 2A.2, and oral users for 2A.3). Former users were also older than current users, and oral users were older than vaginal users. There were no age differences between users of combined estrogen-progestogen and unopposed estrogen. MHT users were also generally younger at menopause than never users, consistent with expected patterns of MHT initiation based on current Canadian, North American, and international recommendations.^{20,22,24} Notably, the oldest group in each categorization also exhibited faster aPWV than younger groups. In other words, differences in arterial stiffness paralleled age distributions across exposure definitions.

There were also patterns in movement behaviours across groups – in particular, differences in MVPA. Former users (Objective 2A.1) and oral users (Objective 2A.2) engaged in less MVPA than controls. Moreover, the median control participant nearly met the Canadian 24-hour movement guidelines of 150 mins/week, whereas the median former users and oral users were approximately 30-38 minutes below the weekly target, respectively.⁷⁶ Another way of framing this is that controls achieved 99% of the recommended weekly amount, while former users and oral users met 80% and 75% of the recommended amount, respectively.

Current users had lower FRS than former users, and while route-based post hoc tests were not significant, vaginal users had the lowest median FRS value. Finally, across all exposure definitions, there were no significant differences in AIX75, SBP, DBP, WC, HDL-C, LDL-C, TG, BMI, or mean arterial pressure. Overall, group differences were mainly demographic and behavioural, with comparatively less evidence of CV differences across MHT exposure categories.

3.3.2 Objective 2B

Objective 2B extends the regression analyses from Objective 1D.2 and 1D.3 by examining CV outcomes by MHT history (2B.1), MHT type (2B.2), and route (2B.3). The regression models continue to use the hierarchical approach to evaluate the extent to which movement behaviours improve model fit beyond covariates and MHT usage, and to compare the relative explanatory value of individual MHT and movement behaviour predictors.

Unadjusted and adjusted regression models were constructed within the full sample and among MHT users only. Unadjusted models were structured in 2 blocks: MHT exposures first (Block 1) followed by movement behaviours (MVPA, StaB, and sleep duration; Block 2) (see Figure 2). Adjusted models were structured into 3 blocks: covariates first (Block 1), then MHT exposures (Block 2), and finally movement behaviours (Block 3) (see Figure 3). Unadjusted and adjusted models are first described in the full sample and then among MHT users only.

The Objective 2B hypothesis that movement behaviours would improve model fit beyond covariates and MHT exposures, and that individual behaviours would be more strongly associated with outcomes than MHT exposures, was broadly supported.

3.3.2.1 Objective 2B.1

The hypothesis for Objective 2B.1 (that movement behaviours would explain a greater proportion of variance in CV outcomes beyond MHT history exposures and covariates, and that individual behaviours would be more strongly associated with outcomes than MHT history) was supported.

Full Sample: Unadjusted Models

Former and current MHT usage were entered in Block 1, with controls (never users) serving as the reference group.

Model fit statistics for unadjusted models are presented in Appendix Table 2a. MHT usage history (Block 1) significantly improved model fit beyond the null for three outcomes: aPWV, logFRS, and logGlucose. Adding movement behaviours (Block 2) significantly improved model fit beyond MHT usage history for all outcomes except for LDL-C. For primary outcomes, these behaviours provided substantial incremental explanatory value, most notably for aPWV

(Adj. R² increased from 0.04 to 0.09; $p < 0.01$; $\Delta AIC = -50.4$) and logFRS (Adj. R² increased from 0.01 to 0.04; $p < 0.01$; $\Delta AIC = -26.2$). Among secondary outcomes, the impact of movement behaviours was particularly pronounced for WC (Adj. R² increased from 0.00 to 0.07; $p < 0.01$; $\Delta AIC = -67.3$) and HDL-C (Adj. R² increased from 0.00 to 0.04; $p < 0.01$; $\Delta AIC = -32.2$).

MHT usage history was independently associated with aPWV, logFRS, and logGlucose (Appendix Table 2b). Relative to controls, former usage was associated with faster aPWV ($\beta = 0.17$, 95% CI [0.11, 0.24]), while current usage was associated with lower logFRS ($\beta = -0.08$, 95% CI [-0.15, -0.02]) and lower logGlucose ($\beta = -0.09$; 95% CI [-0.16, -0.03]). However, compared to MHT history exposures, movement behaviours (particularly MVPA) had more consistent and generally stronger associations with outcomes (Appendix Table 2b). MVPA was favourably associated with all outcomes (except LDL-C, for which it was positively associated). Noteworthy examples include its association with slower aPWV ($\beta = -0.17$, 95% CI [-0.24, -0.10]), lower logFRS ($\beta = -0.16$, 95% CI [-0.24, -0.09]), and lower logGlucose ($\beta = -0.10$, 95% CI [-0.18, 0.03]). StaB was also associated with slower aPWV, lower DBP, and lower HDL-C (Appendix Table 2b). Sleep duration was not associated with any outcome.

Full Sample: Adjusted Models

In adjusted models for Objective 2B.1, former and current MHT usage were entered in Block 2 after the covariates (Block 1), with controls serving as the reference group.

Model fit statistics for the adjusted hierarchical models are summarized in Table 32a. In Block 1, the inclusion of covariates significantly improved model fit beyond the null for all outcomes except AIX75 and DBP, accounting for 1-5% of the observed variance. The addition of MHT history in Block 2 provided further explanatory value for aPWV and logFRS, bringing the total explained variance to 7% and 3%, respectively (both $p < 0.01$; $\Delta AIC = -40.3$ and -12.6 , respectively). MHT history did not, however, significantly improve models for any other outcome beyond the initial covariates.

The subsequent addition of movement behaviours (Block 3) significantly improved model fit for all outcomes except LDL-C and logGlucose (Table 32b; Figure 8). This block yielded substantial gains in explained variance for aPWV (7% to 11%), WC (6% to 12%), and

HDL-C (3% to 7%). Small but statistically significant increases were also observed in AIx75, SBP, DBP, logFRS, and logTG. Across these models, the consistent reduction in AIC values affirms that movement behaviours provide salient incremental explanatory power beyond demographic, medical, and pharmacological history.

The inclusion of covariates did not negate the significant associations between MHT history exposures and CV outcomes (Table 32b). Relative to controls, former MHT usage was still associated with faster aPWV ($\beta = 0.20$, 95% CI [0.13, 0.27]), and current MHT usage was still associated with lower logFRS ($\beta = -0.11$, 95% CI [-0.18, -0.04]) and logGlucose ($\beta = -0.07$; 95% CI [-0.14, 0.00]). Notably, current MHT usage also demonstrated a newly significant independent association with lower SBP following adjustment ($\beta = -0.08$, 95% CI [-0.15, -0.01]).

In contrast, covariate adjustment partially attenuated the independent associations between movement behaviours and CV outcomes. MVPA maintained robust associations with the majority of outcomes. For example, higher average MVPA was associated with slower aPWV ($\beta = -0.17$, 95% CI [-0.24, -0.09]), lower logFRS ($\beta = -0.15$, 95% CI [-0.23, -0.07]), and lower logGlucose ($\beta = -0.10$, 95% CI [-0.17, -0.02]). However, MVPA was no longer significantly associated with LDL-C or logTG after adjusting for covariates. Greater amounts of StaB were still independently associated with faster aPWV ($\beta = 0.08$, 95% CI [0.00, 0.17]), lower DBP, and lower HDL-C. Sleep continued to have no associations with any outcome.

The covariates were also independently associated with the outcomes. Older age was associated with higher SBP, smaller WC, higher HDL-C, lower LDL-C, and lower logTG. Older age at menopause was associated with higher logGlucose. Women who experienced spontaneous menopause had a smaller WC, higher HDL-C, lower logTG, and lower logGlucose than those who experienced other forms of menopause, such as surgically induced menopause. Having a history of vasomotor symptoms was independently associated with slower aPWV and lower AIx75. Having a postsecondary education was associated with lower DBP, smaller WC, and higher HDL-C compared with a high school education or no degree, certificate, or diploma. Lastly, self-identifying as the primary household earner was associated with larger WC, lower HDL-C, and lower LDL-C.

Table 32a. Model Fit Accounting for MHT Usage History in the Full Sample

Outcome	Block	N	R ²	Full Sample Adj. R ²	P Value for change in F	AIC	ΔAIC
aPWV	Block 1	795	0.03	0.02	< 0.01	2443.3	
	Block 2		0.08	0.07	< 0.01	2403.0	-40.3
	Block 3		0.12	0.11	< 0.01	2370.3	-32.7
AIx75	Block 1	795	0.01	0.01	0.08	5944.2	
	Block 2		0.02	0.01	0.15	5944.4	0.2
	Block 3		0.03	0.02	0.01	5938.5	-5.9
SBP	Block 1	795	0.03	0.02	< 0.01	6447.4	
	Block 2		0.03	0.02	0.06	6445.6	-1.8
	Block 3		0.04	0.03	0.03	6442.2	-3.4
DBP	Block 1	795	0.01	0.01	0.12	5943.7	
	Block 2		0.02	0.01	0.11	5943.3	-0.4
	Block 3		0.03	0.02	0.01	5937.6	-5.7
logFRS	Block 1	795	0.02	0.01	0.01	1226.2	
	Block 2		0.04	0.03	< 0.01	1213.6	-12.6
	Block 3		0.06	0.05	< 0.01	1199.9	-13.8
WC	Block 1	795	0.06	0.05	< 0.01	6330.4	
	Block 2		0.06	0.06	0.16	6330.7	0.3
	Block 3		0.13	0.12	< 0.01	6279.0	-51.7
HDL-C	Block 1	795	0.04	0.03	< 0.01	947.5	
	Block 2		0.04	0.03	0.92	951.3	3.8
	Block 3		0.08	0.07	< 0.01	922.6	-28.7
LDL-C	Block 1	795	0.02	0.01	0.01	2008.6	
	Block 2		0.02	0.01	0.71	2011.9	3.3
	Block 3		0.03	0.01	0.33	2014.4	2.5
logTG	Block 1	795	0.03	0.02	< 0.01	862.9	
	Block 2		0.03	0.02	0.87	866.6	3.7
	Block 3		0.04	0.03	0.03	863.5	-3.1
logGlucose	Block 1	794	0.03	0.02	< 0.01	-1086.7	

Block 2	0.04	0.03	0.09	-1087.6	-0.9
Block 3	0.05	0.03	0.13	-1087.3	0.3

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: Former, Current Usage entered

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 or Block 2;

Red bold text used to emphasize statistically significant changes in Block 3.

Table 32b. Coefficients in Models Accounting for MHT Usage History in the Full Sample

Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	-0.01 [-0.03, 0.00]	-0.06 [-0.13, 0.01]	
	Spontaneous menopause	0.20 [-0.01, 0.41]	0.07 [0.00, 0.14]	
	History of VMS	-0.30 [-0.47, -0.13]	-0.12 [-0.18, -0.05]	*
	Postsecondary education	-0.09 [-0.27, 0.10]	-0.03 [-0.10, 0.04]	
	Primary earner status	0.04 [-0.11, 0.19]	0.02 [-0.05, 0.08]	
	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.17 [-0.24, -0.09]	*
	StaB (hours)	0.06 [0.00, 0.12]	0.08 [0.00, 0.17]	*
	Sleep duration (hours)	0.04 [-0.06, 0.14]	0.03 [-0.04, 0.10]	
	Controls (MHT reference group)			
	Former Usage	0.58 [0.38, 0.78]	0.20 [0.13, 0.27]	*
AIx75	Current Usage	-0.15 [-0.40, 0.10]	-0.04 [-0.11, 0.03]	
	Age at menopause (years)	-0.12 [-0.27, 0.02]	-0.06 [-0.14, 0.01]	
	Spontaneous menopause	0.41 [-1.57, 2.39]	0.02 [-0.06, 0.09]	
	History of VMS	-1.78 [-3.38, -0.17]	-0.08 [-0.15, -0.01]	*
	Postsecondary education	-0.25 [-1.98, 1.48]	-0.01 [-0.08, 0.06]	
	Primary earner status	-0.62 [-2.07, 0.83]	-0.03 [-0.10, 0.04]	
	MVPA (mins)	-0.04 [-0.08, 0.00]	-0.08 [-0.16, 0.00]	*

SBP	StaB (hours)	0.40 [-0.15, 0.95]	0.06 [-0.02, 0.15]	
	Sleep duration (hours)	0.35 [-0.61, 1.31]	0.03 [-0.05, 0.11]	
	Controls (MHT reference group)			
	Former Usage	0.48 [-1.39, 2.34]	0.02 [-0.05, 0.09]	
	Current Usage	-1.87 [-4.24, 0.51]	-0.06 [-0.13, 0.02]	
	Age (years)	0.27 [0.09, 0.44]	0.11 [0.04, 0.19]	*
	Age at menopause (years)	-0.03 [-0.23, 0.18]	-0.01 [-0.08, 0.07]	
	Spontaneous menopause	-0.17 [-2.89, 2.55]	0.00 [-0.08, 0.07]	
	History of VMS	-0.99 [-3.21, 1.23]	-0.03 [-0.10, 0.04]	
	Postsecondary education	-1.85 [-4.22, 0.53]	-0.05 [-0.12, 0.02]	
	Primary earner status	0.08 [-1.91, 2.08]	0.00 [-0.07, 0.07]	
	MVPA (mins)	-0.08 [-0.13, -0.03]	-0.12 [-0.20, -0.04]	*
	StaB (hours)	-0.67 [-1.42, 0.09]	-0.08 [-0.16, 0.01]	
	Sleep duration (hours)	-0.34 [-1.66, 0.98]	-0.02 [-0.10, 0.06]	
DBP	Controls (MHT reference group)			
	Former Usage	0.88 [-1.75, 3.51]	0.02 [-0.05, 0.10]	
	Current Usage	-3.63 [-6.89, -0.38]	-0.08 [-0.15, -0.01]	*
	Age (years)	-0.11 [-0.24, 0.02]	-0.06 [-0.14, 0.01]	
	Age at menopause (years)	-0.10 [-0.25, 0.04]	-0.05 [-0.13, 0.02]	
	Spontaneous menopause	0.12 [-1.86, 2.10]	0.00 [-0.07, 0.08]	
	History of VMS	-0.15 [-1.77, 1.46]	-0.01 [-0.08, 0.06]	
	Postsecondary education	-1.75 [-3.48, -0.02]	-0.07 [-0.14, 0.00]	*
	Primary earner status	0.56 [-0.89, 2.01]	0.03 [-0.04, 0.10]	
	MVPA (mins)	-0.05 [-0.09, -0.01]	-0.10 [-0.18, -0.02]	*
	StaB (hours)	-0.84 [-1.39, -0.29]	-0.13 [-0.22, -0.05]	*
	Sleep duration (hours)	-0.22 [-1.18, 0.75]	-0.02 [-0.10, 0.06]	
	Controls (MHT reference group)			
	Former Usage	0.20 [-1.71, 2.11]	0.01 [-0.07, 0.08]	
	Current Usage	-2.58 [-4.95, -0.21]	-0.08 [-0.15, -0.01]	*
logFRS	Age at menopause (years)	0.00 [-0.01, 0.00]	-0.03 [-0.11, 0.04]	
	Spontaneous menopause	-0.02 [-0.12, 0.08]	-0.01 [-0.09, 0.06]	
	History of VMS	-0.06 [-0.14, 0.03]	-0.05 [-0.12, 0.02]	

WC	Postsecondary education	-0.12 [-0.21, -0.04]	-0.10 [-0.16, -0.03]	*
	Primary earner status	0.02 [-0.05, 0.10]	0.02 [-0.05, 0.09]	
	MVPA (mins)	0.00 [-0.01, 0.00]	-0.15 [-0.23, -0.07]	*
	StaB (hours)	0.00 [-0.02, 0.03]	0.01 [-0.07, 0.10]	
	Sleep duration (hours)	0.01 [-0.04, 0.06]	0.01 [-0.06, 0.09]	
	Controls (MHT reference group)			
	Former Usage	0.08 [-0.02, 0.17]	0.06 [-0.01, 0.13]	
	Current Usage	-0.20 [-0.32, -0.07]	-0.11 [-0.18, -0.04]	*
	Age (years)	-0.37 [-0.53, -0.22]	-0.17 [-0.24, -0.10]	*
	Age at menopause (years)	0.07 [-0.11, 0.25]	0.03 [-0.04, 0.10]	
	Spontaneous menopause	-4.06 [-6.52, -1.61]	-0.12 [-0.19, -0.05]	*
	History of VMS	-1.28 [-3.28, 0.73]	-0.04 [-0.11, 0.02]	
	Postsecondary education	-2.66 [-4.80, -0.52]	-0.08 [-0.15, -0.02]	*
	Primary earner status	3.26 [1.46, 5.06]	0.12 [0.05, 0.19]	*
	MVPA (mins)	-0.15 [-0.20, -0.10]	-0.24 [-0.32, -0.17]	*
	StaB (hours)	0.18 [-0.50, 0.86]	0.02 [-0.06, 0.11]	
	Sleep duration (hours)	-1.06 [-2.25, 0.13]	-0.07 [-0.14, 0.01]	
	Controls (MHT reference group)			
	Former Usage	0.50 [-1.87, 2.87]	0.01 [-0.06, 0.09]	
	Current Usage	-2.50 [-5.44, 0.45]	-0.06 [-0.12, 0.01]	
HDL-C	Age (years)	0.01 [0.01, 0.02]	0.14 [0.07, 0.21]	*
	Age at menopause (years)	0.00 [-0.01, 0.00]	-0.04 [-0.11, 0.04]	
	Spontaneous menopause	0.14 [0.05, 0.22]	0.12 [0.04, 0.19]	*
	History of VMS	0.02 [-0.05, 0.09]	0.02 [-0.05, 0.08]	
	Postsecondary education	0.09 [0.01, 0.16]	0.08 [0.01, 0.15]	*
	Primary earner status	-0.07 [-0.13, 0.00]	-0.07 [-0.14, 0.00]	*
	MVPA (mins)	0.00 [0.00, 0.00]	0.11 [0.03, 0.19]	*
	StaB (hours)	-0.04 [-0.06, -0.01]	-0.14 [-0.22, -0.05]	*
	Sleep duration (hours)	-0.01 [-0.05, 0.03]	-0.01 [-0.09, 0.06]	
	Controls (MHT reference group)			
	Former Usage	-0.01 [-0.09, 0.08]	0.00 [-0.08, 0.07]	
	Current Usage	0.01 [-0.10, 0.11]	0.00 [-0.07, 0.07]	

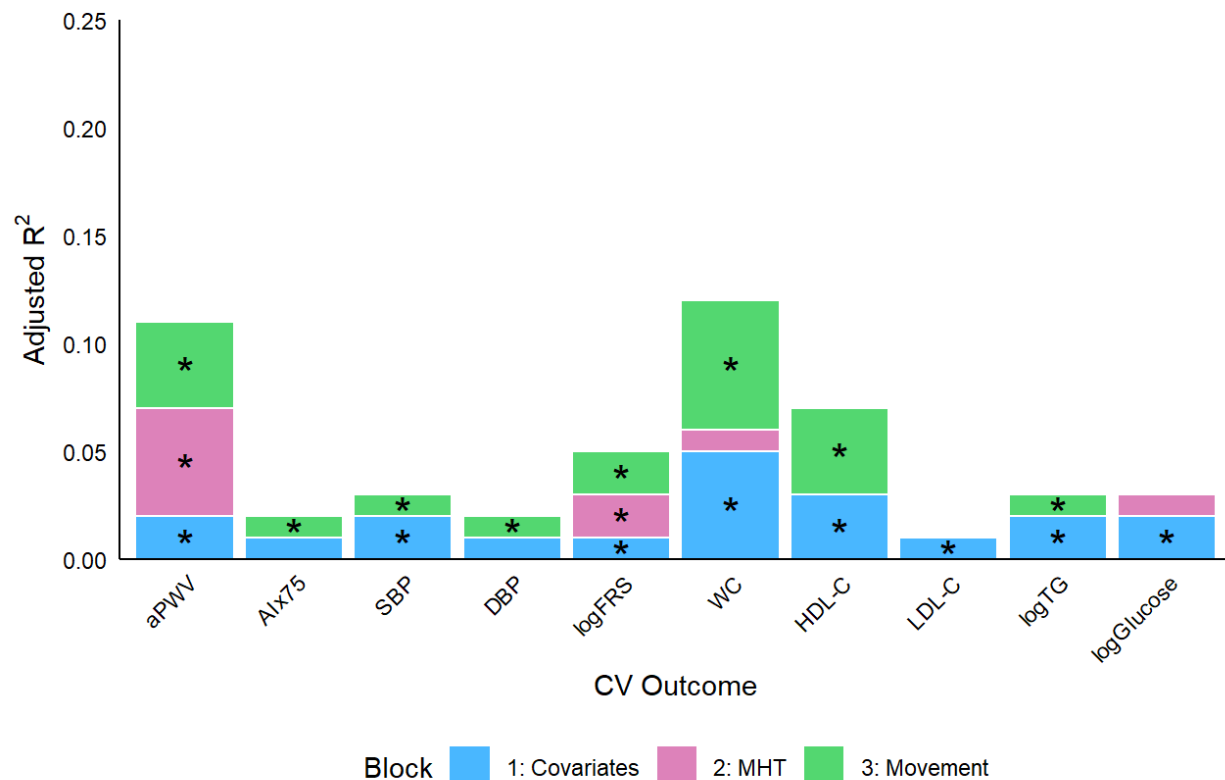
LDL-C	Age (years)	-0.02 [-0.03, -0.01]	-0.12 [-0.19, -0.04]	*
	Age at menopause (years)	0.00 [-0.01, 0.01]	-0.01 [-0.09, 0.06]	
	Spontaneous menopause	0.02 [-0.15, 0.18]	0.01 [-0.07, 0.08]	
	History of VMS	-0.06 [-0.19, 0.08]	-0.03 [-0.10, 0.04]	
	Postsecondary education	0.04 [-0.11, 0.18]	0.02 [-0.05, 0.09]	
	Primary earner status	-0.13 [-0.25, -0.01]	-0.07 [-0.14, 0.00]	*
	MVPA (mins)	0.00 [0.00, 0.01]	0.07 [-0.01, 0.15]	
	StaB (hours)	0.01 [-0.03, 0.06]	0.03 [-0.06, 0.12]	
	Sleep duration (hours)	0.03 [-0.05, 0.11]	0.03 [-0.05, 0.11]	
	Controls (MHT reference group)			
logTG	Former Usage	-0.02 [-0.18, 0.15]	-0.01 [-0.08, 0.07]	
	Current Usage	-0.08 [-0.28, 0.12]	-0.03 [-0.10, 0.04]	
	Age (years)	-0.01 [-0.01, 0.00]	-0.11 [-0.18, -0.03]	*
	Age at menopause (years)	0.00 [-0.01, 0.00]	-0.05 [-0.13, 0.02]	
	Spontaneous menopause	-0.10 [-0.18, -0.02]	-0.09 [-0.16, -0.01]	*
	History of VMS	-0.04 [-0.11, 0.02]	-0.05 [-0.12, 0.02]	
	Postsecondary education	-0.04 [-0.11, 0.03]	-0.04 [-0.11, 0.03]	
	Primary earner status	0.05 [-0.01, 0.11]	0.06 [-0.01, 0.13]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.08 [-0.16, 0.00]	
	StaB (hours)	0.01 [-0.01, 0.04]	0.05 [-0.04, 0.14]	
logGlucose	Sleep duration (hours)	0.01 [-0.03, 0.05]	0.03 [-0.05, 0.10]	
	Controls (MHT reference group)			
	Former Usage	-0.01 [-0.08, 0.07]	-0.01 [-0.08, 0.07]	
	Current Usage	-0.03 [-0.12, 0.07]	-0.02 [-0.09, 0.05]	
	Age (years)	0.00 [0.00, 0.00]	0.04 [-0.03, 0.12]	
	Age at menopause (years)	0.00 [0.00, 0.00]	0.11 [0.03, 0.18]	*
	Spontaneous menopause	-0.04 [-0.06, -0.02]	-0.13 [-0.20, -0.05]	*
	History of VMS	-0.01 [-0.03, 0.01]	-0.05 [-0.12, 0.02]	
	Postsecondary education	-0.02 [-0.04, 0.00]	-0.05 [-0.12, 0.02]	
	Primary earner status	0.01 [0.00, 0.03]	0.05 [-0.02, 0.12]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.10 [-0.17, -0.02]	*
	StaB (hours)	0.00 [-0.01, 0.00]	-0.04 [-0.13, 0.05]	

Sleep duration (hours)	0.00 [-0.02, 0.01]	-0.02 [-0.10, 0.05]	
Controls (MHT reference group)			
Former Usage	0.01 [-0.02, 0.03]	0.02 [-0.06, 0.09]	
Current Usage	-0.03 [-0.06, 0.00]	-0.07 [-0.14, 0.00]	*

Abbreviations: Sig, significance; MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

*denotes $p < 0.05$

Figure 8. Contribution to Model Fit by Covariates, MHT Usage History, and Movement Behaviours



Note. * denotes $p < 0.05$ for F change.

MHT Users Only: Unadjusted Models

Current MHT usage was entered in Block 1, with former users as the reference group.

Model fit statistics for unadjusted models among the MHT user subset are presented in Appendix Table 2c. Current MHT usage alone improved model fit beyond the null for aPWV, SBP, logFRS, and logGlucose, explaining between 1% and 8% of the variance across these markers. The addition of movement behaviours significantly improved model fit beyond MHT usage for aPWV, AIx75, SBP, logFRS, and WC. The most substantial gains were observed for aPWV (Adj. R^2 increase from 0.08 to 0.19; $p < 0.01$; $\Delta AIC = -31.8$) and logFRS (Adj. R^2 increase from 0.04 to 0.10; $p < 0.01$; $\Delta AIC = -13.8$). However, movement behaviours provided

no additional explanatory value for logGlucose, and neither MHT usage nor movement behaviours significantly explained DBP, HDL-C, LDL-C, or logTG beyond the null.

Model coefficients are presented in Appendix Table 2d. Relative to former MHT usage, current MHT usage was independently associated with slower aPWV, lower logFRS, and lower logGlucose. Higher average MVPA was associated with slower aPWV, lower SBP, lower logFRS, smaller WC, and lower logTG. Unlike in the full sample, MVPA was not significantly associated with AIx75, DBP, HDL-C, LDL-C, or logGlucose in the subset of MHT users. Greater amounts of StaB were associated with faster aPWV, but unlike in the full sample, StaB was not associated with DBP or HDL-C when analyzing only MHT users. Sleep duration continued not be associated with any CV outcome.

MHT Users Only: Adjusted Models

Current MHT usage was entered in Block 2 after the covariates (Block 1), with former users serving as the reference group.

Model fit statistics for adjusted models among MHT users only are presented in Table 33a. In Block 1, covariates significantly improved model fit beyond the null for WC, HDL-C, logTG, and logGlucose; notably, this initial block provided the most parsimonious models for HDL-C, logTG, and logGlucose. The addition of MHT history in Block 2 yielded incremental improvements in fit for aPWV, logFRS, and WC (all $p < 0.05$). However, the subsequent inclusion of movement behaviours provided the most substantial improvements to model performance. Specifically, movement behaviours increased the explained variance for aPWV (Adj. R^2 from 0.08 to 0.17; $p < 0.01$; $\Delta AIC = -21.5$), logFRS (Adj. R^2 from 0.06 to 0.11; $p < 0.01$; $\Delta AIC = -10.1$), and WC (Adj. R^2 from 0.08 to 0.18; $p < 0.01$; $\Delta AIC = -24.8$), while also significantly improving the model for SBP (Table 33a).

Following full adjustment for covariates and movement behaviours, current MHT usage predicted a significantly more favourable CV profile relative to former usage (Table 33b). This included slower aPWV ($\beta = -0.28$, 95% CI [-0.39, -0.16]), lower SBP ($\beta = -0.13$, 95% CI [-0.27, 0.00]), lower DBP ($\beta = -0.23$, 95% CI [-0.35, -0.10]), lower logFRS ($\beta = -0.23$, 95% CI [-0.35, -0.10]), and smaller WC ($\beta = 0.15$, 95% CI [-0.27, -0.03]). As observed in the full sample, the

association between current usage and SBP became significant only after covariates were included.

MVPA also maintained broad independent associations with slower aPWV ($\beta = -0.26$, 95% CI [-0.40, -0.12]), lower logFRS, ($\beta = -0.25$, 95% CI [-0.40, -0.11]), and smaller WC ($\beta = -0.31$, 95% CI [-0.45, -0.17]), as well as lower AIx75 and logTG. The association with AIx75 was only detected after adjusting for covariates. Higher average StaB was associated with lower SBP ($\beta = -0.18$, 95% CI [-0.35, -0.02]) and lower DBP ($\beta = -0.18$, 95% CI [-0.35, -0.01]). These associations appeared only after adjusting for covariates, while StaB was no longer positively associated with aPWV. Sleep duration was not associated with any outcome.

Compared to the models in the full sample (Table 32b), individual covariates were relatively less involved in the regression models in the MHT user subset (Table 33b). Older age was associated with smaller WC, lower LDL-C, and higher logGlucose. Older age at menopause was associated with lower logTG and higher logGlucose. Compared to other types of menopause, spontaneous menopause was associated with higher HDL-C. Postsecondary education was associated with smaller WC, while being the primary household earner was associated with larger WC. Having a history of vasomotor symptoms was not associated with any outcome among MHT users only.

Table 23a. Model Fit Accounting for MHT Usage History Among MHT Users

Outcome	Block	N	MHT users Only		P Value for change in F	AIC	Δ AIC
			R ²	Adj. R ²			
aPWV	Block 1	235	0.01	-0.01	0.89	769.9	
	Block 2		0.11	0.08	< 0.01	747.4	-22.6
	Block 3		0.20	0.17	< 0.01	725.9	-21.5
AIx75	Block 1	235	0.01	-0.01	0.77	1814.6	
	Block 2		0.03	0.00	0.07	1813.2	-1.4
	Block 3		0.05	0.01	0.10	1812.7	-0.4
SBP	Block 1	235	0.05	0.02	0.08	1939.3	
	Block 2		0.06	0.03	0.06	1937.7	-1.7
	Block 3		0.10	0.06	0.02	1933.1	-4.5
DBP	Block 1	235	0.02	-0.01	0.65	1798.9	
	Block 2		0.03	0.00	0.05	1797.0	-1.9
	Block 3		0.06	0.02	0.13	1797.2	0.1
logFRS	Block 1	235	0.02	0.00	0.47	378.9	
	Block 2		0.08	0.06	< 0.01	365.5	-13.4
	Block 3		0.14	0.11	< 0.01	355.4	-10.1
WC	Block 1	235	0.08	0.06	< 0.01	1869.3	
	Block 2		0.10	0.08	0.02	1865.7	-3.6
	Block 3		0.22	0.18	< 0.01	1840.9	-24.8
HDL-C	Block 1	235	0.06	0.03	0.04	284.5	
	Block 2		0.06	0.03	0.96	286.5	2.0
	Block 3		0.08	0.04	0.09	285.7	-0.8
LDL-C	Block 1	235	0.05	0.02	0.08	568.6	
	Block 2		0.05	0.02	0.48	570.1	1.5
	Block 3		0.07	0.03	0.24	571.7	1.6
logTG	Block 1	235	0.07	0.05	0.01	242.1	
	Block 2		0.07	0.04	0.86	244.1	2.0
	Block 3		0.09	0.05	0.11	243.8	-0.3
logGlucose	Block 1	235	0.06	0.03	0.03	-282.5	

Block 2	0.07	0.04	0.19	-282.3	0.2
Block 3	0.08	0.04	0.41	-279.3	3.0

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered
Block 2: Current Usage entered
Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 or Block 2;
Red bold text used to emphasize statistically significant changes in Block 3.

Table 33b. Coefficients in Models Accounting for MHT Usage History Among MHT Users

Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	-0.01 [-0.03, 0.02]	-0.03 [-0.16, 0.10]	
	Spontaneous menopause	0.18 [-0.17, 0.53]	0.07 [-0.06, 0.20]	
	History of VMS	-0.14 [-0.50, 0.21]	-0.05 [-0.17, 0.07]	
	Postsecondary education	-0.01 [-0.37, 0.35]	0.00 [-0.12, 0.12]	
	Primary earner status	0.01 [-0.30, 0.32]	0.00 [-0.12, 0.12]	
	MVPA (mins)	-0.02 [-0.02, -0.01]	-0.26 [-0.40, -0.12]	*
	StaB (hours)	0.07 [-0.05, 0.18]	0.09 [-0.06, 0.24]	
	Sleep duration (hours)	-0.02 [-0.22, 0.17]	-0.01 [-0.15, 0.12]	
	Former Usage (MHT reference group)			
	Current Usage	-0.70 [-1.00, -0.40]	-0.28 [-0.39, -0.16]	*
AIx75	Age at menopause (years)	-0.14 [-0.39, 0.11]	-0.08 [-0.22, 0.06]	
	Spontaneous menopause	0.34 [-3.21, 3.88]	0.01 [-0.13, 0.15]	
	History of VMS	-0.65 [-4.27, 2.97]	-0.02 [-0.15, 0.11]	
	Postsecondary education	-0.90 [-4.53, 2.72]	-0.03 [-0.16, 0.10]	
	Primary earner status	0.95 [-2.16, 4.06]	0.04 [-0.09, 0.17]	
	MVPA (mins)	-0.06 [-0.15, 0.02]	-0.11 [-0.27, 0.04]	
	StaB (hours)	0.53 [-0.63, 1.69]	0.08 [-0.09, 0.24]	
	Sleep duration (hours)	0.76 [-1.22, 2.74]	0.06 [-0.09, 0.20]	

SBP	Former Usage (MHT reference group)			
	Current Usage	-2.35 [-5.42, 0.71]	-0.10 [-0.23, 0.03]	
	Age (years)	0.32 [-0.01, 0.66]	0.13 [-0.01, 0.27]	
	Age at menopause (years)	-0.04 [-0.36, 0.28]	-0.02 [-0.15, 0.12]	
	Spontaneous menopause	-0.58 [-5.18, 4.01]	-0.02 [-0.16, 0.12]	
	History of VMS	1.95 [-2.74, 6.63]	0.05 [-0.07, 0.18]	
	Postsecondary education	0.36 [-4.31, 5.04]	0.01 [-0.12, 0.14]	
	Primary earner status	-2.11 [-6.12, 1.91]	-0.07 [-0.19, 0.06]	
	MVPA (mins)	-0.18 [-0.30, -0.07]	-0.24 [-0.39, -0.09]	*
	StaB (hours)	-1.66 [-3.18, -0.15]	-0.18 [-0.35, -0.02]	*
DBP	Sleep duration (hours)	-1.21 [-3.76, 1.34]	-0.07 [-0.21, 0.07]	
	Former Usage (MHT reference group)			
	Current Usage	-4.15 [-8.28, -0.03]	-0.13 [-0.27, 0.00]	*
	Age (years)	-0.24 [-0.49, 0.01]	-0.14 [-0.28, 0.01]	
	Age at menopause (years)	-0.12 [-0.36, 0.12]	-0.07 [-0.21, 0.07]	
	Spontaneous menopause	1.46 [-1.98, 4.90]	0.06 [-0.08, 0.20]	
	History of VMS	0.47 [-3.04, 3.97]	0.02 [-0.11, 0.15]	
	Postsecondary education	-0.41 [-3.92, 3.09]	-0.02 [-0.15, 0.12]	
	Primary earner status	0.33 [-2.68, 3.33]	0.01 [-0.12, 0.14]	
	MVPA (mins)	-0.09 [-0.17, 0.00]	-0.16 [-0.31, 0.00]	
logFRS	StaB (hours)	-1.20 [-2.34, -0.07]	-0.18 [-0.35, -0.01]	*
	Sleep duration (hours)	-0.52 [-2.43, 1.38]	-0.04 [-0.18, 0.10]	
	Former Usage (MHT reference group)			
	Current Usage	-3.18 [-6.27, -0.10]	-0.14 [-0.28, 0.00]	*
	Age at menopause (years)	-0.01 [-0.02, 0.00]	-0.10 [-0.23, 0.03]	
	Spontaneous menopause	0.02 [-0.14, 0.18]	0.02 [-0.12, 0.15]	
	History of VMS	0.02 [-0.14, 0.19]	0.02 [-0.11, 0.14]	
	Postsecondary education	-0.04 [-0.20, 0.13]	-0.03 [-0.15, 0.10]	
	Primary earner status	-0.07 [-0.21, 0.07]	-0.06 [-0.18, 0.06]	
	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.25 [-0.40, -0.11]	*
	StaB (hours)	0.00 [-0.06, 0.05]	-0.01 [-0.17, 0.15]	
	Sleep duration (hours)	-0.01 [-0.10, 0.08]	-0.01 [-0.15, 0.13]	

Former Usage (MHT reference group)				
WC	Current Usage	-0.25 [-0.39, -0.11]	-0.23 [-0.35, -0.10]	*
	Age (years)	-0.70 [-0.98, -0.43]	-0.33 [-0.46, -0.20]	*
	Age at menopause (years)	-0.07 [-0.34, 0.19]	-0.04 [-0.16, 0.09]	
	Spontaneous menopause	-1.95 [-5.72, 1.83]	-0.07 [-0.20, 0.06]	
	History of VMS	1.21 [-2.64, 5.06]	0.04 [-0.08, 0.16]	
	Postsecondary education	-3.93 [-7.77, -0.08]	-0.12 [-0.24, 0.00]	*
	Primary earner status	3.83 [0.53, 7.13]	0.14 [0.02, 0.26]	*
	MVPA (mins)	-0.21 [-0.30, -0.11]	-0.31 [-0.45, -0.17]	*
	StaB (hours)	0.38 [-0.87, 1.62]	0.05 [-0.11, 0.20]	
	Sleep duration (hours)	-1.39 [-3.49, 0.70]	-0.09 [-0.22, 0.04]	
Former Usage (MHT reference group)				
HDL-C	Current Usage	-4.08 [-7.47, -0.69]	-0.15 [-0.27, -0.03]	*
	Age (years)	0.00 [-0.01, 0.01]	0.06 [-0.08, 0.20]	
	Age at menopause (years)	0.00 [-0.01, 0.01]	0.01 [-0.12, 0.15]	
	Spontaneous menopause	0.18 [0.04, 0.32]	0.18 [0.04, 0.32]	*
	History of VMS	-0.04 [-0.19, 0.10]	-0.04 [-0.17, 0.09]	
	Postsecondary education	0.10 [-0.04, 0.24]	0.09 [-0.04, 0.22]	
	Primary earner status	-0.05 [-0.17, 0.07]	-0.06 [-0.18, 0.07]	
	MVPA (mins)	0.00 [0.00, 0.01]	0.08 [-0.07, 0.24]	
	StaB (hours)	-0.03 [-0.08, 0.01]	-0.12 [-0.28, 0.05]	
	Sleep duration (hours)	0.01 [-0.07, 0.08]	0.01 [-0.13, 0.15]	
Former Usage (MHT reference group)				
LDL-C	Current Usage	-0.01 [-0.13, 0.11]	-0.01 [-0.14, 0.12]	
	Age (years)	-0.02 [-0.04, 0.00]	-0.15 [-0.29, -0.01]	*
	Age at menopause (years)	-0.01 [-0.03, 0.01]	-0.09 [-0.22, 0.05]	
	Spontaneous menopause	0.12 [-0.14, 0.37]	0.07 [-0.08, 0.21]	
	History of VMS	-0.10 [-0.36, 0.16]	-0.05 [-0.18, 0.08]	
	Postsecondary education	0.06 [-0.20, 0.32]	0.03 [-0.10, 0.16]	
	Primary earner status	-0.11 [-0.33, 0.12]	-0.06 [-0.19, 0.07]	
	MVPA (mins)	0.00 [0.00, 0.01]	0.08 [-0.07, 0.24]	
	StaB (hours)	-0.03 [-0.11, 0.05]	-0.06 [-0.23, 0.10]	

	Sleep duration (hours)	0.04 [-0.10, 0.18]	0.04 [-0.10, 0.19]	
	Former Usage (MHT reference group)			
	Current Usage	-0.09 [-0.32, 0.14]	-0.05 [-0.19, 0.08]	
logTG	Age (years)	-0.01 [-0.01, 0.00]	-0.08 [-0.22, 0.06]	
	Age at menopause (years)	-0.01 [-0.02, 0.00]	-0.18 [-0.32, -0.05]	*
	Spontaneous menopause	-0.07 [-0.20, 0.05]	-0.08 [-0.22, 0.06]	
	History of VMS	-0.01 [-0.14, 0.12]	-0.01 [-0.14, 0.12]	
	Postsecondary education	-0.07 [-0.20, 0.06]	-0.07 [-0.20, 0.06]	
	Primary earner status	0.05 [-0.06, 0.16]	0.06 [-0.06, 0.19]	
	MVPA (mins)	0.00 [-0.01, 0.00]	-0.16 [-0.31, -0.01]	*
	StaB (hours)	0.00 [-0.04, 0.04]	0.01 [-0.16, 0.17]	
	Sleep duration (hours)	0.02 [-0.05, 0.09]	0.03 [-0.11, 0.17]	
	Former Usage (MHT reference group)			
	Current Usage	-0.01 [-0.12, 0.10]	-0.01 [-0.14, 0.12]	
logGlucose	Age (years)	0.00 [0.00, 0.01]	0.16 [0.01, 0.30]	*
	Age at menopause (years)	0.00 [0.00, 0.01]	0.15 [0.01, 0.29]	*
	Spontaneous menopause	-0.04 [-0.08, 0.01]	-0.12 [-0.26, 0.02]	
	History of VMS	-0.01 [-0.05, 0.03]	-0.03 [-0.16, 0.10]	
	Postsecondary education	0.01 [-0.03, 0.05]	0.03 [-0.10, 0.16]	
	Primary earner status	0.01 [-0.03, 0.05]	0.04 [-0.09, 0.17]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.12 [-0.27, 0.03]	
	StaB (hours)	-0.01 [-0.02, 0.00]	-0.12 [-0.28, 0.05]	
	Sleep duration (hours)	-0.01 [-0.03, 0.01]	-0.06 [-0.20, 0.09]	
	Former Usage (MHT reference group)			
	Current Usage	-0.03 [-0.06, 0.01]	-0.09 [-0.23, 0.04]	

Abbreviations: Sig, significance; MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

*denotes $p < 0.05$

Summary of Objective 2B.1

When modelling outcomes using MHT usage history as the MHT exposure variable, several patterns emerged across the various model specifications.

First, adding MHT usage to models always significantly increased their explanatory value for aPWV and logFRS. For example, in the adjusted models, adding MHT history (Block 2) increased the explained variance of aPWV from 2% to 7% in the full sample, and from -1% to 8% among MHT users only. For logFRS, these values increased from 1% to 3% in the full sample, and from 0% to 6% among MHT users only. There were also some improvements in model fit for SBP, WC, and logGlucose, but these were inconsistent and varied by sample and covariate adjustment.

Second, the addition of movement behaviours significantly improved model fit beyond MHT history (with or without covariates) across most CV outcomes. These behaviours consistently provided incremental explanatory value for aPWV, SBP, logFRS, and WC in all samples and model specifications. For example, compared to Block 2, inclusion of movement behaviours increased explained variance in aPWV from 7% to 11% in the full sample, and from 8% to 17% among MHT users only; for logFRS, explanatory value increased from 3% to 5% in the full sample and from 6% to 11% among MHT users only. Movement behaviours also improved models for A1c75, DBP, HDL-C, and logTG in the full sample, but these gains were not replicated in the MHT user subset. The contribution of movement behaviours to logGlucose was sensitive to covariate adjustment, as the explanatory value was nullified with the inclusion of covariates.

Third, independent associations between MHT usage history and CV outcomes indicate that current usage generally demonstrates a more favourable profile than both controls and former users. Compared to controls, former usage was associated with faster aPWV, whereas current usage predicted lower global risk (logFRS) and lower logGlucose across both unadjusted and adjusted models. Compared with former users, current usage was associated with slower aPWV, lower SBP, lower DBP, and lower logFRS.

Fourth, there were consistent associations between MVPA and several outcomes. Regardless of model specification, greater MVPA was consistently associated with slower

aPWV, lower SBP, lower logFRS, and smaller WC. Associations with lower AIx75, lower DBP, higher HDL-C, and lower logGlucose were observed in the full sample, but not in the MHT user subset. It was also inconsistently associated with higher LDL-C and lower logTG, depending on the models' sample and specifications. It is also important to note that the standardized coefficients for MVPA were relatively large and, in most models, among the largest of all predictors included. In other words, beyond demonstrating independent associations with most outcomes, MVPA frequently contributed as much or more than other predictors to the model's fit and explanatory power.

Fifth, StaB was independently (but inconsistently) involved in a smaller set of outcomes. In the full sample, higher average StaB was associated with faster aPWV, lower DBP, and lower HDL-C. Among MHT users only, it was associated with faster aPWV in unadjusted models and with SBP and DBP in fully adjusted models. Lastly, sleep duration was not independently associated with any outcome in any model specification.

3.3.2.2 Objective 2B.2

The hypothesis for Objective 2B.2 (that movement behaviours would explain a greater proportion of variance in CV outcomes beyond MHT type exposures and covariates, and that individual behaviours would be more strongly associated with outcomes than MHT type) was supported.

Full Sample: Unadjusted Models

Combined estrogen-progestogen and unopposed estrogen usage were entered into Block 1, with controls serving as the reference group.

Unadjusted model fit statistics for the full sample are presented in Appendix Table 3a. MHT type alone (Block 1) significantly improved model fit beyond the null for aPWV (Adjusted $R^2 = 0.02$; $p < 0.01$) and HDL-C (Adjusted $R^2 = 0.01$; $p = 0.02$). Adding movement behaviours (Block 2) significantly improved model fit beyond MHT type alone (Block 1) for all outcomes except for LDL-C (Appendix Table 3a). Compared to Block 1, Block 2 increased the amount of explained variance from 2% to 7% for aPWV ($p < 0.01$; $\Delta AIC = -43.1$) and 1% to 5% for HDL-C ($p < 0.01$; $\Delta AIC = -34.7$).

Unadjusted model coefficients for the full sample are presented in Appendix Table 3b. Relative to controls, combined estrogen-progestogen usage was associated with faster aPWV ($\beta = 0.14$, 95% CI [0.07, 0.20]), smaller WC ($\beta = -0.07$, 95% CI [-0.14, -0.01]), and higher HDL-C ($\beta = 0.08$, 95% CI [0.02, 0.15]). Unopposed estrogen usage was not independently associated with any outcome.

In contrast, MVPA was independently associated with all outcomes in these models. To list a few examples, higher average MVPA was associated with slower aPWV ($\beta = -0.17$, 95% CI [-0.25, -0.10]), smaller WC ($\beta = -0.23$, 95% CI [-0.31, -0.16]), and higher HDL-C ($\beta = 0.14$, 95% CI [0.06, 0.21]). Greater amounts of StaB were also associated with faster aPWV ($\beta = 0.11$, 95% CI [0.03, 0.19]) and lower HDL-C ($\beta = -0.12$, 95% CI [-0.21, -0.04]), as well as lower DBP. Sleep duration was not associated with any outcome.

Full Sample: Adjusted Models

Combined estrogen-progestogen and unopposed estrogen usage were entered into Block 2 following the covariates (Block 1), with controls serving as the reference group.

Covariates alone (Block 1) significantly improved model fit beyond the null for aPWV, SBP, logFRS, WC, HDL-C, LDL-C, logTG, and logGlucose (Table 34a). The models did not explain statistically significant variance in AIx75 or DBP. The models predicting LDL-C, logTG, and logGlucose were ultimately the most parsimonious compared to Block 2 and Block 3 models. Adding MHT type (Block 2) continued to improved model fit for aPWV, increasing the estimated amount of explained variance from 2% to 6% (Adjusted $R^2 = 0.06$; $p < 0.01$; $\Delta AIC = -22.6$). Unlike the unadjusted models, it did not add any significant explanatory value for HDL-C after accounting for covariates.

Entering movement behaviours into the models (Block 3) significantly increased the explanatory ability of models for aPWV, AIx75, SBP, DBP, logFRS, WC, and HDL-C (Figure 9). For example, the estimate of explained variance for aPWV increased from 6% to 10% after adding movement behaviours (Adj. $R^2 = 0.10$; $p < 0.01$; $\Delta AIC = -28.1$). However, movement behaviours did not significantly improve model fit for LDL-C, logTG, or logGlucose.

Model coefficients are presented in Table 34b. After controlling for covariates and movement behaviours, combined estrogen-progestogen use was associated with faster aPWV

than in controls ($\beta = 0.17$, 95% CI [0.10, 0.25]). Its associations with WC and HDL-C observed in the unadjusted models were nullified with the inclusion of covariates. Unopposed estrogen usage continued to have no statistically significant relationship with any outcome in these models.

MVPA was independently and favourably associated with all outcomes except for LDL-C and logTG after adjusting for covariates and MHT type. For example, more MVPA was strongly associated with slower aPWV ($\beta = -0.17$, 95% CI [-0.25, -0.09]), lower SBP ($\beta = -0.12$, 95% CI [-0.20, -0.04]), lower logFRS ($\beta = -0.15$, 95% CI [-0.23, -0.07]), and smaller WC ($\beta = -0.22$, 95% CI [-0.30, -0.14]). These MVPA coefficients represented the largest relative effect sizes among all predictors included in the model. Greater average StaB was associated with lower DBP and lower HDL-C but was no longer independently associated with aPWV after covariate adjustment. Sleep duration continued to not be associated with any outcome.

Regarding individual covariates, older age was associated with higher SBP, smaller WC, higher HDL-C, lower LDL-C, and lower logTG. Older age at menopause was associated with higher logGlucose. Experiencing spontaneous menopause was associated with a smaller WC, higher HDL-C, and lower logGlucose. Having a history of vasomotor symptoms was associated with slower aPWV and lower AIX75. Completing a postsecondary education was associated with lower logFRS and higher HDL-C. Lastly, self-identifying as the primary household earner was associated with a larger WC, lower HDL-C, and lower LDL-C.

Table 34a. Model Fit Accounting for MHT Type in the Full Sample.

Outcome	Block	N	R ²	Full Sample Adj. R ²	P Value for change in F	AIC	ΔAIC
aPWV	Block 1	713	0.03	0.02	< 0.01	2166.2	
	Block 2		0.07	0.06	< 0.01	2143.6	-22.6
	Block 3		0.11	0.10	< 0.01	2115.5	-28.1
AIx75	Block 1	713	0.01	0.01	0.07	5339.2	
	Block 2		0.02	0.01	0.19	5339.9	0.7
	Block 3		0.03	0.02	0.02	5336.3	-3.6
SBP	Block 1	713	0.02	0.01	0.02	5768.8	
	Block 2		0.02	0.01	0.68	5772.0	3.2
	Block 3		0.03	0.02	0.04999	5770.1	-1.9
DBP	Block 1	713	0.01	0.00	0.25	5299.9	
	Block 2		0.01	0.00	0.64	5303.0	3.1
	Block 3		0.03	0.01	0.03	5299.8	-3.3
logFRS	Block 1	713	0.02	0.01	0.02	1093.6	
	Block 2		0.02	0.01	0.32	1095.3	1.7
	Block 3		0.05	0.03	< 0.01	1084.0	-11.3
WC	Block 1	713	0.07	0.06	< 0.01	5670.4	
	Block 2		0.07	0.06	0.83	5674.0	3.6
	Block 3		0.12	0.11	< 0.01	5638.1	-35.9
HDL-C	Block 1	713	0.04	0.04	< 0.01	827.3	
	Block 2		0.05	0.04	0.13	827.2	-0.1
	Block 3		0.09	0.08	< 0.01	798.3	-28.8
LDL-C	Block 1	713	0.03	0.02	< 0.01	1802.0	
	Block 2		0.03	0.02	0.38	1804.0	2.0
	Block 3		0.03	0.02	0.50	1807.6	3.6
logTG	Block 1	713	0.03	0.02	< 0.01	782.7	
	Block 2		0.03	0.02	0.67	785.9	3.2
	Block 3		0.04	0.02	0.11	785.7	-0.2
logGlucose	Block 1	712	0.04	0.03	< 0.01	-998.3	

Block 2	0.04	0.03	0.95	-994.4	3.9
Block 3	0.04	0.03	0.16	-993.7	0.7

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose.

Block 1: Covariates entered
Block 2: Combined Estrogen-Progestogen, Unopposed Estrogen usage entered
Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 or Block 2;
Red bold text used to emphasize statistically significant changes in Block 3.

Table 34b. Coefficients in Models Accounting for MHT Type in the Full Sample.

Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	-0.01 [-0.03, 0.01]	-0.05 [-0.13, 0.03]	
	Spontaneous menopause	0.12 [-0.10, 0.35]	0.04 [-0.03, 0.12]	
	History of VMS	-0.36 [-0.53, -0.18]	-0.14 [-0.21, -0.07]	*
	Postsecondary education	-0.08 [-0.27, 0.11]	-0.03 [-0.10, 0.04]	
	Primary earner status	0.04 [-0.12, 0.20]	0.02 [-0.05, 0.09]	
	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.17 [-0.25, -0.09]	*
	StaB (hours)	0.06 [0.00, 0.12]	0.08 [-0.01, 0.17]	
	Sleep duration (hours)	0.03 [-0.08, 0.14]	0.02 [-0.06, 0.10]	
	Controls (MHT reference group)			
	Combined Estrogen-Progestogen	0.68 [0.40, 0.96]	0.17 [0.10, 0.25]	*
AIx75	Unopposed Estrogen	0.02 [-0.23, 0.27]	0.00 [-0.07, 0.08]	
	Age at menopause (years)	-0.15 [-0.31, 0.01]	-0.08 [-0.16, 0.01]	
	Spontaneous menopause	0.54 [-1.60, 2.68]	0.02 [-0.06, 0.10]	
	History of VMS	-1.95 [-3.64, -0.26]	-0.09 [-0.16, -0.01]	*
	Postsecondary education	0.02 [-1.81, 1.85]	0.00 [-0.07, 0.07]	
	Primary earner status	-0.96 [-2.51, 0.58]	-0.05 [-0.12, 0.03]	
	MVPA (mins)	-0.04 [-0.08, 0.00]	-0.08 [-0.17, 0.00]	*
	StaB (hours)	0.34 [-0.25, 0.92]	0.05 [-0.04, 0.15]	

SBP	Sleep duration (hours)	0.12 [-0.91, 1.16]	0.01 [-0.07, 0.09]	
	Controls (MHT reference group)			
	Combined Estrogen-Progestogen	1.81 [-0.86, 4.47]	0.05 [-0.02, 0.13]	
	Unopposed Estrogen	-1.08 [-3.48, 1.32]	-0.04 [-0.11, 0.04]	
	Age (years)	0.24 [0.06, 0.42]	0.10 [0.02, 0.18]	*
	Age at menopause (years)	0.05 [-0.17, 0.26]	0.02 [-0.06, 0.10]	
	Spontaneous menopause	-0.38 [-3.28, 2.53]	-0.01 [-0.09, 0.07]	
	History of VMS	-1.56 [-3.88, 0.76]	-0.05 [-0.12, 0.02]	
	Postsecondary education	-1.58 [-4.06, 0.89]	-0.05 [-0.12, 0.03]	
	Primary earner status	0.11 [-1.99, 2.21]	0.00 [-0.07, 0.08]	
DBP	MVPA (mins)	-0.08 [-0.13, -0.02]	-0.12 [-0.20, -0.04]	*
	StaB (hours)	-0.56 [-1.35, 0.24]	-0.07 [-0.16, 0.03]	
	Sleep duration (hours)	-0.20 [-1.59, 1.20]	-0.01 [-0.10, 0.07]	
	Controls (MHT reference group)			
	Combined Estrogen-Progestogen	0.93 [-2.75, 4.60]	0.02 [-0.06, 0.10]	
	Unopposed Estrogen	-0.89 [-4.14, 2.36]	-0.02 [-0.10, 0.06]	
	Age (years)	-0.12 [-0.25, 0.01]	-0.07 [-0.15, 0.01]	
	Age at menopause (years)	-0.03 [-0.19, 0.12]	-0.02 [-0.10, 0.06]	
	Spontaneous menopause	0.11 [-1.98, 2.20]	0.00 [-0.08, 0.08]	
	History of VMS	-0.35 [-2.02, 1.32]	-0.02 [-0.09, 0.06]	
logFRS	Postsecondary education	-1.75 [-3.53, 0.03]	-0.07 [-0.15, 0.00]	
	Primary earner status	0.55 [-0.96, 2.06]	0.03 [-0.05, 0.10]	
	MVPA (mins)	-0.05 [-0.09, -0.01]	-0.10 [-0.19, -0.02]	*
	StaB (hours)	-0.70 [-1.28, -0.13]	-0.12 [-0.21, -0.02]	*
	Sleep duration (hours)	-0.07 [-1.08, 0.93]	-0.01 [-0.09, 0.08]	
	Controls (MHT reference group)			
	Combined Estrogen-Progestogen	0.42 [-2.22, 3.06]	0.01 [-0.06, 0.09]	
	Unopposed Estrogen	-0.90 [-3.24, 1.44]	-0.03 [-0.11, 0.05]	
	Age at menopause (years)	0.00 [-0.01, 0.01]	-0.02 [-0.10, 0.06]	
	Spontaneous menopause	-0.03 [-0.14, 0.08]	-0.02 [-0.10, 0.06]	
	History of VMS	-0.07 [-0.16, 0.01]	-0.06 [-0.14, 0.01]	
	Postsecondary education	-0.12 [-0.21, -0.03]	-0.09 [-0.17, -0.02]	*

	Primary earner status	0.02 [-0.06, 0.10]	0.02 [-0.06, 0.09]	
	MVPA (mins)	0.00 [-0.01, 0.00]	-0.15 [-0.23, -0.07]	*
	StaB (hours)	0.00 [-0.03, 0.03]	0.01 [-0.08, 0.11]	
	Sleep duration (hours)	0.01 [-0.05, 0.06]	0.01 [-0.07, 0.09]	
	Controls (MHT reference group)			
	Combined Estrogen-Progestogen	0.04 [-0.10, 0.17]	0.02 [-0.05, 0.09]	
	Unopposed Estrogen	-0.08 [-0.20, 0.04]	-0.05 [-0.13, 0.03]	
WC	Age (years)	-0.37 [-0.54, -0.21]	-0.16 [-0.24, -0.09]	*
	Age at menopause (years)	0.11 [-0.08, 0.31]	0.04 [-0.03, 0.12]	
	Spontaneous menopause	-4.65 [-7.29, -2.00]	-0.13 [-0.21, -0.06]	*
	History of VMS	-1.87 [-3.98, 0.25]	-0.06 [-0.13, 0.01]	
	Postsecondary education	-2.00 [-4.26, 0.26]	-0.06 [-0.13, 0.01]	
	Primary earner status	3.15 [1.24, 5.07]	0.12 [0.05, 0.19]	*
	MVPA (mins)	-0.14 [-0.19, -0.09]	-0.22 [-0.30, -0.14]	*
	StaB (hours)	0.17 [-0.56, 0.90]	0.02 [-0.07, 0.11]	
	Sleep duration (hours)	-1.00 [-2.27, 0.28]	-0.06 [-0.14, 0.02]	
	Controls (MHT reference group)			
	Combined Estrogen-Progestogen	-1.08 [-4.42, 2.27]	-0.02 [-0.10, 0.05]	
	Unopposed Estrogen	0.21 [-2.75, 3.18]	0.01 [-0.07, 0.08]	
HDL-C	Age (years)	0.01 [0.01, 0.02]	0.16 [0.08, 0.23]	*
	Age at menopause (years)	0.00 [-0.01, 0.00]	-0.04 [-0.12, 0.04]	
	Spontaneous menopause	0.10 [0.01, 0.19]	0.09 [0.01, 0.17]	*
	History of VMS	0.02 [-0.05, 0.09]	0.02 [-0.05, 0.09]	
	Postsecondary education	0.09 [0.01, 0.17]	0.08 [0.01, 0.16]	*
	Primary earner status	-0.07 [-0.13, -0.01]	-0.08 [-0.15, -0.01]	*
	MVPA (mins)	0.00 [0.00, 0.00]	0.12 [0.04, 0.20]	*
	StaB (hours)	-0.04 [-0.06, -0.02]	-0.15 [-0.24, -0.06]	*
	Sleep duration (hours)	-0.01 [-0.06, 0.03]	-0.02 [-0.10, 0.06]	
	Controls (MHT reference group)			
	Combined Estrogen-Progestogen	0.06 [-0.05, 0.18]	0.04 [-0.03, 0.11]	
	Unopposed Estrogen	-0.07 [-0.17, 0.03]	-0.05 [-0.13, 0.02]	
LDL-C	Age (years)	-0.02 [-0.03, -0.01]	-0.12 [-0.19, -0.04]	*

	Age at menopause (years)	0.00 [-0.02, 0.01]	-0.02 [-0.10, 0.06]	*
	Spontaneous menopause	0.04 [-0.14, 0.22]	0.02 [-0.06, 0.10]	
	History of VMS	-0.04 [-0.19, 0.10]	-0.02 [-0.10, 0.05]	
	Postsecondary education	0.05 [-0.10, 0.21]	0.03 [-0.05, 0.10]	
	Primary earner status	-0.16 [-0.29, -0.03]	-0.09 [-0.17, -0.02]	
	MVPA (mins)	0.00 [0.00, 0.01]	0.07 [-0.02, 0.15]	
	StaB (hours)	0.02 [-0.03, 0.07]	0.04 [-0.05, 0.13]	
	Sleep duration (hours)	0.02 [-0.06, 0.11]	0.02 [-0.06, 0.11]	
	Controls (MHT reference group)			
	Combined Estrogen-Progestogen	-0.15 [-0.38, 0.08]	-0.05 [-0.13, 0.03]	
logTG	Unopposed Estrogen	-0.04 [-0.24, 0.16]	-0.02 [-0.09, 0.06]	*
	Age (years)	-0.01 [-0.01, 0.00]	-0.11 [-0.19, -0.03]	
	Age at menopause (years)	0.00 [-0.01, 0.00]	-0.05 [-0.13, 0.03]	
	Spontaneous menopause	-0.09 [-0.18, 0.00]	-0.08 [-0.16, 0.00]	
	History of VMS	-0.04 [-0.11, 0.03]	-0.04 [-0.12, 0.03]	
	Postsecondary education	-0.02 [-0.10, 0.05]	-0.02 [-0.10, 0.05]	
	Primary earner status	0.04 [-0.02, 0.10]	0.05 [-0.03, 0.12]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.06 [-0.15, 0.02]	
	StaB (hours)	0.01 [-0.01, 0.04]	0.05 [-0.04, 0.15]	
	Sleep duration (hours)	0.01 [-0.03, 0.05]	0.02 [-0.06, 0.11]	
logGlucose	Controls (MHT reference group)			*
	Combined Estrogen-Progestogen	-0.04 [-0.15, 0.07]	-0.03 [-0.10, 0.05]	
	Unopposed Estrogen	0.02 [-0.08, 0.12]	0.02 [-0.06, 0.09]	
	Age (years)	0.00 [0.00, 0.00]	0.04 [-0.04, 0.11]	
	Age at menopause (years)	0.00 [0.00, 0.00]	0.11 [0.03, 0.19]	
	Spontaneous menopause	-0.04 [-0.07, -0.02]	-0.13 [-0.21, -0.05]	
	History of VMS	-0.02 [-0.04, 0.00]	-0.06 [-0.14, 0.01]	
	Postsecondary education	-0.02 [-0.04, 0.00]	-0.06 [-0.14, 0.01]	
	Primary earner status	0.02 [0.00, 0.03]	0.06 [-0.01, 0.14]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.10 [-0.18, -0.01]	
	StaB (hours)	0.00 [-0.01, 0.00]	-0.04 [-0.14, 0.05]	*
	Sleep duration (hours)	0.00 [-0.01, 0.01]	-0.02 [-0.10, 0.07]	

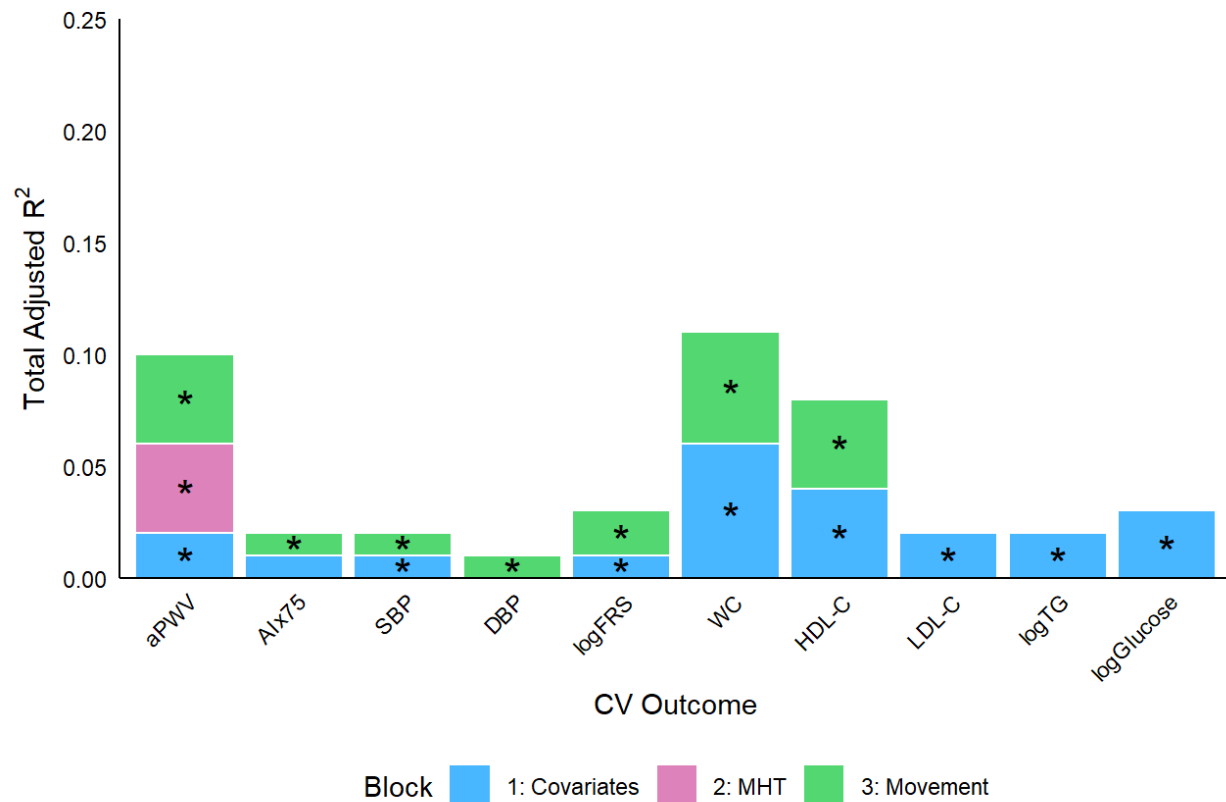
Controls (MHT reference group)

Combined Estrogen-Progestogen	-0.01 [-0.04, 0.02]	-0.02 [-0.09, 0.06]
Unopposed Estrogen	0.00 [-0.03, 0.03]	-0.01 [-0.09, 0.07]

Abbreviations: Sig, significance; MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose.

*denotes $p < 0.05$

Figure 9. Contribution to Model Fit by Covariates, MHT Type, and Movement Behaviours



Note. * denotes $p < 0.05$ for F change.

MHT Users Only: Unadjusted Models

Unopposed estrogen use was entered into Block 1, with combined estrogen-progestogen as the reference group.

Block 1 improved model fit beyond the null for aPWV, HDL-C, and logTG (Appendix Table 3c). Entering movement behaviours (Block 2) improved model fit beyond Block 1 for aPWV, SBP, logFRS, and LDL-C. A notable example is that the variance explained by aPWV in the model increased from 4% to 21% when movement behaviours were added (Adjusted $R^2 = 0.21$; $p < 0.01$; $\Delta AIC = -30.1$). Block 2 did not add significant additional explanatory value in models predicting HDL-C and logTG. AIx75, DBP, WC, and logGlucose were not well explained by either Block 1 or Block 2 models ($p > 0.05$ for all; Appendix Table 3c).

Unadjusted model coefficients in the MHT user subset are presented in Appendix Table 3d. Relative to combined estrogen-progestogen usage, unopposed estrogen usage was associated

with slower aPWV ($\beta = -0.22$, 95% CI [-0.36, -0.09]), lower HDL-C, and lower logTG. Higher average MVPA was associated with slower aPWV ($\beta = -0.36$, 95% CI [-0.52, -0.20]), lower SBP, lower logFRS, and lower logGlucose. Neither StaB nor sleep duration was independently associated with any outcome in these models. Additionally, no predictors were independently associated with AIx75, DBP, WC, or LDL-C.

MHT Users Only: Adjusted Models

Unopposed estrogen use was entered in Block 2 following covariates (Block 1), with combined estrogen-progestogen as the reference group.

Covariates alone (Block 1) significantly improved model fit beyond the null for WC, LDL-C, and logGlucose (Table 35a). Subsequently adding unopposed estrogen (Block 2) significantly improved model fit for aPWV and HDL-C. Entering movement behaviours (Block 3) significantly improved the explanatory ability of models for aPWV, SBP, logFRS, and WC. For example, Block 3 increased the amount of explained variance in aPWV from 5% to 21% (Adjusted $R^2 = 0.21$; $p < 0.01$; $\Delta AIC = -24.6$). Block 1 provided the most parsimonious models for LDL-C and logTG, while Block 2 models fit HDL-C better than Block 1 and Block 3. AIx75, DBP, and logGlucose were not well explained by any model.

As with the unadjusted models, unopposed estrogen use was independently associated with slower aPWV and lower HDL-C relative to combined estrogen-progestogen use (Table 35b). However, unlike the unadjusted models, it was not independently associated with logTG after full adjustment. Higher average MVPA remained associated with slower aPWV, lower SBP, and lower logFRS; furthermore, associations with lower DBP and smaller WC were detected after covariate adjustment. MVPA also had the largest magnitude of association compared to other predictors for aPWV ($\beta = -0.37$, 95% CI [-0.55, -0.19]), SBP ($\beta = -0.34$, 95% CI [-0.55, -0.14]), DBP ($\beta = -0.25$, 95% CI [-0.46, -0.05]), and logFRS ($\beta = -0.37$, 95% CI [-0.56, -0.17]). As with the unadjusted models, there were no associations between StaB and sleep duration with CV outcomes after covariate adjustment.

Regarding covariates, only age and age at menopause were independently associated with outcomes in these models. Older age was associated with lower DBP, smaller WC, and higher logGlucose. Older age at menopause was associated with lower logTG and higher logGlucose.

Table 35a. Model Fit Accounting for MHT Type Among MHT Users

Outcome	Block	N	MHT users Only		P Value for change in F	AIC	Δ AIC
			R ²	Adj. R ²			
aPWV	Block 1	153	0.01	-0.02	0.92	500.0	
	Block 2		0.09	0.05	< 0.01	489.5	-10.5
	Block 3		0.25	0.21	< 0.01	464.9	-24.6
AIx75	Block 1	153	0.01	-0.02	0.88	1206.0	
	Block 2		0.02	-0.02	0.17	1206.1	0.1
	Block 3		0.05	-0.01	0.24	1207.6	1.5
SBP	Block 1	153	0.04	0.00	0.36	1262.0	
	Block 2		0.05	0.00	0.61	1263.8	1.7
	Block 3		0.11	0.05	0.01	1258.3	-5.5
DBP	Block 1	153	0.04	0.00	0.39	1154.4	
	Block 2		0.05	0.00	0.49	1155.9	1.5
	Block 3		0.08	0.02	0.12	1155.6	-0.3
logFRS	Block 1	153	0.02	-0.01	0.67	246.7	
	Block 2		0.03	-0.01	0.18	246.9	0.1
	Block 3		0.15	0.09	< 0.01	233.6	-13.3
WC	Block 1	153	0.12	0.08	< 0.01	1211.5	
	Block 2		0.12	0.08	0.70	1213.4	1.8
	Block 3		0.20	0.14	< 0.01	1204.7	-8.6
HDL-C	Block 1	153	0.07	0.03	0.11	165.6	
	Block 2		0.10	0.06	0.02	162.2	-3.4
	Block 3		0.14	0.08	0.07	160.5	-1.6
LDL-C	Block 1	153	0.11	0.07	0.01	355.7	
	Block 2		0.11	0.07	0.42	357.0	1.3
	Block 3		0.12	0.06	0.71	361.5	4.5
logTG	Block 1	153	0.09	0.05	0.03	161.0	
	Block 2		0.10	0.05	0.24	161.5	0.5
	Block 3		0.11	0.05	0.53	165.1	3.6
logGlucose	Block 1	153	0.08	0.04	0.06	-188.7	

Block 2	0.08	0.04	0.37	-187.5	1.1
Block 3	0.11	0.04	0.27	-185.7	1.8

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose.

Block 1: Covariates entered
Block 2: Unopposed Estrogen usage entered
Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 or Block 2;
Red bold text used to emphasize statistically significant changes in Block 3.

Table 35b. Coefficients in Models Accounting for MHT Type Among MHT Users

Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	0.00 [-0.03, 0.02]	-0.02 [-0.18, 0.14]	
	Spontaneous menopause	0.05 [-0.36, 0.47]	0.02 [-0.14, 0.18]	
	History of VMS	-0.33 [-0.74, 0.09]	-0.11 [-0.26, 0.03]	
	Postsecondary education	-0.02 [-0.44, 0.40]	-0.01 [-0.16, 0.14]	
	Primary earner status	-0.05 [-0.43, 0.33]	-0.02 [-0.17, 0.13]	
	MVPA (mins)	-0.02 [-0.04, -0.01]	-0.37 [-0.55, -0.19]	*
	StaB (hours)	0.04 [-0.11, 0.19]	0.05 [-0.15, 0.26]	
	Sleep duration (hours)	-0.13 [-0.38, 0.11]	-0.09 [-0.26, 0.08]	
	Combined Estrogen-Progestogen (MHT reference group)			
	Unopposed Estrogen	-0.66 [-1.03, -0.30]	-0.28 [-0.43, -0.12]	*
AIx75	Age at menopause (years)	-0.23 [-0.54, 0.08]	-0.13 [-0.31, 0.05]	
	Spontaneous menopause	1.28 [-3.43, 5.99]	0.05 [-0.13, 0.23]	
	History of VMS	-0.84 [-5.57, 3.88]	-0.03 [-0.19, 0.13]	
	Postsecondary education	-0.13 [-4.91, 4.65]	0.00 [-0.17, 0.16]	
	Primary earner status	0.08 [-4.25, 4.41]	0.00 [-0.16, 0.17]	
	MVPA (mins)	-0.10 [-0.24, 0.03]	-0.15 [-0.36, 0.05]	
	StaB (hours)	0.20 [-1.49, 1.89]	0.03 [-0.20, 0.25]	
	Sleep duration (hours)	-0.13 [-2.92, 2.66]	-0.01 [-0.20, 0.18]	

Combined Estrogen-Progestogen (MHT reference group)				
SBP	Unopposed Estrogen	-2.64 [-6.79, 1.51]	-0.11 [-0.28, 0.06]	
	Age (years)	0.17 [-0.25, 0.60]	0.07 [-0.11, 0.25]	
	Age at menopause (years)	0.09 [-0.28, 0.45]	0.04 [-0.13, 0.21]	
	Spontaneous menopause	0.63 [-4.91, 6.17]	0.02 [-0.16, 0.20]	
	History of VMS	0.71 [-4.93, 6.34]	0.02 [-0.14, 0.18]	
	Postsecondary education	1.94 [-3.70, 7.57]	0.06 [-0.11, 0.22]	
	Primary earner status	-3.75 [-8.84, 1.35]	-0.12 [-0.28, 0.04]	
	MVPA (mins)	-0.28 [-0.45, -0.11]	-0.34 [-0.55, -0.14]	*
	StaB (hours)	-1.80 [-3.80, 0.20]	-0.20 [-0.42, 0.02]	
	Sleep duration (hours)	-1.78 [-5.08, 1.51]	-0.10 [-0.29, 0.09]	
Combined Estrogen-Progestogen (MHT reference group)				
DBP	Unopposed Estrogen	-1.18 [-6.28, 3.92]	-0.04 [-0.21, 0.13]	
	Age (years)	-0.39 [-0.69, -0.08]	-0.23 [-0.41, -0.05]	*
	Age at menopause (years)	0.03 [-0.23, 0.29]	0.02 [-0.15, 0.20]	
	Spontaneous menopause	2.80 [-1.16, 6.76]	0.13 [-0.05, 0.31]	
	History of VMS	-0.64 [-4.66, 3.39]	-0.03 [-0.19, 0.14]	
	Postsecondary education	-0.17 [-4.20, 3.86]	-0.01 [-0.17, 0.16]	
	Primary earner status	0.04 [-3.61, 3.68]	0.00 [-0.16, 0.16]	
	MVPA (mins)	-0.15 [-0.27, -0.03]	-0.25 [-0.46, -0.05]	*
	StaB (hours)	-0.85 [-2.28, 0.58]	-0.13 [-0.36, 0.09]	
	Sleep duration (hours)	-0.47 [-2.83, 1.88]	-0.04 [-0.23, 0.15]	
Combined Estrogen-Progestogen (MHT reference group)				
logFRS	Unopposed Estrogen	-1.20 [-4.84, 2.45]	-0.06 [-0.23, 0.12]	
	Age at menopause (years)	-0.01 [-0.02, 0.00]	-0.11 [-0.27, 0.06]	
	Spontaneous menopause	0.06 [-0.14, 0.25]	0.05 [-0.12, 0.23]	
	History of VMS	0.00 [-0.20, 0.19]	0.00 [-0.16, 0.15]	
	Postsecondary education	0.02 [-0.18, 0.22]	0.01 [-0.14, 0.17]	
	Primary earner status	-0.17 [-0.35, 0.01]	-0.15 [-0.31, 0.01]	
	MVPA (mins)	-0.01 [-0.02, -0.01]	-0.37 [-0.56, -0.17]	*
	StaB (hours)	-0.02 [-0.09, 0.05]	-0.06 [-0.27, 0.16]	
Sleep duration (hours)	-0.05 [-0.17, 0.06]	-0.08 [-0.27, 0.10]		

Combined Estrogen-Progestogen (MHT reference group)				
WC	Unopposed Estrogen	-0.10 [-0.27, 0.08]	-0.09 [-0.25, 0.07]	
	Age (years)	-0.83 [-1.19, -0.48]	-0.40 [-0.57, -0.23]	*
	Age at menopause (years)	-0.04 [-0.35, 0.26]	-0.02 [-0.19, 0.14]	
	Spontaneous menopause	-2.52 [-7.17, 2.14]	-0.09 [-0.26, 0.08]	
	History of VMS	-0.03 [-4.76, 4.70]	0.00 [-0.15, 0.15]	
	Postsecondary education	-2.10 [-6.83, 2.63]	-0.07 [-0.22, 0.09]	
	Primary earner status	3.21 [-1.07, 7.49]	0.11 [-0.04, 0.27]	
	MVPA (mins)	-0.18 [-0.32, -0.04]	-0.25 [-0.44, -0.06]	*
	StaB (hours)	0.48 [-1.20, 2.16]	0.06 [-0.15, 0.27]	
	Sleep duration (hours)	-1.58 [-4.35, 1.18]	-0.10 [-0.28, 0.08]	
Combined Estrogen-Progestogen (MHT reference group)				
HDL-C	Unopposed Estrogen	0.21 [-4.07, 4.49]	0.01 [-0.16, 0.17]	
	Age (years)	0.01 [0.00, 0.02]	0.11 [-0.07, 0.28]	
	Age at menopause (years)	0.00 [-0.01, 0.01]	0.04 [-0.13, 0.21]	
	Spontaneous menopause	0.09 [-0.06, 0.24]	0.10 [-0.07, 0.28]	
	History of VMS	-0.05 [-0.21, 0.11]	-0.05 [-0.21, 0.11]	
	Postsecondary education	0.12 [-0.04, 0.28]	0.12 [-0.04, 0.28]	
	Primary earner status	-0.07 [-0.21, 0.07]	-0.08 [-0.23, 0.08]	
	MVPA (mins)	0.00 [0.00, 0.01]	0.12 [-0.08, 0.32]	
	StaB (hours)	-0.04 [-0.09, 0.02]	-0.15 [-0.37, 0.07]	
	Sleep duration (hours)	-0.01 [-0.10, 0.08]	-0.02 [-0.21, 0.16]	
Combined Estrogen-Progestogen (MHT reference group)				
LDL-C	Unopposed Estrogen	-0.15 [-0.29, -0.01]	-0.18 [-0.35, -0.01]	*
	Age (years)	-0.02 [-0.04, 0.00]	-0.17 [-0.35, 0.01]	
	Age at menopause (years)	-0.02 [-0.04, 0.00]	-0.14 [-0.31, 0.03]	
	Spontaneous menopause	0.24 [-0.05, 0.54]	0.15 [-0.03, 0.32]	
	History of VMS	-0.06 [-0.36, 0.25]	-0.03 [-0.19, 0.13]	
	Postsecondary education	0.19 [-0.11, 0.49]	0.10 [-0.06, 0.26]	
	Primary earner status	-0.23 [-0.50, 0.04]	-0.13 [-0.29, 0.03]	
	MVPA (mins)	0.00 [-0.01, 0.01]	0.05 [-0.15, 0.25]	
	StaB (hours)	-0.03 [-0.14, 0.07]	-0.07 [-0.29, 0.15]	

	Sleep duration (hours)	0.00 [-0.17, 0.18]	0.00 [-0.19, 0.19]	
	Combined Estrogen-Progestogen (MHT reference group)			
	Unopposed Estrogen	0.13 [-0.14, 0.40]	0.08 [-0.09, 0.25]	
logTG	Age (years)	0.00 [-0.02, 0.01]	-0.07 [-0.25, 0.11]	
	Age at menopause (years)	-0.02 [-0.03, 0.00]	-0.25 [-0.43, -0.08]	*
	Spontaneous menopause	-0.02 [-0.17, 0.14]	-0.02 [-0.20, 0.16]	
	History of VMS	0.06 [-0.10, 0.21]	0.06 [-0.10, 0.22]	
	Postsecondary education	-0.02 [-0.18, 0.14]	-0.02 [-0.18, 0.14]	
	Primary earner status	-0.02 [-0.16, 0.12]	-0.02 [-0.18, 0.14]	
	MVPA (mins)	0.00 [-0.01, 0.00]	-0.13 [-0.33, 0.07]	
	StaB (hours)	0.00 [-0.06, 0.05]	-0.01 [-0.23, 0.21]	
	Sleep duration (hours)	0.01 [-0.09, 0.10]	0.01 [-0.18, 0.20]	
	Combined Estrogen-Progestogen (MHT reference group)			
	Unopposed Estrogen	0.08 [-0.06, 0.23]	0.10 [-0.07, 0.27]	
logGlucose	Age (years)	0.00 [0.00, 0.01]	0.20 [0.02, 0.38]	*
	Age at menopause (years)	0.00 [0.00, 0.01]	0.18 [0.01, 0.36]	*
	Spontaneous menopause	-0.03 [-0.08, 0.02]	-0.10 [-0.27, 0.08]	
	History of VMS	-0.02 [-0.07, 0.03]	-0.06 [-0.22, 0.10]	
	Postsecondary education	0.00 [-0.05, 0.05]	0.01 [-0.15, 0.17]	
	Primary earner status	0.02 [-0.03, 0.07]	0.07 [-0.09, 0.23]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.16 [-0.37, 0.04]	
	StaB (hours)	-0.02 [-0.03, 0.00]	-0.20 [-0.42, 0.03]	
	Sleep duration (hours)	-0.01 [-0.03, 0.02]	-0.03 [-0.22, 0.15]	
	Combined Estrogen-Progestogen (MHT reference group)			
	Unopposed Estrogen	0.02 [-0.02, 0.07]	0.10 [-0.08, 0.27]	

Abbreviations: Sig, significance; MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose.

*denotes $p < 0.05$

Summary of Objective 2B.2

First, similar to the results for Objective 2B.1, adding MHT type always significantly improved model fit for aPWV. The amount of variance in aPWV explained by models incorporating MHT type ranged from 2% to 6%, depending on the sample and model structure. However, unlike MHT usage history (Objective 2B.1), adding MHT type did not elicit any significant improvements in models predicting logFRS. There were additional, inconsistent improvements in some model specifications for HDL-C and logTG when MHT type was added, which were not present when MHT usage history was the exposure.

Second, movement behaviours continued to broadly improve models beyond the MHT exposure. These blocks always increased the explanatory value of models for aPWV, SBP, and logFRS. Models for AIx75, DBP, WC, and HDL-C were improved in the full sample by adding movement behaviours. LDL-C, logTG, and logGlucose models were inconsistently improved by movement behaviours.

Third, independent associations between MHT type and CV outcomes were most robust for aPWV and HDL-C. Combined estrogen-progestogen use was associated with faster aPWV compared to controls in both unadjusted and adjusted models, and with higher HDL-C in unadjusted models. Relative to combined usage, unopposed estrogen use was associated with slower aPWV and lower HDL-C in both unadjusted and adjusted models, as well as higher logTG in the unadjusted model.

Fourth, MVPA was, again, involved in nearly every outcome. In the full sample, more MVPA was associated with slower aPWV, lower AIx75, lower SBP, lower DBP, lower logFRS, smaller WC, higher HDL-C, and lower logGlucose. It was also associated with higher LDL-C and lower logTG in unadjusted models. Among MHT users, more MVPA was associated with slower aPWV, lower SBP, and lower logFRS. There were also inconsistent associations with DBP, WC, and logGLucose, depending on the sample and covariate adjustment.

Fifth, StaB was associated with lower DBP and lower HDL-C in both unadjusted and adjusted models in the full sample, and with faster aPWV in unadjusted models. It was not associated with any outcome when the sample was restricted to MHT users. Sleep duration remained statistically unrelated to any outcome across all model specifications.

3.3.2.3 Objective 2B.3

Full Sample: Unadjusted Models

Oral, transdermal, and vaginal routes of MHT administration were entered into Block 1, with controls as the reference group.

Route of administration (Block 1) significantly improved model fit beyond the null for aPWV, explaining an estimated 3% of its variance (Appendix Table 4a). However, Block 1 was no different from a null model in its ability to explain the remaining CV outcomes. Entering movement behaviours (Block 2) improved model fit beyond Block 1 for all outcomes except for LDL-C. Most notably, movement behaviours increased the amount of variance explained by the models from 3% to 8% for aPWV (Adjusted $R^2 = 0.08$; $p < 0.01$; $\Delta AIC = -40.7$) and to 7% for WC (Adjusted $R^2 = 0.07$; $p < 0.01$; $\Delta AIC = -62.5$). It should also be noted that although there was a statistically significant improvement in model fit from Block 1 to Block 2 for logTG, the adjusted R^2 value still indicated that 0% of the variance in this outcome was explained ($p = 0.03$; $\Delta AIC = -3.1$).

Unadjusted model coefficients are presented in Appendix Table 4b. Relative to controls, oral route of MHT administration was associated with faster aPWV ($\beta = 0.15$, 95% CI [-0.09, 0.22]), while vaginal usage was associated with lower logFRS ($\beta = -0.08$, 95% CI [-0.15, -0.02]). As with some previous specifications, MVPA was independently associated with every outcome in this set of models. Higher average MVPA was associated with slower aPWV ($\beta = -0.16$, 95% CI [-0.23, -0.09]), lower AIx75, lower SBP, lower DBP ($\beta = -0.11$ [-0.19, -0.04]), lower log FRS ($\beta = -0.16$, 95% CI [-0.24, -0.09]), smaller WC ($\beta = -0.25$, 95% CI [-0.32, -0.17]), higher HDL-C ($\beta = 0.13$, 95% CI [0.05, 0.20]), higher LDL-C, lower logTG, and lower logGlucose. Higher average StaB was associated with faster aPWV ($\beta = 0.11$, 95% CI [0.03, 0.19]), lower DBP ($\beta = -0.12$, 95% CI [-0.21, -0.04]), and lower HDL-C ($\beta = -0.11$, 95% CI [-0.20, -0.03]). For the first time in these analyses, sleep duration was independently associated with a CV outcome: longer average sleep duration was associated with smaller WC ($\beta = -0.08$, 95% CI [-0.16, -0.01]).

Full Sample: Adjusted Models

Oral, transdermal, and vaginal routes of MHT administration were entered into Block 2 following the covariates (Block 1), with controls as the reference group.

Covariates alone (Block 1) significantly improved model fit beyond the null for aPWV, SBP, logFRS, WC, HDL-C, LDL, logTG, and logGlucose (Table 36a). It did not provide additional explanatory value beyond a null model for AIx75 and DBP. Adding MHT routes (Block 2) significantly improved model fit for aPWV (Adj. $R^2 = 0.06$; $p < 0.01$; $\Delta AIC = -25.9$) and logFRS (Adj. $R^2 = 0.02$; $p = 0.04$; $\Delta AIC = -2.2$). It did not add additional explanatory value beyond covariates alone for any other outcome.

Compared to Block 2, entering movement behaviours (Block 3) significantly improved model fit for aPWV, AIx75, SBP, DBP, logFRS, WC, and HDL-C (Figure 10). For example, including movement behaviours increased the estimate of explained variance from 6% to 10% for aPWV (Adj. $R^2 = 0.10$; $p < 0.01$; $\Delta AIC = -26.5$), 2% to 4% for logFRS (Adj. $R^2 = 0.04$; $p < 0.01$; $\Delta AIC = -11.4$), 6% to 12% for WC (Adj. $R^2 = 0.12$; $p < 0.01$; $\Delta AIC = -46.2$), and 3% to 7% for HDL-C (Adj. $R^2 = 0.07$; $p < 0.01$; $\Delta AIC = -28.2$). Block 3 did not improve model fit for LDL-C, logTG, or logGlucose; in these cases, Block 1 models were the most parsimonious.

As with the unadjusted models, oral MHT usage was independently associated with faster aPWV ($\beta = 0.17$, 95% CI [0.10, 0.24]) compared to controls, and vaginal usage was associated with lower logFRS ($\beta = -0.09$, 95% CI [-0.16, -0.02]) compared to controls (Table 36b). Transdermal usage was not independently associated with any outcome.

MVPA was independently and favourably associated with aPWV, AIx75, SBP, DBP, logFRS, WC, HDL-C, and logGlucose (Table 28b). Examples to highlight are its association with slower aPWV ($\beta = -0.16$, 95% CI [-0.24, -0.08]), lower SBP ($\beta = -0.12$, 95% CI [-0.21, -0.04]), lower DBP ($\beta = -0.11$, 95% CI [-0.20, -0.03]), lower logFRS ($\beta = -0.15$, 95% CI [-0.23, -0.07]), and smaller WC ($\beta = -0.23$, 95% CI [-0.31, -0.15]). Unlike the unadjusted models, MVPA was not independently associated with LDL-C or logTG after accounting for covariates. StaB continued to have independent negative associations with DBP ($\beta = -0.13$, 95% CI [-0.22, -0.03]) and HDL-C ($\beta = -0.15$, 95% CI [-0.23, -0.06]) but was no longer associated with aPWV after covariate adjustment. Furthermore, the association between longer sleep duration and smaller WC also disappeared after covariate adjustment.

Older age was associated with higher SBP, smaller WC, higher HDL-C, lower LDL-C, and lower logTG. Older age at menopause was associated with higher logGlucose. Experiencing spontaneous menopause was associated with faster aPWV, smaller WC, higher HDL-C, lower

logTG, and lower logGlucose. A history of vasomotor symptoms was associated with slower aPWV. Completing a postsecondary education was associated with lower DBP, lower logFRS, smaller WC, and higher HDL-C. Lastly, self-identifying as the primary household earner was associated with larger WC, lower HDL-C, and lower LDL-C (Table 28b).

Table 36a. Model Fit Accounting for MHT Route in the Full Sample

Outcome	Block	N	R ²	Full Sample		AIC	ΔAIC
				Adj. R ²	P Value for change in F		
aPWV	Block 1	743	0.03	0.02	< 0.01	2257.6	
	Block 2		0.07	0.06	< 0.01	2231.7	-25.9
	Block 3		0.11	0.10	< 0.01	2205.2	-26.5
AIx75	Block 1	743	0.01	0.00	0.14	5566.2	
	Block 2		0.01	0.00	0.95	5571.9	5.7
	Block 3		0.03	0.01	0.02	5567.6	-4.3
SBP	Block 1	743	0.02	0.01	0.02	6024.4	
	Block 2		0.02	0.01	0.52	6028.2	3.7
	Block 3		0.03	0.02	0.04	6025.5	-2.7
DBP	Block 1	743	0.01	0.00	0.15	5535.4	
	Block 2		0.01	0.00	0.91	5540.9	5.4
	Block 3		0.03	0.01	0.01	5536.2	-4.7
logFRS	Block 1	743	0.02	0.01	0.02	1137.8	
	Block 2		0.03	0.02	0.04	1135.6	-2.2
	Block 3		0.05	0.04	< 0.01	1124.2	-11.4
WC	Block 1	743	0.07	0.06	< 0.01	5912.0	
	Block 2		0.07	0.06	0.66	5916.4	4.4
	Block 3		0.13	0.12	< 0.01	5870.2	-46.2
HDL-C	Block 1	743	0.04	0.04	< 0.01	843.6	
	Block 2		0.05	0.03	0.66	848.0	4.4
	Block 3		0.09	0.07	< 0.01	819.8	-28.2
LDL-C	Block 1	743	0.02	0.02	0.01	1879.9	
	Block 2		0.03	0.01	0.73	1884.6	4.7
	Block 3		0.03	0.01	0.37	1887.4	2.8
logTG	Block 1	743	0.03	0.02	< 0.01	803.4	
	Block 2		0.03	0.02	0.97	809.1	5.8
	Block 3		0.04	0.02	0.10	808.8	-0.3
logGlucose	Block 1	742	0.03	0.03	< 0.01	-1000.2	

Block 2	0.04	0.02	0.46	-996.9	3.4
Block 3	0.04	0.03	0.18	-995.8	1.0

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose.

Block 1: Covariates entered

Block 2: Oral, Transdermal, Vaginal usage entered

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 or Block 2;

Red bold text used to emphasize statistically significant changes in Block 3.

Table 36b. Coefficients in Models Accounting for MHT Route in the Full Sample

Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	-0.01 [-0.02, 0.01]	-0.04 [-0.11, 0.04]	
	Spontaneous menopause	0.23 [0.02, 0.45]	0.08 [0.01, 0.16]	*
	History of VMS	-0.34 [-0.52, -0.17]	-0.14 [-0.21, -0.07]	*
	Postsecondary education	-0.04 [-0.23, 0.15]	-0.01 [-0.08, 0.05]	
	Primary earner status	0.03 [-0.13, 0.19]	0.01 [-0.06, 0.08]	
	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.16 [-0.24, -0.08]	*
	StaB (hours)	0.05 [-0.01, 0.11]	0.07 [-0.01, 0.16]	
	Sleep duration (hours)	0.03 [-0.07, 0.14]	0.03 [-0.05, 0.10]	
	Controls (MHT reference group)			
	Oral	0.59 [0.34, 0.84]	0.17 [0.10, 0.24]	*
	Transdermal	0.34 [0.00, 0.68]	0.07 [0.00, 0.14]	
	Vaginal	-0.15 [-0.45, 0.14]	-0.04 [-0.11, 0.03]	
AIx75	Age at menopause (years)	-0.13 [-0.28, 0.03]	-0.07 [-0.14, 0.01]	
	Spontaneous menopause	0.87 [-1.22, 2.97]	0.03 [-0.05, 0.11]	
	History of VMS	-1.65 [-3.32, 0.02]	-0.07 [-0.14, 0.00]	
	Postsecondary education	-0.03 [-1.82, 1.77]	0.00 [-0.07, 0.07]	
	Primary earner status	-0.73 [-2.25, 0.79]	-0.03 [-0.11, 0.04]	
	MVPA (mins)	-0.04 [-0.08, 0.00]	-0.09 [-0.17, 0.00]	*

	StaB (hours)	0.34 [-0.24, 0.91]	0.05 [-0.04, 0.14]	
	Sleep duration (hours)	0.20 [-0.81, 1.20]	0.02 [-0.07, 0.10]	
	Controls (MHT reference group)			
	Oral	0.12 [-2.28, 2.51]	0.00 [-0.07, 0.08]	
	Transdermal	0.38 [-2.91, 3.67]	0.01 [-0.07, 0.08]	
	Vaginal	-0.20 [-3.02, 2.62]	-0.01 [-0.08, 0.07]	
SBP	Age (years)	0.23 [0.05, 0.40]	0.09 [0.02, 0.17]	*
	Age at menopause (years)	0.02 [-0.19, 0.23]	0.01 [-0.07, 0.09]	
	Spontaneous menopause	0.51 [-2.35, 3.36]	0.01 [-0.06, 0.09]	
	History of VMS	-1.36 [-3.65, 0.93]	-0.04 [-0.12, 0.03]	
	Postsecondary education	-1.60 [-4.04, 0.85]	-0.05 [-0.12, 0.02]	
	Primary earner status	0.05 [-2.02, 2.12]	0.00 [-0.07, 0.07]	
	MVPA (mins)	-0.08 [-0.14, -0.03]	-0.12 [-0.21, -0.04]	*
	StaB (hours)	-0.57 [-1.36, 0.21]	-0.07 [-0.16, 0.02]	
	Sleep duration (hours)	-0.40 [-1.77, 0.97]	-0.02 [-0.11, 0.06]	
	Controls (MHT reference group)			
	Oral	-0.08 [-3.39, 3.23]	0.00 [-0.08, 0.07]	
	Transdermal	1.98 [-2.51, 6.46]	0.03 [-0.04, 0.11]	
	Vaginal	-1.99 [-5.83, 1.84]	-0.04 [-0.11, 0.03]	
DBP	Age (years)	-0.11 [-0.24, 0.02]	-0.07 [-0.14, 0.01]	
	Age at menopause (years)	-0.06 [-0.21, 0.09]	-0.03 [-0.11, 0.05]	
	Spontaneous menopause	0.43 [-1.62, 2.49]	0.02 [-0.06, 0.10]	
	History of VMS	-0.21 [-1.86, 1.44]	-0.01 [-0.08, 0.06]	
	Postsecondary education	-1.83 [-3.59, -0.08]	-0.08 [-0.15, 0.00]	*
	Primary earner status	0.58 [-0.91, 2.07]	0.03 [-0.04, 0.10]	
	MVPA (mins)	-0.05 [-0.09, -0.01]	-0.11 [-0.20, -0.03]	*
	StaB (hours)	-0.77 [-1.34, -0.21]	-0.13 [-0.22, -0.03]	*
	Sleep duration (hours)	-0.27 [-1.26, 0.71]	-0.02 [-0.10, 0.06]	
	Controls (MHT reference group)			
	Oral	-0.98 [-3.36, 1.40]	-0.03 [-0.11, 0.04]	
	Transdermal	-0.65 [-3.87, 2.58]	-0.01 [-0.09, 0.06]	
	Vaginal	0.20 [-2.56, 2.96]	0.01 [-0.07, 0.08]	

logFRS	Age at menopause (years)	0.00 [-0.01, 0.01]	-0.01 [-0.09, 0.06]	
	Spontaneous menopause	0.00 [-0.10, 0.11]	0.00 [-0.07, 0.08]	
	History of VMS	-0.07 [-0.15, 0.01]	-0.06 [-0.13, 0.01]	
	Postsecondary education	-0.11 [-0.20, -0.02]	-0.09 [-0.16, -0.02]	*
	Primary earner status	0.02 [-0.06, 0.09]	0.02 [-0.06, 0.09]	
	MVPA (mins)	0.00 [-0.01, 0.00]	-0.15 [-0.23, -0.07]	*
	StaB (hours)	0.00 [-0.03, 0.03]	0.01 [-0.08, 0.10]	
	Sleep duration (hours)	0.00 [-0.05, 0.05]	0.01 [-0.08, 0.09]	
	Controls (MHT reference group)			
	Oral	0.02 [-0.10, 0.14]	0.01 [-0.06, 0.08]	
WC	Transdermal	0.05 [-0.11, 0.22]	0.02 [-0.05, 0.10]	
	Vaginal	-0.18 [-0.32, -0.04]	-0.09 [-0.16, -0.02]	*
	Age (years)	-0.38 [-0.54, -0.22]	-0.17 [-0.24, -0.10]	*
	Age at menopause (years)	0.07 [-0.12, 0.26]	0.03 [-0.05, 0.10]	
	Spontaneous menopause	-4.10 [-6.67, -1.53]	-0.12 [-0.19, -0.04]	*
	History of VMS	-1.66 [-3.73, 0.40]	-0.06 [-0.13, 0.01]	
	Postsecondary education	-2.32 [-4.52, -0.12]	-0.07 [-0.14, 0.00]	*
	Primary earner status	3.24 [1.38, 5.11]	0.12 [0.05, 0.19]	*
	MVPA (mins)	-0.15 [-0.20, -0.10]	-0.23 [-0.31, -0.15]	*
	StaB (hours)	0.18 [-0.52, 0.89]	0.02 [-0.06, 0.11]	
HDL-C	Sleep duration (hours)	-1.16 [-2.40, 0.07]	-0.07 [-0.15, 0.00]	
	Controls (MHT reference group)			
	Oral	-1.59 [-4.58, 1.39]	-0.04 [-0.11, 0.03]	
	Transdermal	1.12 [-2.91, 5.16]	0.02 [-0.05, 0.09]	
	Vaginal	-1.22 [-4.68, 2.23]	-0.02 [-0.09, 0.04]	
	Age (years)	0.01 [0.01, 0.02]	0.16 [0.09, 0.24]	*
	Age at menopause (years)	0.00 [-0.01, 0.00]	-0.04 [-0.12, 0.03]	
	Spontaneous menopause	0.13 [0.04, 0.21]	0.11 [0.04, 0.19]	*
	History of VMS	0.02 [-0.05, 0.08]	0.02 [-0.05, 0.09]	
	Postsecondary education	0.09 [0.01, 0.16]	0.08 [0.01, 0.15]	*
	Primary earner status	-0.07 [-0.13, 0.00]	-0.07 [-0.14, 0.00]	*
	MVPA (mins)	0.00 [0.00, 0.00]	0.11 [0.03, 0.19]	*

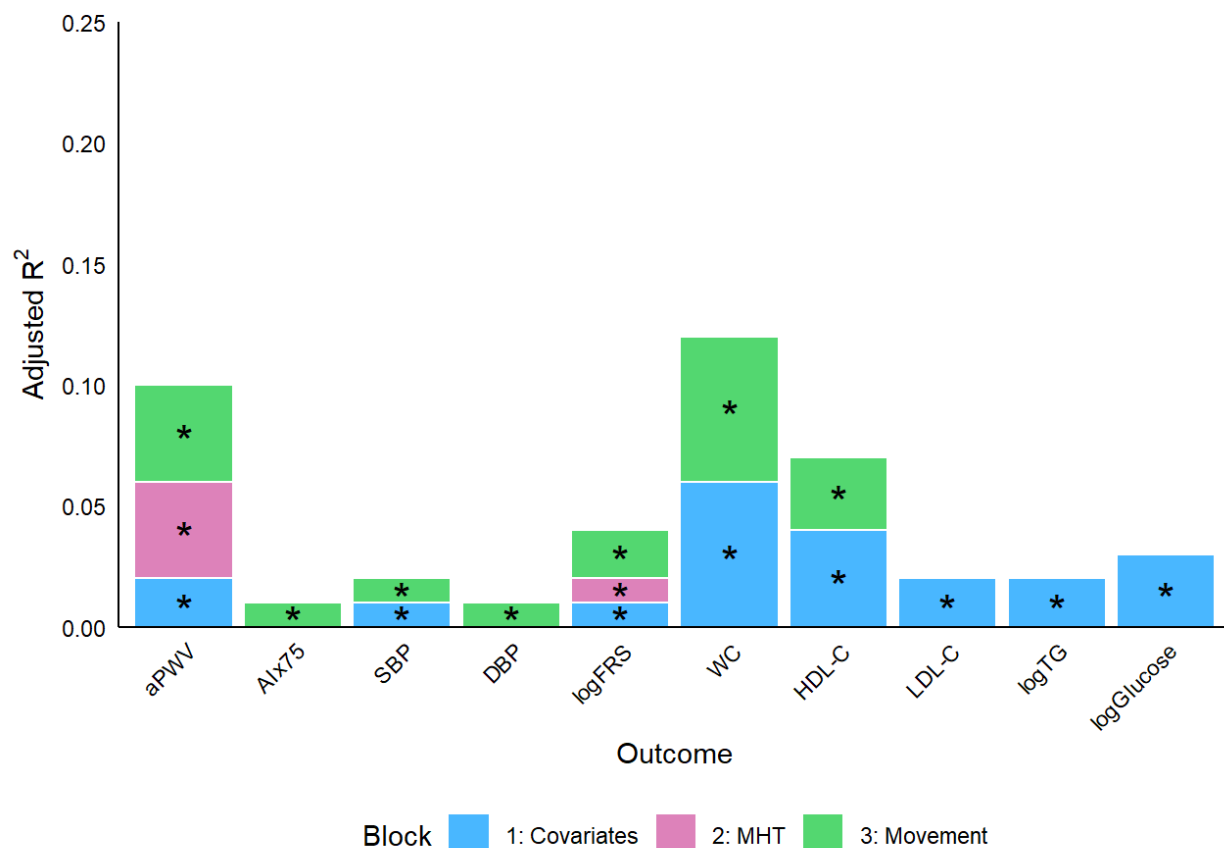
	StaB (hours)	-0.04 [-0.06, -0.02]	-0.15 [-0.23, -0.06]	*
	Sleep duration (hours)	-0.02 [-0.06, 0.03]	-0.03 [-0.11, 0.05]	
	Controls (MHT reference group)			
	Oral	0.00 [-0.10, 0.10]	0.00 [-0.07, 0.07]	
	Transdermal	0.06 [-0.08, 0.19]	0.03 [-0.04, 0.10]	
	Vaginal	-0.06 [-0.17, 0.06]	-0.03 [-0.11, 0.04]	
LDL-C	Age (years)	-0.02 [-0.03, -0.01]	-0.11 [-0.19, -0.04]	*
	Age at menopause (years)	0.00 [-0.02, 0.01]	-0.02 [-0.10, 0.06]	
	Spontaneous menopause	0.03 [-0.15, 0.20]	0.01 [-0.07, 0.09]	
	History of VMS	-0.06 [-0.20, 0.08]	-0.03 [-0.10, 0.04]	
	Postsecondary education	0.04 [-0.11, 0.19]	0.02 [-0.05, 0.09]	
	Primary earner status	-0.16 [-0.29, -0.03]	-0.09 [-0.16, -0.02]	*
	MVPA (mins)	0.00 [0.00, 0.01]	0.07 [-0.01, 0.16]	
	StaB (hours)	0.02 [-0.03, 0.06]	0.03 [-0.06, 0.12]	
	Sleep duration (hours)	0.02 [-0.07, 0.10]	0.02 [-0.06, 0.10]	
	Controls (MHT reference group)			
	Oral	-0.09 [-0.30, 0.11]	-0.03 [-0.11, 0.04]	
	Transdermal	-0.01 [-0.29, 0.27]	0.00 [-0.08, 0.07]	
	Vaginal	-0.08 [-0.32, 0.16]	-0.02 [-0.10, 0.05]	
logTG	Age (years)	-0.01 [-0.01, 0.00]	-0.11 [-0.19, -0.04]	*
	Age at menopause (years)	0.00 [-0.01, 0.00]	-0.05 [-0.13, 0.03]	
	Spontaneous menopause	-0.10 [-0.19, -0.02]	-0.09 [-0.17, -0.02]	*
	History of VMS	-0.05 [-0.12, 0.02]	-0.05 [-0.13, 0.02]	
	Postsecondary education	-0.03 [-0.11, 0.04]	-0.03 [-0.10, 0.04]	
	Primary earner status	0.04 [-0.02, 0.10]	0.05 [-0.02, 0.12]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.06 [-0.15, 0.02]	
	StaB (hours)	0.01 [-0.01, 0.04]	0.05 [-0.04, 0.14]	
	Sleep duration (hours)	0.01 [-0.03, 0.05]	0.02 [-0.06, 0.10]	
	Controls (MHT reference group)			
	Oral	-0.02 [-0.12, 0.08]	-0.02 [-0.09, 0.06]	
	Transdermal	-0.04 [-0.17, 0.10]	-0.02 [-0.09, 0.05]	
	Vaginal	-0.01 [-0.12, 0.11]	0.00 [-0.08, 0.07]	

logGlucose	Age (years)	0.00 [0.00, 0.00]	0.05 [-0.03, 0.12]	
	Age at menopause (years)	0.00 [0.00, 0.00]	0.11 [0.03, 0.19]	*
	Spontaneous menopause	-0.04 [-0.06, -0.01]	-0.12 [-0.20, -0.04]	*
	History of VMS	-0.02 [-0.04, 0.00]	-0.06 [-0.13, 0.01]	
	Postsecondary education	-0.01 [-0.04, 0.01]	-0.05 [-0.12, 0.02]	
	Primary earner status	0.02 [0.00, 0.03]	0.06 [-0.01, 0.13]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.09 [-0.18, -0.01]	*
	StaB (hours)	0.00 [-0.01, 0.00]	-0.04 [-0.13, 0.05]	
	Sleep duration (hours)	0.00 [-0.01, 0.01]	-0.01 [-0.09, 0.07]	
	Controls (MHT reference group)			
	Oral	0.01 [-0.02, 0.04]	0.02 [-0.05, 0.10]	
	Transdermal	0.02 [-0.02, 0.06]	0.03 [-0.04, 0.11]	
	Vaginal	-0.02 [-0.05, 0.02]	-0.04 [-0.11, 0.03]	

Abbreviations: Sig, significance; MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose.

*denotes $p < 0.05$

Figure 10. Contribution to Model Fit by Covariates, MHT Route, and Movement Behaviours



Note. * denotes $p < 0.05$ for F change.

MHT Users Only: Unadjusted Models

Transdermal and vaginal routes of MHT administration were entered into Block 1, with oral usage as the reference group.

Unadjusted model fit statistics are presented in Appendix Table 4c. MHT route of administration (Block 1) significantly improved model fit beyond the null for aPWV (Adj. $R^2 = 0.07$; $p < 0.01$) and logFRS (Adj. $R^2 = 0.03$; $p = 0.02$). Entering movement behaviours (Block 2) further improved these models, increasing the amount of explained variance from 7% to 17% for aPWV ($p < 0.01$; $\Delta AIC = -21.3$) and from 3% to 9% for logFRS ($p < 0.01$; $\Delta AIC = -10.1$). Block 2 also significantly improved model fit for SBP and WC. No other outcomes were well explained by either Block 1 or Block 2.

Regarding individual predictors, only vaginal MHT usage and MVPA were independently associated with outcomes in these models (Appendix Table 4d). There were no associations between transdermal MHT use, StaB, or sleep duration and CV outcomes. Relative to oral usage, vaginal usage was associated with slower aPWV ($\beta = -0.26$, 95% CI $[-0.39, -0.12]$) and lower logFRS ($\beta = -0.16$, 95% CI $[-0.30, -0.02]$). Higher average MVPA was associated with slower aPWV ($\beta = -0.27$, 95% CI $[-0.42, -0.12]$) and lower logFRS ($\beta = -0.24$, 95% CI $[-0.40, -0.08]$), as well as lower SBP and smaller WC.

MHT Users Only: Adjusted Models

Transdermal and vaginal routes of MHT administration were entered into Block 2 following covariates (Block 1), with oral usage as the reference group.

Covariates alone (Block 1) improved model fit beyond the null for WC, LDL-C, logTG, and logGlucose (Table 37a). Entering transdermal and vaginal MHT routes (Block 2) improved model fit beyond Block 1 for aPWV (Adjusted $R^2 = 0.07$; $p < 0.01$; $\Delta AIC = -14.1$) and logFRS (Adjusted $R^2 = 0.03$; $p = 0.01$; $\Delta AIC = -5.1$). Adding movement behaviours (Block 3) further improved these models, increasing the amount of explained variance from 7% to 16% for aPWV (Adj. $R^2 = 0.16$; $p < 0.01$; $\Delta AIC = -16.2$) and from 3% to 9% for logFRS (Adj. $R^2 = 0.09$; $p < 0.01$; $\Delta AIC = -9.2$). Block 3 also significantly improved model fit beyond Block 2 for SBP and WC.

Coefficients for the adjusted models are presented in Table 37b. Similar to the unadjusted models, vaginal MHT use was associated with slower aPWV ($\beta = -0.28$, 95% CI $[-0.42, -0.13]$) and lower logFRS ($\beta = -0.16$, 95% CI $[-0.31, 0.00]$) compared with oral MHT use. Transdermal usage was not associated with any outcome. Furthermore, after covariate adjustment, higher average MVPA remained independently associated with slower aPWV ($\beta = -0.27$, 95% CI $[-0.44, -0.11]$) and lower logFRS ($\beta = -0.29$, 95% CI $[-0.47, -0.12]$), as well as lower SBP and smaller WC. It was also associated with lower DBP after adjusting for covariates. StaB and sleep duration remained statistically unrelated to CV outcomes in these models.

Regarding individual covariates, older age was associated with lower DBP, smaller WC, and higher logGlucose. Older age at menopause was associated with lower logTG and higher logGlucose. Experiencing spontaneous menopause was associated with higher HDL-C. Self-

identifying as the primary household earner was associated with a larger WC. Having a history of vasomotor symptoms or completing a postsecondary education was not associated with any outcome in these models (Table 37b).

Table 37a. Model Fit Accounting for MHT Route Among MHT Users

Outcome	Block	N	MHT users Only		P Value for change in F	AIC	Δ AIC
			R ²	Adj. R ²			
aPWV	Block 1	183	0.01	-0.02	0.82	589.9	
	Block 2		0.11	0.07	< 0.01	575.8	-14.1
	Block 3		0.21	0.16	< 0.01	559.5	-16.2
AIx75	Block 1	183	0.01	-0.02	0.85	1432.1	
	Block 2		0.01	-0.03	0.93	1436.0	3.8
	Block 3		0.04	-0.02	0.19	1437.0	1.0
SBP	Block 1	183	0.03	-0.01	0.56	1517.5	
	Block 2		0.04	0.00	0.32	1519.1	1.6
	Block 3		0.10	0.04	0.01	1513.6	-5.4
DBP	Block 1	183	0.04	0.00	0.35	1389.9	
	Block 2		0.04	-0.01	0.96	1393.8	3.9
	Block 3		0.08	0.02	0.06	1392.1	-1.8
logFRS	Block 1	183	0.02	-0.01	0.63	290.3	
	Block 2		0.07	0.03	0.01	285.2	-5.1
	Block 3		0.14	0.09	< 0.01	276.0	-9.2
WC	Block 1	183	0.12	0.09	< 0.01	1451.0	
	Block 2		0.13	0.09	0.36	1452.9	1.9
	Block 3		0.25	0.20	< 0.01	1430.1	-22.8
HDL-C	Block 1	183	0.07	0.03	0.06	178.7	
	Block 2		0.08	0.04	0.21	179.3	0.7
	Block 3		0.12	0.06	0.10	178.6	-0.7
LDL-C	Block 1	183	0.07	0.04	0.04	437.5	
	Block 2		0.08	0.03	0.77	440.9	3.4
	Block 3		0.10	0.04	0.22	442.3	1.3
logTG	Block 1	183	0.09	0.05	0.01	182.5	
	Block 2		0.09	0.05	0.81	186.1	3.6
	Block 3		0.10	0.04	0.47	189.4	3.3
logGlucose	Block 1	183	0.07	0.04	0.04	-199.4	

Block 2	0.08	0.04	0.38	-197.4	2.0
Block 3	0.10	0.04	0.48	-194.0	3.4

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose.

Block 1: Covariates entered
Block 2: Transdermal, Vaginal usage entered
Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 or Block 2;
Red bold text used to emphasize statistically significant changes in Block 3.

Table 37b. Coefficients in Models Accounting for MHT Route Among MHT Users

Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	0.00 [-0.02, 0.03]	0.01 [-0.14, 0.16]	
	Spontaneous menopause	0.32 [-0.07, 0.71]	0.12 [-0.03, 0.28]	
	History of VMS	-0.27 [-0.65, 0.12]	-0.09 [-0.23, 0.04]	
	Postsecondary education	0.14 [-0.25, 0.53]	0.05 [-0.09, 0.19]	
	Primary earner status	-0.05 [-0.40, 0.30]	-0.02 [-0.16, 0.12]	
	MVPA (mins)	-0.02 [-0.03, -0.01]	-0.27 [-0.44, -0.11]	*
	StaB (hours)	0.05 [-0.08, 0.18]	0.07 [-0.11, 0.25]	
	Sleep duration (hours)	-0.08 [-0.30, 0.14]	-0.06 [-0.21, 0.10]	
	Oral (MHT reference group)			
	Transdermal	-0.22 [-0.63, 0.19]	-0.08 [-0.23, 0.07]	
AIx75	Vaginal	-0.71 [-1.08, -0.33]	-0.28 [-0.42, -0.13]	*
	Age at menopause (years)	-0.17 [-0.45, 0.12]	-0.09 [-0.26, 0.07]	
	Spontaneous menopause	1.69 [-2.58, 5.96]	0.07 [-0.10, 0.23]	
	History of VMS	0.30 [-3.97, 4.57]	0.01 [-0.14, 0.16]	
	Postsecondary education	-0.29 [-4.58, 4.01]	-0.01 [-0.16, 0.14]	
	Primary earner status	1.17 [-2.65, 5.00]	0.05 [-0.10, 0.20]	
	MVPA (mins)	-0.10 [-0.22, 0.02]	-0.15 [-0.34, 0.03]	
	StaB (hours)	0.18 [-1.29, 1.64]	0.02 [-0.18, 0.22]	

SBP	Sleep duration (hours)	0.17 [-2.23, 2.57]	0.01 [-0.16, 0.18]	
	Oral (MHT reference group)			
	Transdermal	0.57 [-3.94, 5.07]	0.02 [-0.14, 0.18]	
	Vaginal	0.18 [-3.96, 4.32]	0.01 [-0.16, 0.17]	
	Age (years)	0.13 [-0.26, 0.52]	0.05 [-0.11, 0.21]	
	Age at menopause (years)	0.04 [-0.31, 0.39]	0.02 [-0.14, 0.17]	
	Spontaneous menopause	1.95 [-3.34, 7.25]	0.06 [-0.10, 0.22]	
	History of VMS	1.18 [-4.11, 6.48]	0.03 [-0.12, 0.18]	
	Postsecondary education	1.48 [-3.80, 6.76]	0.04 [-0.11, 0.19]	
	Primary earner status	-2.81 [-7.52, 1.90]	-0.09 [-0.23, 0.06]	
	MVPA (mins)	-0.24 [-0.39, -0.09]	-0.30 [-0.48, -0.12]	*
	StaB (hours)	-1.55 [-3.36, 0.27]	-0.17 [-0.36, 0.03]	
DBP	Sleep duration (hours)	-2.19 [-5.14, 0.77]	-0.12 [-0.29, 0.04]	
	Oral (MHT reference group)			
	Transdermal	2.05 [-3.52, 7.63]	0.06 [-0.10, 0.22]	
	Vaginal	-1.70 [-6.97, 3.57]	-0.05 [-0.22, 0.11]	
	Age (years)	-0.33 [-0.61, -0.05]	-0.19 [-0.35, -0.03]	*
	Age at menopause (years)	-0.02 [-0.28, 0.23]	-0.02 [-0.17, 0.14]	
	Spontaneous menopause	3.10 [-0.69, 6.90]	0.13 [-0.03, 0.30]	
	History of VMS	-0.09 [-3.89, 3.71]	0.00 [-0.15, 0.15]	
	Postsecondary education	-0.51 [-4.30, 3.28]	-0.02 [-0.17, 0.13]	
	Primary earner status	0.55 [-2.82, 3.93]	0.02 [-0.12, 0.17]	
	MVPA (mins)	-0.14 [-0.25, -0.04]	-0.25 [-0.43, -0.07]	*
	StaB (hours)	-1.12 [-2.42, 0.18]	-0.17 [-0.37, 0.03]	
logFRS	Sleep duration (hours)	-1.05 [-3.17, 1.07]	-0.08 [-0.25, 0.08]	
	Oral (MHT reference group)			
	Transdermal	0.48 [-3.52, 4.48]	0.02 [-0.14, 0.18]	
	Vaginal	0.58 [-3.20, 4.36]	0.03 [-0.14, 0.19]	
	Age at menopause (years)	-0.01 [-0.02, 0.00]	-0.09 [-0.24, 0.06]	
	Spontaneous menopause	0.11 [-0.07, 0.29]	0.10 [-0.06, 0.25]	
	History of VMS	-0.01 [-0.19, 0.17]	-0.01 [-0.15, 0.14]	
	Postsecondary education	0.01 [-0.17, 0.19]	0.01 [-0.13, 0.16]	

	Primary earner status	-0.13 [-0.29, 0.03]	-0.11 [-0.26, 0.03]	
	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.29 [-0.47, -0.12]	*
	StaB (hours)	-0.02 [-0.08, 0.05]	-0.05 [-0.24, 0.14]	
	Sleep duration (hours)	-0.04 [-0.14, 0.06]	-0.07 [-0.23, 0.09]	
	Oral (MHT reference group)			
	Transdermal	0.05 [-0.13, 0.24]	0.04 [-0.11, 0.20]	
	Vaginal	-0.18 [-0.35, -0.01]	-0.16 [-0.31, 0.00]	*
WC	Age (years)	-0.81 [-1.12, -0.50]	-0.38 [-0.52, -0.23]	*
	Age at menopause (years)	-0.11 [-0.39, 0.17]	-0.05 [-0.20, 0.09]	
	Spontaneous menopause	-0.96 [-5.18, 3.25]	-0.03 [-0.18, 0.11]	
	History of VMS	0.25 [-3.96, 4.47]	0.01 [-0.13, 0.14]	
	Postsecondary education	-2.90 [-7.10, 1.31]	-0.09 [-0.23, 0.04]	
	Primary earner status	3.86 [0.11, 7.61]	0.14 [0.00, 0.27]	*
	MVPA (mins)	-0.23 [-0.35, -0.12]	-0.33 [-0.49, -0.16]	*
	StaB (hours)	0.33 [-1.12, 1.77]	0.04 [-0.14, 0.22]	
	Sleep duration (hours)	-2.06 [-4.41, 0.30]	-0.13 [-0.28, 0.02]	
	Oral (MHT reference group)			
	Transdermal	2.64 [-1.80, 7.08]	0.09 [-0.06, 0.23]	
	Vaginal	-0.36 [-4.55, 3.84]	-0.01 [-0.16, 0.14]	
HDL-C	Age (years)	0.01 [0.00, 0.02]	0.11 [-0.04, 0.27]	
	Age at menopause (years)	0.00 [-0.01, 0.01]	0.02 [-0.13, 0.18]	
	Spontaneous menopause	0.17 [0.03, 0.31]	0.20 [0.04, 0.36]	*
	History of VMS	-0.07 [-0.21, 0.07]	-0.07 [-0.22, 0.08]	
	Postsecondary education	0.11 [-0.02, 0.25]	0.12 [-0.02, 0.27]	
	Primary earner status	-0.05 [-0.17, 0.07]	-0.06 [-0.20, 0.09]	
	MVPA (mins)	0.00 [0.00, 0.01]	0.08 [-0.10, 0.26]	
	StaB (hours)	-0.03 [-0.08, 0.01]	-0.14 [-0.34, 0.05]	
	Sleep duration (hours)	-0.02 [-0.10, 0.06]	-0.04 [-0.20, 0.12]	
	Oral (MHT reference group)			
	Transdermal	0.06 [-0.09, 0.20]	0.06 [-0.09, 0.22]	
	Vaginal	-0.09 [-0.22, 0.05]	-0.10 [-0.27, 0.06]	
LDL-C	Age (years)	-0.02 [-0.04, 0.00]	-0.14 [-0.30, 0.02]	

logTG	Age at menopause (years)	-0.02 [-0.03, 0.00]	-0.13 [-0.28, 0.03]	
	Spontaneous menopause	0.19 [-0.10, 0.47]	0.11 [-0.06, 0.27]	
	History of VMS	-0.12 [-0.40, 0.17]	-0.06 [-0.21, 0.09]	
	Postsecondary education	0.10 [-0.18, 0.38]	0.05 [-0.09, 0.20]	
	Primary earner status	-0.21 [-0.46, 0.04]	-0.12 [-0.27, 0.03]	
	MVPA (mins)	0.00 [0.00, 0.01]	0.11 [-0.07, 0.29]	
	StaB (hours)	-0.04 [-0.13, 0.06]	-0.07 [-0.27, 0.12]	
	Sleep duration (hours)	0.01 [-0.15, 0.17]	0.01 [-0.16, 0.18]	
	Oral (MHT reference group)			
	Transdermal	0.09 [-0.21, 0.39]	0.05 [-0.11, 0.21]	
	Vaginal	-0.03 [-0.31, 0.25]	-0.02 [-0.18, 0.15]	
	Age (years)	-0.01 [-0.02, 0.01]	-0.08 [-0.24, 0.08]	
	Age at menopause (years)	-0.01 [-0.02, 0.00]	-0.22 [-0.38, -0.06]	*
	Spontaneous menopause	-0.08 [-0.22, 0.06]	-0.09 [-0.26, 0.07]	
logGlucose	History of VMS	0.00 [-0.14, 0.14]	0.00 [-0.15, 0.15]	
	Postsecondary education	-0.07 [-0.21, 0.07]	-0.07 [-0.22, 0.08]	
	Primary earner status	0.01 [-0.12, 0.14]	0.01 [-0.13, 0.16]	
	MVPA (mins)	0.00 [-0.01, 0.00]	-0.12 [-0.30, 0.06]	
	StaB (hours)	0.00 [-0.05, 0.05]	0.00 [-0.20, 0.19]	
	Sleep duration (hours)	0.00 [-0.08, 0.07]	-0.01 [-0.17, 0.16]	
	Oral (MHT reference group)			
	Transdermal	-0.01 [-0.16, 0.14]	-0.01 [-0.17, 0.15]	
	Vaginal	0.05 [-0.09, 0.19]	0.06 [-0.11, 0.22]	
	Age (years)	0.00 [0.00, 0.01]	0.18 [0.02, 0.34]	*
	Age at menopause (years)	0.00 [0.00, 0.01]	0.16 [0.00, 0.31]	*
	Spontaneous menopause	-0.03 [-0.08, 0.02]	-0.08 [-0.25, 0.08]	
	History of VMS	-0.02 [-0.07, 0.03]	-0.05 [-0.20, 0.10]	
	Postsecondary education	0.01 [-0.04, 0.06]	0.04 [-0.11, 0.19]	
	Primary earner status	0.02 [-0.02, 0.06]	0.07 [-0.08, 0.21]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.11 [-0.29, 0.07]	
	StaB (hours)	-0.01 [-0.03, 0.01]	-0.13 [-0.33, 0.06]	
	Sleep duration (hours)	0.00 [-0.03, 0.03]	-0.01 [-0.17, 0.16]	

Oral (MHT reference group)		
Transdermal	0.02 [-0.04, 0.07]	0.05 [-0.11, 0.21]
Vaginal	-0.02 [-0.07, 0.03]	-0.06 [-0.23, 0.10]

Abbreviations: Sig, significance; MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

*denotes $p < 0.05$

Summary of Objective 2B.3

First, adding the MHT route of administration added significant explanatory value for only two outcomes: aPWV and logFRS. Unlike when MHT usage history or type were added, entering MHT route could not explain additional variance in any other outcome beyond the null and/or once covariates were included.

Second, movement behaviours remained the main contributors to explanatory value compared to MHT exposures. Entering movement behaviours improved model fit beyond the MHT route for aPWV, SBP, logFRS, and WC in all model specifications. In the full sample, both unadjusted and adjusted models for AIx75, DBP, and HDL-C improved after adding movement behaviours, whereas improvements for logTG and logGlucose were present only in the unadjusted models. No models for LDL-C were affected after adding movement behaviours.

Third, individual MHT routes were consistently associated with aPWV and logFRS. Compared to controls, oral usage was associated with faster aPWV, and vaginal usage was associated with lower logFRS. Oral usage was also associated with a smaller WC in unadjusted models. In the MHT user subset, vaginal usage was associated with slower aPWV and lower logFRS compared to oral usage.

Fourth, MVPA persisted as the most consistent predictor of CV outcomes. In the full sample, more MVPA was independently associated with slower aPWV, lower AIx75, lower SBP, lower DBP, lower logFRS, smaller WC, higher HDL-C, and lower logGlucose in both unadjusted and adjusted models. It was also associated with higher LDL-C and lower logGlucose in unadjusted models. Among MHT users, more MVPA was associated with slower aPWV, lower SBP, lower logFRS, and smaller WC in both unadjusted and adjusted models. It was also associated with lower DBP in adjusted models only.

Fifth, StaB was associated with lower DBP and lower HDL-C in unadjusted and adjusted models in the full sample, as well as faster aPWV in unadjusted models. For the first and only time in these analyses, sleep duration had an independent association with a CV outcome: it was negatively associated with WC in unadjusted models in the full sample. However, neither StaB nor sleep duration was associated with any outcome when the sample was restricted to MHT users.

3.3.2.4 Summary of Objective 2B Results

Across all three MHT exposure definitions, MHT variables most consistently improved model fit for aPWV, and to a lesser extent, logFRS. Improvements for other outcomes (e.g., SBP, WC, HDL-C, logTG, logGlucose) were inconsistent and often dependent on the specific exposure definition, sample restriction, or covariate adjustment. MHT usage history showed the broadest pattern of associations (i.e., current usage being associated with aPWV, SBP, DBP, logFRS, WC, and logGlucose), whereas MHT type and route produced more selective effects. In general, independent MHT associations paralleled the improvements in fit, and were most often associated with aPWV and logFRS. Consistent favourable patterns were observed for current MHT usage (relative to controls and former MHT users) and vaginal usage (relative to controls and oral users). However, with the exception of aPWV and logFRS, MHT exposures rarely explained substantial additional variance from null models and/or those with covariates.

In contrast, movement behaviours generally demonstrated consistent and substantial explanatory contributions across all objectives and model specifications. Regardless of whether MHT exposure was defined by history, type, or route, entering movement behaviours always improved model fit for aPWV, SBP, and logFRS, and frequently improved fit for AIx75, DBP, WC, HDL-C, and logGlucose. Moreover, MVPA showed stable and favourable independent associations with these outcomes across virtually all specifications, and its standardized coefficients were typically among the largest in the models. The only exception was LDL-C, with MVPA rarely independently associated; when an association was observed, it was unfavourable. StaB showed more limited and sample-dependent associations; that is, associations were observed primarily for DBP and HDL-C in the full sample, and rarely among MHT users only. Sleep duration was generally unrelated to outcomes, with only a single isolated association observed.

The evidence from Objective 2B analyses ultimately suggests that, while MHT exposures were involved in explaining some CV outcomes (particularly aPWV and FRS), most relationships were better explained by other variables, particularly movement behaviours. The dominant and most reproducible finding across all modelling specifications was the independent and comparatively strong contribution of MVPA to CV outcomes. These findings support the original hypothesis for Objective 2B: movement behaviours generally improved model fit

beyond covariates and MHT exposures, and individual behaviours broadly demonstrated greater explanatory value than MHT exposures.

3.3.3 Summary of Objective 2 Results

The hypothesis for Objective 2A was unsupported. Comparative analyses revealed that MHT exposure definitions (history, type, and route) did not yield significant differences across most tested variables. Consistent differences were observed in age, age at menopause, and aPWV, as well as MVPA, logFRS, and logGlucose in some analyses. Age was the most consistent differentiator, with younger controls contrasting older MHT subgroups in former users, combined estrogen-progestogen users, and oral users. Relatedly, the differences in aPWV paralleled those observed with age; that is, the older groups had higher aPWV than the controls. Former and current MHT users also engaged in significantly less MVPA than controls. These findings suggest that some of the observed differences across MHT categorizations may be more reflective of demographic and lifestyle profiles than of distinct clinical CV risk signatures.

In contrast, the hypothesis for Objective 2B was supported. Hierarchical regression models demonstrated that, while specific MHT parameters (e.g., current usage, vaginal administration) consistently contributed to variance in aPWV and FRS, their explanatory utility for other CV markers was inconsistent. Movement behaviours, however, provided substantial and reproducible improvements in model fit regardless of MHT exposure for nearly all outcomes. MVPA emerged as the dominant independent predictor, associated with most outcomes, and often yielding larger standardized coefficients than MHT variables. These findings substantiate the argument that movement behaviours possess superior explanatory value for CV risk compared to MHT exposure definitions.

The synthesis of Objective 2 indicates a hierarchy of influence regarding CV risk in the WARM Hearts cohort. MHT exposures were related to some CV outcomes (namely, aPWV and FRS), but they do not appear to be substantial contributors to CV outcome variance more broadly. The predictive superiority of MVPA suggests that lifestyle behaviours could be more effective determinants of CV health than the pharmacological nuances of hormone therapy. Ultimately, movement behaviours explained CV risk more effectively than MHT history, type, or route of administration.

3.4 Sensitivity Analyses

3.4.1 Controlling for BMI

Tables summarizing the model fit statistics and coefficients, with and without BMI included in the models, are displayed in Appendix Tables 5a through 5f. Including BMI in the covariate block (Block 1) significantly improved model fit relative to the null model for most models, irrespective of the definition of MHT exposure. Compared to the primary models, the explained variance in Block 1 was noticeably larger when BMI was included in SBP, DBP, logFRS, HDL-C, logTG, and logGlucose models across all MHT exposure definitions. Conversely, the models for aPWV and LDL-C were approximately the same, irrespective of BMI adjustment. The subsequent addition of MHT parameters (Block 2) did not alter fit patterns for MHT type or route; however, when parameterized by MHT history, Block 2 gained significant explanatory value for HDL-C that was absent in the primary models.

Adjusting for BMI attenuated the overall explanatory power of the movement behaviours block (Block 3). While the addition of movement variables consistently improved fit for aPWV and DBP, it no longer contributed significantly to SBP across any MHT definition, and its explanatory value for AIx75, logFRS, and HDL-C varied by MHT parameterization. This attenuation aligns with the observed shifts in coefficients. BMI demonstrated independent and unfavourable associations with AIx75, SBP, DBP, logFRS, HDL-C, logTG, and logGlucose. Consequently, the independent effects of MVPA were heavily attenuated, losing significant associations with AIx75, SBP, DBP, and logGlucose across all models. For logFRS, with which both MVPA and BMI were associated, the magnitude of its association with MVPA systematically decreased (e.g., β attenuating from -0.15 to -0.10).

Associations for StaB remained largely consistent with the primary models, except for a negative association with SBP specifically within the MHT history model. Regarding MHT exposures, adjusting for BMI nullified the associations between current MHT usage and SBP, DBP, and logGlucose. Former usage remained significantly associated with aPWV. Notably, within the MHT route model, transdermal use was associated with a slower aPWV, a finding not observed in the primary analyses.

Models were evidently highly sensitive to the inclusion of BMI, particularly concerning the movement block and the independent effects of MVPA. The substantial attenuation of MVPA's predictive value when adjusting for adiposity suggests a notable degree of shared variance between the variables. Therefore, these findings support the methodological decision to exclude BMI from the primary models to prevent overadjustment and preserve the ability to detect the independent contributions of movement behaviours on CV outcomes.

3.4.2 Age-Stratified Group Comparisons

Results from group comparisons by MHT exposure within each age stratum are presented in Appendix Tables 6a through 6f.

Age 55-64 Stratum

For each MHT parameterization, differences in variables in the younger sample were limited and associated with small statistical effect sizes (Appendix Tables 6a, 6b, 6c). When grouped by MHT history, former users exhibited higher DBP (81 ± 10 mmHg) compared to controls (77 ± 10 mmHg) and current users (76 ± 11 mmHg). Although the omnibus tests indicated significant differences in age at menopause across all MHT definitions, post-hoc pairwise comparisons were only significant for MHT type, suggesting that unopposed estrogen users (50 [44, 53] years) were younger at menopause than controls (53 [51, 55] years).

Age 65 and Older Stratum

In the older sample, group differences were more pronounced. Irrespective of the MHT exposure definition, groups differed significantly in age, age at menopause, MVPA, and aPWV (Appendix Tables 6d, 6e, 6f).

When grouped by history, former users were older (70 [67, 74] years) than controls (69 [66, 72] years) and current users (68 [66, 71] years); were younger at menopause (51 [47, 53] years) than controls (52 [51, 55] years); and engaged in less MVPA (13.0 [5.0, 24.5] mins/day) than controls (18.9 [7.3, 35.0] mins/day). Current users were also younger at menopause (51 [46, 53]) compared to controls. Although the omnibus test for aPWV was significant, post-hoc tests were non-significant.

When grouped by type, combined estrogen-progestogen users were older (71 [68, 75] years) than controls; were less active (10.9 [4.0, 21.6] mins/day) than controls; and had faster aPWV (10.2 [9.7, 11.2] m/s) than controls (9.8 [9.3, 10.4] m/s). Unopposed estrogen users were also younger at menopause (50 [45, 52] years) than controls.

When grouped by route, oral users were older (72 [67, 75] years) than controls; younger at menopause (51 [45, 53] years) than controls; engaged in less MVPA (12.9 [5.6, 20.8] mins/day) than controls; and had faster aPWV (10.2 [9.5, 11.1] m/s) than vaginal users (9.3 [9.1, 9.9]) m/s. Transdermal users were also younger at menopause (50 [44, 53] years) than controls. Although the omnibus test for FRS was significant, the post-hoc tests were not significant.

The analyses suggest that the patterns of differences observed in the primary analyses may be disproportionately influenced by the older stratum (age 65 and older), as, in the younger cohort (age 55-64), MHT status did not appreciably differentiate CV or behavioural profiles. Additionally, the patterns of group differences in the older stratum paralleled those in the primary analyses; that is, virtually the same variables differed between groups in both analyses.

3.4.3 Controlling for Age in aPWV, AIx75, and FRS

Including age in models substantially altered the interpretation of models predicting aPWV, somewhat altered the interpretation of models predicting AIx75, and minimally impacted the interpretation of models predicting logFRS (Appendix Tables 7a through 7f). For aPWV, age explained the vast majority of the variance (Adjusted $R^2 = 0.80-0.81$), dwarfing the fit of the primary models and rendering the subsequent additions of MHT and movement behaviours negligible. Age also improved the Block 1 model fit for AIx75 and logFRS, although the improvement was relatively small for AIx75 (+ 0.01 – 0.02 in adj. R^2 compared to primary models), and movement behaviours retained significant explanatory value for logFRS.

Across all models, age was the dominant predictor with the strongest effect magnitude (e.g., aPWV $\beta = 0.88 - 0.89$; AIx75 $\beta = 0.12 - 0.14$; logFRS $\beta = 0.34 - 0.36$). Consequently, the independent effects of MVPA were universally attenuated; MVPA lost significance entirely for AIx75, demonstrated substantially reduced standardized coefficients for aPWV, and slightly reduced coefficients for logFRS. StaB also lost any significant associations with aPWV. Importantly, adjusting for age completely nullified the previously observed associations between

MHT usage (former, combined estrogen-progestogen, and oral) and faster aPWV. In contrast, MHT associations with logFRS were robust to age adjustment, with current and vaginal usage maintaining significant negative associations and virtually unchanged standardized coefficients.

These findings were expected, since age is mathematically factored into the calculation of these three variables. However, the extreme sensitivity of aPWV to age adjustment (which completely nullified the apparent unfavourable associations of former usage, combined estrogen-progestogen usage, and oral usage) calls into question the validity of the primary findings for this outcome. Given that the older groups exhibited the slowest aPWV, the previously observed MHT associations could reflect age-related confounding rather than a true physiological effect of MHT. Conversely, the associations between current usage and vaginal usage with lower logFRS were robust to age adjustment. Whether these associations are due to the direct effects of MHT or to underlying differences in baseline health and selection into MHT is an important area for future investigation.

3.4.4 Controlling for MHT duration among MHT users

MHT duration was entered into adjusted regression models in Block 2 alongside the MHT exposures. Overall, incorporating this variable did not alter the interpretation of the main findings (Appendix Tables 8a-8f).

The most notable changes were observed in models predicting aPWV. For example, the adjusted R^2 for Block 2 was 0.02 to 0.04 units higher relative to the primary analyses for aPWV, depending on the central MHT exposure analyzed (history, type, or route). Furthermore, a longer duration of MHT use was consistently and independently associated with faster aPWV ($\beta = 0.20$ to 0.21 , depending on MHT exposure). This association might reflect the confounding influence of chronological age. That is, individuals with longer MHT usage durations could also be more likely to be older in age. Since age is strongly associated with aPWV, MHT duration acts as a proxy for age under this reasoning.

Beyond aPWV, MHT duration was not independently associated with any other outcome, and additional minor shifts in regression outputs were not inconsistent or contradictory of the primary results.

3.4.5 Accounting for MHT timing among MHT users

To account for MHT timing in accordance with the timing hypothesis, group differences were re-assessed with alternative categorizations, and regression models were re-fit with this variable included. Differences in outcomes were assessed by groups categorized by MHT timing: controls vs. delayed MHT initiation (≥ 10 years post-menopause) vs. within 10 years of menopause (Appendix Table 9). Differences were observed in three variables: age, age at menopause, and aPWV. Individuals who initiated MHT within 10 years of menopause were older (66 [60, 70] years) than controls (63 [60, 67] years), and had faster aPWV (9.1 [8.4, 10.0] m/s) than controls (8.8 [8.2, 9.7] m/s). Controls were younger at age of menopause (53 [51, 55] years) than those with delayed MHT initiation (45 [41, 51] years) and those who initiated MHT within 10 years of menopause (51 [47, 54]); individuals with delayed MHT initiation were also significantly younger than those who initiated MHT within 10 years of menopause.

In adjusted regression models, delayed MHT initiation was entered into Block 2 alongside MHT exposures (Appendix Tables 10a-10f). There were a small number of minor changes in regression outputs, but none that were discordant with the primary findings. Relative to initiation within 10 years of menopause, delayed initiation was not independently associated with any outcome.

3.4.6 Controlling for APOs

A history of APOs was entered into Block 1 of adjusted regression models alongside covariates (Appendix Tables 11a to 11f). Model outputs were virtually unchanged with this variable included.

Chapter 4: Discussion

4.1 Main Analyses Summary and Review of Hypotheses

A summary of the hypotheses and their support is presented in Table 38. The primary hypothesis for Objective 1, which sought to replicate and extend the work of Kalenga et al. (2022), was partially supported. In alignment with the foundational findings of the original study, increasing the sample size (Objective 1A) confirmed specific associations, most notably the relationship between oral estrogen usage and faster aPWV. This consistency could mean that certain estrogen-route-specific influences on arterial stiffness are robust and generalizable within this population. However, the lack of support for Hypotheses 1B and 1C indicates that these associations may be highly specific to certain parameters and do not necessarily extend to a broader range of CV markers or alternative variable operationalizations. The predictive utility of movement behaviours (Hypothesis 1D) further suggests that, although there are associations with the estrogen route, lifestyle factors could provide a more substantial contribution to the explanation of variance in CV outcomes.

Objective 2 was also partially supported, as the explanatory dominance of movement behaviours (Objective 2B) was confirmed across alternative MHT exposure definitions, despite a lack of broad descriptive group differences (Objective 2A). Comparative analyses (Objective 2A) revealed that MHT history, type, and route did not yield significant differences across the majority of CV and behavioural outcomes; however, there were consistent differences in age, age at menopause, and aPWV across all exposure definitions, as well as differences in MVPA and FRS by history and route groupings. Hypothesis 2B (that movement behaviours would improve model fit beyond covariates and MHT exposures and would demonstrate greater explanatory value than MHT exposures) was robustly supported across all sub-objectives. Hierarchical regression models demonstrated that the addition of movement behaviours significantly improved model fit beyond MHT exposures and covariates, with MVPA emerging as the most consistent and among the strongest predictors of CV risk.

It is critical to note that, while models indicated that certain MHT exposures (namely, former and oral usage) may be less favorable to CV health (compared to e.g., controls, current, and vaginal usage), these findings should be interpreted as relative differences within a cohort

that was clinically healthy overall. For most outcomes, the mean and median values for all groups remained within normative benchmarks (Table 9), indicating that these associations reflect subclinical variations in CV risk rather than diseased states. In other words, MHT usage did not appear to confer clinically significant CV risk or harm within the WARM Hearts cohort.

These findings collectively validate the foundational observations regarding MHT and arterial stiffness from Kalenga et al., while situating them within a more comprehensive behavioural and demographic framework. In healthy postmenopausal women, the influence of MHT on CV markers was eclipsed by the inclusion of sex and gender-based covariates and movement behaviours. MVPA, in particular, demonstrated substantially greater relevance than MHT, regardless of exposure classification. Therefore, this research introduces a novel perspective, in that assessments of the influence of MHT on CV health might be incomplete if not accounting for movement behaviours.

Table 38. Summary of Hypotheses and Their Support

Objective	Hypothesis	Status	Rationale/Evidence
1	Estrogen MHT route associates with CV outcomes, but movement behaviours contribute more substantially to their variance in the framework of Kalenga et al. (2022)	Partially supported	1D.2 and 1D.3 supported. 1A and 1D.1 are partially supported. 1B and 1C are not supported.
	1A Associations between estrogen MHT route and CV outcomes from Kalenga et al. (2022) persist with a larger sample size	Partially supported	Replicated aPWV and D1SBP differences; failed to replicate AIx75 or transdermal route associations.
	1B Associations from Kalenga et al. (2022) persist across alternative variable operationalizationsw	Not supported	Findings were unstable; aPWV models were highly sensitive to age, and SBP was inconsistent across measurement days and the number of trials.
	1C Differences across MHT routes extend to a broader set of CV and movement variables beyond those selected in Kalenga et al. (2022)	Not supported	Groups differed on only 3 of 17 variables (age, age at menopause, aPWV)
	1D Movement behaviours account for greater variance in CV outcomes compared to MHT route	Supported	1D.1 is partially supported 1D.2 and 1D.3 are supported
	1D.1 Movement behaviours improve model fit when added to the original model structure in Kalenga et al. (2022)	Partially supported	Improved fir for aPWV, AIx75, and DBP in the full sample, but no improvements among MHT users alone.

1D.2	Movement behaviours explain greater variance in unadjusted models beyond the estrogen MHT route, and individual behaviours will be more strongly associated with outcomes	Supported	Improved fit for all outcomes except HDL-C in the full sample; MVPA associated with most markers
1D.3	Movement behaviours explain greater variance and adjusted models beyond the estrogen MHT route, and individual behaviours will be more strongly associated with outcomes	Supported	Improved fir for aPWV, AIx75, logFRS, WC, and HDL-C in the full sample; MVPA remained a robust predictor.
2	CV outcomes are associated with various MHT definitions, but movement behaviours account for greater variance in CV risk	Partially supported	2A is not supported 2B is supported
2A	Demographic, behavioural, and CV variables differ across groups defined by MHT exposure definitions (usage history, type, route)	Not supported	None of the sub-hypotheses (2A.1, 2A.2, 2A.3) are supported
2A.1	The tested variables differ by MHT usage history (controls vs. former usage vs. current usage)	Not supported	Significant differences were observed for only 6 of 17 variables (age, age at menopause, MVPA, aPWV, FRS, glucose)
2A.2	The tested variables differ by MHT type (controls vs. combined estrogen-progestogen vs. unopposed estrogen)	Not supported	Significant differences were observed for 3 of 17 variables (age, age at menopause, aPWV)

2A.3	The tested variables differ by MHT route of administration (controls vs. oral vs. transdermal vs. vaginal)	Not supported	Significant differences were observed for 5 of 17 variables (age, age at menopause, MVPA, aPWV, FRS)
2B	Movement behaviours improve model fit and demonstrate greater explanatory value than MHT exposures	Supported	All sub-hypotheses (2B.1, 2B.2, 2B.3) were supported
2B.1	Movement behaviours account for more variance than MHT history, and individual behaviours will be more strongly associated with outcomes	Supported	Movement improved fit beyond history for most outcomes; MVPA was the most consistent, and often the strongest, independent predictor
2B.2	Movement behaviours account for more variance than MHT type, and individual behaviours will be more strongly associated with outcomes	Supported	Movement improved fit beyond type for most outcomes; MVPA was the most consistent, and often the strongest, independent predictor
2B.3	Movement behaviours account for more variance than MHT route, and individual behaviours will be more strongly associated with outcomes	Supported	Movement improved fit beyond route for most outcomes; MVPA was the most consistent, and often the strongest, independent predictor

4.2 Clinical and Practical Recommendations

Based on the findings from this thesis and other literature, the following sections will describe recommendations for taking MHT, engaging in movement behaviours, and updating clinical guidelines. It will also propose directions for future research regarding movement behaviours and MHT.

4.2.1 Choice of MHT

As discussed in Chapter 1.2, postmenopausal women may be concerned or fearful about the safety and efficacy of MHT, and unsure if MHT is a suitable option for their unique needs.^{25,58–61} Additionally, healthcare professionals may be unaware of the current consensus on its safety, when to recommend its usage, and what formulations to prescribe.^{24,65–67} This cross-sectional thesis analysis is not appropriate for making causal claims about the safety of MHT, nor can it be used to recommend MHT as a primary or secondary prevention strategy for CVD. However, its findings can support women to make decisions about treatment and lifestyle choices and help inform updates to clinical guidelines for MHT.

The essential conclusion from this thesis regarding MHT is that, in general, its usage does not appear to be associated with clinically significant CV risk in a cohort of healthy Manitoban women. This aligns with messaging published since 2020 by eight Canadian and international societies (Appendix Table 12).^{22–24,55–57,215,337} Of the position statements and guidelines consulted, the British Menopause Society, the Korean Society of Menopause, and the International Menopause Society are the most liberal in their recommendations, stating that MHT likely has a neutral or beneficial effect on CV health in healthy symptomatic women.^{23,56,215} They also suggest that, although they should receive additional counselling and monitoring, individuals beyond 10 years post-menopause or over the age of 60 are unlikely to be at increased risk of CVD based on current evidence. Other societies are comparatively more cautious. The Society of Obstetricians and Gynecologists of Canada, the Menopause Society (formerly the North American Menopause Society), the American College of Cardiology, and the European Society of Endocrinology agree that initiating MHT within 10 years of menopause or before age 60 is unlikely to be associated with increased CVD risk.^{22,55,57,337} However, they warn against a slightly increased absolute risk of CVD when initiating MHT more than 10 years after

menopause or older than age 60 (supporting the timing hypothesis) and recommend thorough counselling and individualized approaches for these individuals. As no clear conclusions regarding safety can be drawn from its data, this thesis supports the more cautious recommendations and advises older women and those further past menopause who seek symptom relief to weigh the possible benefits and risks of MHT usage with their healthcare providers.

The type of MHT was not consistently linked to CV outcomes in this thesis. Combined estrogen-progestogen usage was associated with greater arterial stiffness, but this relationship was confounded by age and may not be clinically significant.^{288,289} Otherwise, unopposed estrogen and combined estrogen-progestogen therapies appeared to have a neutral relationship with CV outcomes in this analysis. Interpretations of these findings are also limited by the lack of granularity regarding the specific types of estrogen and progestogen used. In particular, the type of progestogen appears to be influential. Expert groups agree that micronized progesterone, which is effectively identical to endogenous progesterone, and other biologically similar progestogens (such as dydrogesterone) are likely neutral or favourable for cardiometabolic health.^{22–24,56,57,215,337–339} Other evidence suggests that certain synthetic progestins (e.g., medroxyprogesterone acetate, norethisterone acetate) may influence lipid profiles, but the consistency and direction of associations are mixed.³⁴⁰ Canadian guidelines suggest that general combined estrogen-progestogen usage could increase the risk of venous thromboembolism, which was not an outcome available for examination in this analysis.⁵⁷ Progestogens are only indicated for women with an intact uterus to prevent endometrial hyperplasia and cancer, so the choice of progestogen is not relevant for all individuals. Regarding the choice of estrogen, there is no clear consensus on which options (e.g., conjugated equine estrogens, estradiol, estrone) are best.^{20,56} Some groups recommend estradiol over conjugated equine estrogens due to a possible increased risk of venous thromboembolism with the latter, as well as estradiol being more “natural.”^{23,215,337} The findings of this thesis do not (and cannot) contradict the current evidence and therefore support existing clinical guidance. The choice of MHT type should be made in consultation with healthcare providers and tailored to individual needs and preferences.

Findings from this thesis suggested that vaginal MHT users have a lower 10-year risk of CV events (measured by the FRS) compared to controls and oral users after adjustment for

confounders, as well as after adjusting for age in sensitivity analyses. Transdermal use was not associated with increased or decreased CV risk compared with the other groups. Thus, non-oral routes may broadly be preferable to oral routes, consistent with current guidelines. All recent publications from expert groups consulted for this thesis have highlighted potential risks of oral MHT for certain CV outcomes, namely venous thromboembolism.^{22–24,55–57,215,337} As such, oral MHT is contraindicated for women at risk for venous thromboembolism or who have other CVD risk factors (e.g., uncontrolled hypertension). It may also be associated with increased risk of stroke, particularly in women over age 60.²³ That said, although oral usage was associated with a relatively worse CV profile in this thesis, the differences were not clinically concerning, and the median oral user would be classified as having low CV risk (Table 9, Table 23a). The International Menopause Society has stated that there is little reason to avoid prescribing oral MHT for women without contraindications, and the findings from this analysis could fit with that judgment.²⁴ Therefore, this thesis supports guidance that generally recommends non-oral routes over oral routes, but that oral routes may still be preferred for some women.

It should be noted that most oral users in this cohort were former MHT users, and most vaginal users were current users (Figure 6a). Similarly, most former users were oral users, and most current users were vaginal users (Figure 6b). These were the MHT exposure categories most consistently associated with CV outcomes, where current and vaginal users had relatively better CV health. However, this trend should not be interpreted as ‘former users of oral MHT have worse CV health’, or that ‘actively using vaginal MHT leads to better CV health’. Rather, underlying factors associated with individuals' choices to initiate and discontinue certain MHT regimens may contribute to the observed patterns. For example, data from several Western countries show that the popularity of oral MHT declined following the Women’s Health Initiative reports in 2002 and subsequent updates to clinical guidelines; in some cases, there were simultaneous increases in non-oral formulations, including systemic and local vaginal MHT.^{41,44,47,48,64,341} Some authors suggested that these patterns could indicate different profiles of MHT users, where the healthiest individuals began to choose non-oral routes over oral ones after 2002, aligning with changing recommendations.³⁴¹ A similar trend could explain the pattern seen in this thesis. The current and vaginal users might reflect a demographic of women who are more active health consumers; they may be more up to date with public health advice and regularly

consult with healthcare providers about managing menopausal symptoms. Still, these ideas are speculative, and additional analyses of the data are needed to validate this conjecture.

To summarize, individuals seeking MHT to manage symptoms of menopause should generally not be concerned about adverse effects on their CV health. Choices about what regimens to take should be made in collaboration with healthcare providers based on symptoms, individual preferences, lifestyle, reproductive status, and current CV risk. Individuals may prefer non-oral routes, which have a less controversial safety profile than oral routes, particularly for women at high risk of CV events. Lastly, MHT should not be used as a primary or secondary prevention strategy for CVD. Instead, postmenopausal women should prioritize lifestyle modifications, including a focus on movement behaviours, to promote health.

4.2.2 Importance of Movement Behaviours

The benefits of MVPA (and PA in general) on numerous health outcomes are well known and were identified in Chapter 1.3.^{74,79–83} Unlike MHT, regular PA is recommended for the primary and secondary prevention of CVD.^{269,342} In the WARM Hearts cohort, MVPA had the most consistent and overall strongest associations with CV outcomes, compared to StaB, sleep duration, and MHT usage. It was associated with a more favourable 10-year CVD risk, arterial stiffness, blood pressure, waist circumference, and metabolic indicators, consistent with current evidence.^{74,79,81,83} When comparing MVPA across MHT exposure groups, former users and oral users averaged 4 to 5 minutes less per day than controls. These differences may seem small, but the Canadian 24HMG emphasize that any progression towards activity targets will result in at least some health benefits.⁷⁶ In fact, two recent studies found that as little as an additional 2 to 5 minutes per day of MVPA is associated with increases in lifespan and healthspan, and with a 10% reduction in mortality in the general population.^{343,344} If postmenopausal women are to choose one intervention or behaviour to reduce CV risk, this thesis recommends increasing their daily MVPA. Improved knowledge mobilization, improved women's health curricula in medical schools, more accessible and flexible options for community-based PA tailored to women, and continual evaluation of existing primary and secondary prevention programs are needed to support women in this area.^{68,88,342,345}

StaB was also associated with CV outcomes, namely DBP and HDL-C, although these associations were generally weaker and less consistent than those with MVPA after adjusting for covariates. Interestingly, while StaB was negatively associated with HDL-C, consistent with previous research, it was also negatively associated with DBP.⁷⁵ This implies that more time spent stationary lowers DBP, which is counterintuitive and not entirely consistent with other studies.^{136,137} Limitations with the measurement tool and analytical choices may explain these findings. As discussed at length in Chapter 2.5.2.4, the behaviour measured in this study was StaB, and not purely SB, due to the usage of wrist-worn accelerometers.¹²¹ This makes it different from studies that use inclinometers, hip-worn, or thigh-worn accelerometers, which can better distinguish between sitting and standing.^{223,224} Furthermore, the data for StaB was operationalized as its cumulative duration, but research suggests that breaking up long durations of SB with standing or various intensities of PA can offset its negative effects, including changes in blood pressure.^{132–137} Conversely, this thesis analysis treated long periods of uninterrupted sitting, interrupted sitting, and non-mobile standing all as the same behaviour, which may have influenced the findings. Considering these limitations, this thesis recommends that women aim to reduce sitting time and break up long periods of sitting with short bouts of activity, in line with the 24HMG.⁷⁶

Sleep duration was not associated with any CV outcome after adjusting for covariates in this cohort. Two possible explanations are proposed to explain this finding. First, the modelling strategy may not have been appropriate for this variable. The relationship between sleep duration and various health outcomes has been proposed to follow a U- or J-shaped pattern, where the highest risks are associated with excessively short or long sleep durations.^{140–146} This analysis used linear regression, whereas other non-linear approaches (such as polynomial regression, Lind & Mehlum's test, or the two-lines test) could have offered a better fit.^{346,347} Second, other measures of sleep, such as sleep quality and sleep regularity, may be as important, or even more important, for CV health as sleep duration.^{153,348–354} Future analyses could redo the models in this thesis, replacing sleep duration with measures of sleep quality (e.g., the Pittsburgh Sleep Quality Index) and regularity (e.g., the Sleep Regularity Index) to determine whether other sleep measures are more relevant.^{355,356}

4.2.3 Recommendations for Updates to Clinical Guidelines

This section will provide recommendations for updates to the Society of Obstetricians and Gynaecologists of Canada guidelines for the usage of MHT (Guidelines No. 422a through 422g). Given the scope of this thesis, recommendations will be provided specifically for Guideline No. 422e: Menopause and Cardiovascular Disease.⁵⁷

First, since lifestyle modifications are not a component of Guideline No. 422e, this thesis recommends including this important aspect of health promotion in future updates.⁵⁷ Doing so would align with the current International Menopause Society guidelines.⁵⁶ The International Menopause Society publication, which provides a comprehensive set of recommendations on MHT use across multiple health topics, includes a dedicated section on lifestyle, diet, and exercise.⁵⁶ They mention that PA can improve domains such as CV health and musculoskeletal health and reduce mortality risk. Therefore, Canadian guidelines could add a similar section, with an emphasis on obtaining sufficient MVPA to promote CV health. If space or scope is an issue, they can encourage readers to refer to the Canadian 24HMG for more information.⁷⁶

Second, the guidelines should explicitly mention that PA is recommended for both primary and secondary prevention of CVD.^{269,342} As such, women should be encouraged to adopt an active lifestyle, regardless of their interest in or concerns about MHT. Notably, while breast cancer is outside of the scope of this thesis, other international guidelines stated that the risks of taking MHT on breast cancer should be put into perspective with other uncontroversial risk factors.^{22,215} That is, the risk of breast cancer from taking MHT may be comparable to being physically inactive.^{22,215} In this thesis analysis, MVPA was more strongly associated with the 10-year risk of CVD (and other CV outcomes) than MHT, suggesting that the risks of physical inactivity on CV health are greater than those of MHT. As such, women who are uncertain about taking MHT due to fears about CV risk should be aware that, in addition to current evidence suggesting neutral or beneficial effects of this treatment, PA is a much more consistent effector of improvements in CV health.¹⁹⁶

Lastly, updates to the guidelines should refer to SB and sleep behaviours as other contributors to CV health. Although the evidence on these behaviours is relatively newer compared to that of PA, they have been associated with CV health in postmenopausal women independent of MHT and are key areas of intervention in the Canadian 24HMG.

^{75,76,136,139,143,145,172,357} It would be prudent, at the very least, to mention these behaviours in future updates. That said, the evidence for PA and MVPA is more established and consistent across the three behaviours analyzed in this thesis and could therefore be a larger focus of clinical guidelines.

4.2.4 Future Research Directions

Future analyses of the WARM Hearts dataset could continue to address knowledge gaps identified in Chapter 2.1, address analytical limitations of this thesis, and pursue additional areas of interest based on the current findings. For example, analyzing the interactions between meeting the Canadian 24HMG and MHT usage on CV health could be a logical extension of this analysis. Examining sleep measures beyond duration, such as quality and regularity, would provide further insights. Additional outcomes available in the dataset, such as frailty, heart rate variability, and quality of life, could be investigated using similar approaches as this thesis.⁷² Lastly, 5-year follow-up data on adverse CV outcomes based on health administrative data will be available for this cohort in 2028, providing opportunities to assess the longitudinal associations between MHT use and movement behaviours with adverse cardiovascular health outcomes.

Outside of the WARM Hearts cohort, observational studies should better integrate or acknowledge various lifestyle behaviours into analyses and discussions of results. The analytical approach could be used to analyze (or re-analyze) data from other cohorts with similar available variables (i.e., CV markers, MHT history, and movement behaviours), such as the Canadian Longitudinal Study on Aging (CLSA), UK BioBank, and the National Health and Nutrition Examination Survey (NHANES).^{358–360} If possible, studies should investigate specific types of estrogens and progestogens, given the potential variability in their effects. Regarding social and temporal factors, there could be more qualitative studies that aim to elucidate women's perceptions of MHT and reasons for initiating and discontinuing MHT, with a specific focus on the extent to which changes in public health messaging affected beliefs and choices. More randomized controlled studies intentionally designed to examine movement behaviours and MHT together are needed. Lastly, women's health research in general must remain a research priority.

4.3 Strengths and Limitations

This thesis has several strengths. While prior observational studies have relied on self-reported behavioural measures, this analysis benefits from objective accelerometry-derived estimates of MVPA, StaB, and sleep duration, offering greater precision and minimizing recall bias in these areas. The availability of detailed, self-reported MHT data further enables multidimensional exposure classification using definitions of usage history, MHT type, and route of administration. This may help prevent the conflation of all MHT regimens, a limitation of some seminal research.^{27,33,36,361} The statistical approach used enabled more precise estimates of differences in associations between MHT use, movement behaviours, and covariates, as well as the ability to compare the relative contributions of each exposure to CV health. It also expanded on previous work from our research group and better contextualized and qualified the original findings.⁷¹ As discussed in Chapter 2.8, the analysis adjusts for sex and gender-specific covariates as per guidelines from the Canadian Institutes of Health Research.

This work also has several limitations that must be considered when interpreting the findings. Given the cross-sectional design, causal relationships between MHT, movement behaviours, and CV outcomes cannot be established. Healthy user bias is a potential concern, as individuals who use MHT may differ systematically from non-users in their preventive care engagement, attitudes toward medical interventions, and overall health consciousness, all of which are variables not included in this thesis.^{362,363} Additionally, self-selection into the WARM Hearts cohort may bias results, because women who enrolled in the study were likely generally health-literate and interested in women's health. Another limitation is the reliance on self-reported MHT exposure data. Some participants, particularly those who had discontinued MHT years earlier, had difficulty recalling specific details about the hormone type, dosage, or route. This introduces the risk of misclassification, particularly among those who selected "Other" for hormone type despite likely using conventional estrogen or progestogen formulations.

Given the study's objectives and to prevent overadjustment, this analysis prioritized movement behaviours at the expense of other lifestyle factors that may influence CV health, such as diet, alcohol intake, and smoking status. Additionally, although accelerometry offers an objective estimate of movement, it does not distinguish between sitting and standing postures, limiting our ability to operationalize sedentary behaviour per current guidelines. Lastly,

analyzing sleep duration as a linear variable rather than a U-shaped one may have limited the ability to detect associations with CV health, as mentioned in Chapter 4.2.2.

4.4 Conclusion

This thesis examined and compared associations between MHT and 24-hour movement behaviours with CV outcomes in postmenopausal women in the WARM Hearts cohort.⁷² Replicating previous work from our research group with a larger sample size validated the original findings: unopposed oral estrogen use was associated with greater arterial stiffness and higher blood pressure.⁷¹ However, updating models to include movement behaviours indicated that these behaviours, particularly MVPA, provided a more substantial explanation of variance in these CV outcomes. The same patterns were observed in the new analyses when examining MHT by usage history, type, and route of administration. Movement behaviours demonstrated stronger predictive utility than MHT for CV outcomes, with the strongest and most consistent associations observed with MVPA. MVPA was associated with more favourable 10-year CVD risk, arterial stiffness, blood pressure, waist circumference, and metabolic indicators. In sum, the findings indicate that MVPA is more important in promoting and protecting CV health than MHT usage. Moreover, while some associations between former and oral MHT usage with less favourable CV outcomes were statistically significant independent of MVPA, they were not clinically significant. That is, CV markers of the average MHT user, regardless of regimen and usage history, were within normal ranges.

The findings support current international guidelines suggesting that, in the absence of contraindications, MHT is likely safe for most postmenopausal women. As such, those who struggle with menopausal symptoms should not avoid pursuing this option solely due to perceived health risks. Non-oral routes may be preferred if CV risk is a relevant concern and should be recommended for women with existing CV risk factors seeking treatment. All decisions about initiation, type of estrogen and progestogens, and route of administration should be made in collaboration with healthcare providers and individualized based on symptom burden, reproductive history, risk profiles, lifestyle, and preferences. Regardless of interest or concern about MHT, modifiable lifestyle and movement behaviours should always be emphasized and part of conversations about health during the menopausal transition. To reiterate, movement behaviours, particularly MVPA, were more strongly associated with CV outcomes

compared to MHT usage in this thesis. Therefore, updates to clinical practice guidelines for MHT usage should ardently promote movement behaviours as effective strategies for general health promotion in postmenopausal women.

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Appendix A: Appendix Tables

Appendix Table 1. Studies on MHT and CV Health that Account for Movement Behaviours from Kim et al. (2020).²¹⁰

First author (Year), Country	Study / Cohort Name	N Analyzed	MHT Exposure Groups (relative to controls)	Covariates	Movement Behaviours and Measurement	Outcomes	Relevant Findings
Løkkegaard et al. (2003) ²⁰⁵ , Denmark	DNS	13,122	History: Ever, Former, Current; History/Type: Current Unopposed Estrogen, Current Combined Estrogen- Progestogen	Familial predisposition, smoking, alcohol consumption, BMI, PA, hypertension, angina, diabetes, thyroid disease, self-rated health	Self-reported leisure time PA (> 4 hours/week vigorous, >4 hours/week moderate, or sedentary)	Ischemic or hemorrhagic stroke	MHT usage was associated with increased risk of stroke in hypertensive but not normotensive participants, particularly for combined estrogen-progestogen usage, after adjustment for covariates
Løkkegaard et al. (2003) ²⁰⁴ , Denmark	DNS	19,898	History: Ever, Former, Current; History/Type: Current Unopposed Estrogen, Current Combined Estrogen- Progestogen	Smoking, alcohol, BMI, PA, hypertension, angina, diabetes, metabolic disease	Self-reported leisure time PA (> 4 hours/week vigorous, >4 hours/week moderate, or sedentary)	Ischemic heart disease, myocardial infarction, death	After adjustment, MHT usage among women with diabetes was associated with increased risk of all-cause and ischemic heart disease mortality; no increased risk among women without diabetes

First author (Year), Country	Study / Cohort Name	N Analyzed	MHT Exposure Groups (relative to controls)	Covariates	Movement Behaviours and Measurement	Outcomes	Relevant Findings
Stram et al. (2011) ²⁰³ , USA	CTS	71,237	History: Former, Current Type: Unopposed Estrogen only, Combined Estrogen- Progestogen only, Mixed Unopposed and Combined Usage	BMI, smoking, alcohol, PA, caloric intake, diabetes, hypertension, myocardial infarction or heart disease, cancer, stroke	Self-reported PA; hours/week	All-cause mortality, ischemic heart disease mortality	Current users were more likely to be physically active than former users or controls; After adjustment, current MHT usage associated with lower risk of all-cause and ischemic heart disease mortality compared to former users and controls; former MHT users had lower all- cause mortality risk than controls
Carrasquilla et al. (2015) ²⁰⁹ , Sweden	SHEEP	846	History: Ever, Former, Current; Route: Oral, Transdermal	Age, residential area, hysterectomy, oophorectomy, smoking, PA, alcohol, BMI, socioeconomic status, lipids, glucose metabolism, coagulation/fibrinolysis markers, inflammatory markers, homocysteine	Self-reported leisure-time PA; binary variable of 'active' versus 'inactive'	MI	No association between MHT usage and incident non-fatal MI after adjusting for covariates
Bhupathiraju et al. (2018) ²⁰⁸ , USA	NHS	53,797	History: Former, Current Route: Vaginal	Race, smoking, alcohol, PA, BMI, aspirin use, age at menopause, bilateral oophorectomy, past systemic MHT use, history of disease (hypertension, hypercholesterolemia, type 2 diabetes,) family history of early myocardial infarction and cancer	Self-reported PA; MET- hours/week, assessed via NHS questionnaire	MI, stroke, pulmonary embolism/deep vein thrombosis, cancer (breast, ovarian, endometrial, colorectal)	Vaginal MHT users had slightly higher PA levels than controls; after adjusting for covariates, there were no differences in risk of outcomes between controls and vaginal MHT users

First author (Year), Country	Study / Cohort Name	N Analyzed	MHT Exposure Groups (relative to controls)	Covariates	Movement Behaviours and Measurement	Outcomes	Relevant Findings
Crandall et al. (2018) ²⁰⁶ , USA	WHI-OS	45,663	History: Former, Current Route: Vaginal	Age, PA, education, history of disease (CVD, cancer, venous thromboembolism, diabetes), race/ethnicity, Gail breast cancer risk score, previous fracture, smoking, household income, alcohol intake	Self-reported PA; Total MET-hours/week, assessed via WHI PA questionnaire	Coronary heart disease, cancer (breast, colorectal, endometrial), stroke, pulmonary embolism, hip fracture, death	After adjustment for covariates, there was no increased risk of outcomes among vaginal MHT users.
Holm et al. (2019) ²⁰⁷ , Denmark	Diet, Cancer, and Health	29,243	History: Former, Current; Type: Unopposed estrogen, combined estrogen-progestogen Route: Oral, Other systemic (non-oral e.g., transdermal), Local (vaginal)	Age, PA, alcohol intake, smoking, BMI, education)	Self-reported leisure-time PA; binary variable of 'active' versus 'inactive	All-cause mortality, CVD mortality, cancer mortality	After adjustment for covariates, MHT use was not associated with mortality outcomes, regardless of usage history, type, or route
Abbreviations: MHT, menopausal hormone therapy; CV, cardiovascular; DNS, Danish Nurses' Study; BMI, body mass index; PA, physical activity; CTS, California Teachers' Study; SHEEP, Stockholm Heart Epidemiology Program; MI, myocardial infarction; NHS, Nurses' Health Study; MET, metabolic equivalent; WHI-OS, Women's Health Initiative Observational Study; CVD, cardiovascular disease							

Appendix Table 2a. Objective 2B.1 Unadjusted Model Fit, Full Sample

Outcome	Block	N	R ²	Full Sample Adj. R ²	F change P-Value	AIC	ΔAIC
aPWV	Block 1	929	0.04	0.04	< 0.01	2859.9	
	Block 2		0.10	0.09	< 0.01	2809.5	-50.4
AIx75	Block 1	929	0.00	0.00	0.30	6959.6	
	Block 2		0.02	0.01	< 0.01	6949.7	-9.9
SBP	Block 1	929	0.01	0.00	0.08	7532.3	
	Block 2		0.02	0.02	< 0.01	7524.2	-8.0
DBP	Block 1	929	0.00	0.00	0.62	6943.7	
	Block 2		0.01	0.01	0.01	6937.6	-6.1
logFRS	Block 1	929	0.01	0.01	< 0.01	1423.5	
	Block 2		0.05	0.04	< 0.01	1397.4	-26.2
WC	Block 1	929	0.00	0.00	0.46	7450.5	
	Block 2		0.08	0.07	< 0.01	7383.2	-67.3
HDL-C	Block 1	929	0.00	0.00	0.59	1131.1	
	Block 2		0.04	0.04	< 0.01	1098.9	-32.2
LDL-C	Block 1	929	0.00	0.00	0.81	2350.8	
	Block 2		0.01	0.00	0.10	2350.4	-0.4
logTG	Block 1	929	0.00	0.00	0.99	1063.5	
	Block 2		0.01	0.01	< 0.01	1056.3	-7.2
logGlucose	Block 1	928	0.01	0.01	0.02	-1279.6	
	Block 2		0.02	0.02	0.01	-1284.8	-5.1

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Former MHT usage and Current MHT usage entered

Block 2: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1;

Red bold text used to emphasize statistically significant changes in Block 2

Appendix Table 2b. Objective 2B.1 Unadjusted Model, Coefficients, Full Sample

Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	MVPA (mins)	-0.01 [-0.01, -0.01]	-0.17 [-0.24, -0.10]	*
	StaB (hours)	0.08 [0.03, 0.14]	0.12 [0.04, 0.20]	*
	Sleep duration (hours)	0.03 [-0.06, 0.13]	0.03 [-0.04, 0.10]	
	Controls (MHT reference group)			
	Former Usage	0.51 [0.33, 0.70]	0.17 [0.11, 0.24]	*
AIx75	Current Usage	-0.15 [-0.39, 0.08]	-0.04 [-0.10, 0.02]	
	MVPA (mins)	-0.04 [-0.08, -0.01]	-0.09 [-0.16, -0.02]	*
	StaB (hours)	0.42 [-0.08, 0.93]	0.07 [-0.01, 0.15]	
	Sleep duration (hours)	0.46 [-0.40, 1.32]	0.04 [-0.03, 0.11]	
	Controls (MHT reference group)			
SBP	Former Usage	0.79 [-0.92, 2.49]	0.03 [-0.04, 0.10]	
	Current Usage	-0.89 [-3.07, 1.28]	-0.03 [-0.09, 0.04]	
	MVPA (mins)	-0.09 [-0.13, -0.04]	-0.13 [-0.21, -0.06]	*
	StaB (hours)	-0.27 [-0.96, 0.41]	-0.03 [-0.11, 0.05]	
	Sleep duration (hours)	-0.38 [-1.56, 0.79]	-0.02 [-0.10, 0.05]	
DBP	Controls (MHT reference group)			
	Former Usage	1.48 [-0.84, 3.81]	0.04 [-0.02, 0.11]	
	Current Usage	-2.23 [-5.20, 0.73]	-0.05 [-0.11, 0.02]	
	MVPA (mins)	-0.05 [-0.08, -0.01]	-0.10 [-0.17, -0.02]	*
	StaB (hours)	-0.80 [-1.30, -0.30]	-0.13 [-0.21, -0.05]	*
logFRS	Sleep duration (hours)	-0.33 [-1.18, 0.53]	-0.03 [-0.10, 0.05]	
	Controls (MHT reference group)			
	Former Usage	0.14 [-1.55, 1.84]	0.01 [-0.06, 0.07]	
	Current Usage	-1.08 [-3.24, 1.08]	-0.03 [-0.10, 0.03]	
	MVPA (mins)	0.00 [-0.01, 0.00]	-0.16 [-0.24, -0.09]	*
WC	StaB (hours)	0.01 [-0.01, 0.04]	0.04 [-0.04, 0.12]	
	Sleep duration (hours)	0.01 [-0.04, 0.05]	0.01 [-0.06, 0.08]	
	Controls (MHT reference group)			
	Former Usage	0.07 [-0.01, 0.16]	0.05 [-0.01, 0.12]	
	Current Usage	-0.14 [-0.25, -0.03]	-0.08 [-0.15, -0.02]	*
WC	MVPA (mins)	-0.16 [-0.20, -0.11]	-0.25 [-0.32, -0.18]	*
	StaB (hours)	0.21 [-0.43, 0.85]	0.03 [-0.05, 0.10]	
	Sleep duration (hours)	-1.02 [-2.10, 0.07]	-0.07 [-0.14, 0.00]	
	Controls (MHT reference group)			

	Former Usage	-1.60 [-3.76, 0.56]	-0.05 [-0.11, 0.02]	
	Current Usage	-1.67 [-4.42, 1.08]	-0.04 [-0.10, 0.02]	
HDL-C	MVPA (mins)	0.00 [0.00, 0.00]	0.13 [0.06, 0.20]	*
	StaB (hours)	-0.03 [-0.05, -0.01]	-0.10 [-0.18, -0.02]	*
	Sleep duration (hours)	0.00 [-0.04, 0.04]	0.00 [-0.07, 0.07]	
	Controls (MHT reference group)			
	Former Usage	0.05 [-0.02, 0.12]	0.04 [-0.02, 0.11]	
	Current Usage	0.03 [-0.06, 0.12]	0.02 [-0.04, 0.08]	
LDL-C	MVPA (mins)	0.00 [0.00, 0.01]	0.08 [0.01, 0.16]	*
	StaB (hours)	0.01 [-0.03, 0.05]	0.02 [-0.07, 0.10]	
	Sleep duration (hours)	0.03 [-0.04, 0.10]	0.03 [-0.04, 0.10]	
	Controls (MHT reference group)			
	Former Usage	-0.03 [-0.17, 0.12]	-0.01 [-0.08, 0.05]	
	Current Usage	-0.04 [-0.22, 0.14]	-0.01 [-0.08, 0.05]	
logTG	MVPA (mins)	0.00 [0.00, 0.00]	-0.10 [-0.18, -0.03]	*
	StaB (hours)	0.01 [-0.01, 0.03]	0.03 [-0.05, 0.11]	
	Sleep duration (hours)	0.01 [-0.02, 0.05]	0.03 [-0.05, 0.10]	
	Controls (MHT reference group)			
	Former Usage	-0.01 [-0.08, 0.06]	-0.01 [-0.07, 0.06]	
	Current Usage	0.00 [-0.09, 0.09]	0.00 [-0.06, 0.07]	
logGlucose	MVPA (mins)	0.00 [0.00, 0.00]	-0.10 [-0.18, -0.03]	*
	StaB (hours)	0.00 [-0.01, 0.01]	0.00 [-0.08, 0.08]	
	Sleep duration (hours)	0.00 [-0.01, 0.01]	-0.03 [-0.10, 0.05]	
	Controls (MHT reference group)			
	Former Usage	0.00 [-0.02, 0.02]	0.00 [-0.06, 0.07]	
	Current Usage	-0.04 [-0.06, -0.01]	-0.09 [-0.16, -0.03]	*

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 2c. Objective 2B.1 Unadjusted Model Fit, MHT Users

Outcome	Block	N	R ²	MHT users Only	Sig. F Change	AIC	ΔAIC
				Adj. R ²			
aPWV	Block 1	269	0.08	0.08	< 0.01	839.5	
	Block 2		0.20	0.19	< 0.01	807.8	-31.8
AIx75	Block 1	269	0.01	0.00	0.17	2054.9	
	Block 2		0.04	0.03	0.03	2051.9	-3.0
SBP	Block 1	269	0.02	0.01	0.04	2218.3	
	Block 2		0.05	0.04	0.02	2214.7	-3.6
DBP	Block 1	269	0.00	0.00	0.39	2061.2	
	Block 2		0.01	0.00	0.47	2064.6	3.4
logFRS	Block 1	269	0.05	0.04	< 0.01	405.1	
	Block 2		0.11	0.10	< 0.01	391.3	-13.8
WC	Block 1	269	0.00	0.00	0.73	2141.9	
	Block 2		0.08	0.07	< 0.01	2124.4	-17.5
HDL-C	Block 1	269	0.00	0.00	0.90	329.9	
	Block 2		0.02	0.01	0.12	330.0	0.1
LDL-C	Block 1	269	0.00	0.00	0.97	656.3	
	Block 2		0.02	0.01	0.09	655.8	-0.5
logTG	Block 1	269	0.00	0.00	0.96	285.7	
	Block 2		0.02	0.01	0.10	285.4	-0.3
logGlucose	Block 1	269	0.02	0.02	0.02	-349.0	
	Block 2		0.03	0.02	0.41	-345.9	3.1

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Current MHT usage entered

Block 2: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1;

Red bold text used to emphasize statistically significant changes in Block 2

Appendix Table 2d. Objective 2B.1 Unadjusted Model, Coefficients, MHT Users

Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	MVPA (mins)	-0.02 [-0.02, -0.01]	-0.25 [-0.38, -0.12]	*
	StaB (hours)	0.10 [0.00, 0.21]	0.14 [0.01, 0.28]	*
	Sleep duration (hours)	-0.02 [-0.18, 0.15]	-0.01 [-0.13, 0.11]	
	Former Usage (MHT reference group)			
	Current Usage	-0.65 [-0.92, -0.38]	-0.26 [-0.37, -0.15]	*
AIx75	MVPA (mins)	-0.05 [-0.13, 0.03]	-0.09 [-0.23, 0.05]	
	StaB (hours)	0.82 [-0.19, 1.84]	0.12 [-0.03, 0.27]	
	Sleep duration (hours)	0.83 [-0.82, 2.48]	0.07 [-0.07, 0.20]	
	Former Usage (MHT reference group)			
	Current Usage	-1.57 [-4.29, 1.16]	-0.07 [-0.19, 0.05]	
SBP	MVPA (mins)	-0.14 [-0.25, -0.03]	-0.18 [-0.32, -0.04]	*
	StaB (hours)	-0.36 [-1.74, 1.01]	-0.04 [-0.19, 0.11]	
	Sleep duration (hours)	-1.62 [-3.86, 0.61]	-0.10 [-0.23, 0.04]	
	Former Usage (MHT reference group)			
	Current Usage	-3.62 [-7.31, 0.06]	-0.12 [-0.24, 0.00]	
DBP	MVPA (mins)	-0.05 [-0.13, 0.03]	-0.08 [-0.22, 0.06]	
	StaB (hours)	-0.70 [-1.74, 0.34]	-0.10 [-0.26, 0.05]	
	Sleep duration (hours)	-1.05 [-2.74, 0.64]	-0.08 [-0.22, 0.05]	
	Former Usage (MHT reference group)			
	Current Usage	-1.24 [-4.03, 1.55]	-0.05 [-0.17, 0.07]	
logFRS	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.23 [-0.36, -0.09]	*
	StaB (hours)	0.02 [-0.03, 0.06]	0.05 [-0.10, 0.19]	
	Sleep duration (hours)	-0.02 [-0.10, 0.05]	-0.04 [-0.16, 0.09]	
	Former Usage (MHT reference group)			
	Current Usage	-0.21 [-0.33, -0.08]	-0.19 [-0.31, -0.08]	*
WC	MVPA (mins)	-0.17 [-0.26, -0.08]	-0.25 [-0.39, -0.12]	*
	StaB (hours)	0.42 [-0.74, 1.58]	0.05 [-0.09, 0.20]	
	Sleep duration (hours)	-0.59 [-2.48, 1.30]	-0.04 [-0.17, 0.09]	
	Former Usage (MHT reference group)			
	Current Usage	0.02 [-3.10, 3.14]	0.00 [-0.12, 0.12]	

HDL-C	MVPA (mins)	0.00 [0.00, 0.00]	0.08 [-0.06, 0.22]	
	StaB (hours)	-0.02 [-0.07, 0.02]	-0.09 [-0.24, 0.06]	
	Sleep duration (hours)	0.00 [-0.06, 0.07]	0.01 [-0.12, 0.14]	
	Former Usage (MHT reference group)			
	Current Usage	-0.02 [-0.13, 0.09]	-0.02 [-0.14, 0.10]	
LDL-C	MVPA (mins)	0.01 [0.00, 0.01]	0.13 [-0.01, 0.27]	
	StaB (hours)	-0.01 [-0.09, 0.06]	-0.03 [-0.18, 0.12]	
	Sleep duration (hours)	0.04 [-0.08, 0.16]	0.04 [-0.09, 0.18]	
	Former Usage (MHT reference group)			
	Current Usage	-0.02 [-0.22, 0.18]	-0.01 [-0.13, 0.11]	
logTG	MVPA (mins)	0.00 [-0.01, 0.00]	-0.16 [-0.30, -0.02]	*
	StaB (hours)	0.00 [-0.04, 0.04]	-0.01 [-0.16, 0.14]	
	Sleep duration (hours)	-0.01 [-0.07, 0.05]	-0.02 [-0.16, 0.11]	
	Former Usage (MHT reference group)			
	Current Usage	0.01 [-0.09, 0.11]	0.01 [-0.11, 0.13]	
logGlucose	MVPA (mins)	0.00 [0.00, 0.00]	-0.12 [-0.26, 0.03]	
	StaB (hours)	0.00 [-0.02, 0.01]	-0.05 [-0.20, 0.10]	
	Sleep duration (hours)	-0.01 [-0.03, 0.01]	-0.05 [-0.18, 0.08]	
	Former Usage (MHT reference group)			
	Current Usage	-0.04 [-0.07, -0.01]	-0.14 [-0.26, -0.02]	*

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 3a. Objective 2B.2 Unadjusted Model Fit, Full Sample

Outcome	Block	N	R ²	Full Sample Adj. R ²	F change P-Value	AIC	ΔAIC
aPWV	Block 1	831	0.02	0.02	< 0.01	2562.7	
	Block 2		0.08	0.07	< 0.01	2519.6	-43.1
AIx75	Block 1	831	0.00	0.00	0.18	6240.1	
	Block 2		0.02	0.01	0.01	6234.2	-5.9
SBP	Block 1	831	0.00	0.00	0.53	6716.5	
	Block 2		0.02	0.01	< 0.01	6709.1	-7.4
DBP	Block 1	831	0.00	0.00	0.92	6159.1	
	Block 2		0.01	0.01	0.01	6153.1	-6.0
logFRS	Block 1	831	0.00	0.00	0.79	1285.1	
	Block 2		0.03	0.03	< 0.01	1263.0	-22.1
WC	Block 1	831	0.00	0.00	0.19	6658.9	
	Block 2		0.07	0.06	< 0.01	6608.5	-50.4
HDL-C	Block 1	831	0.01	0.01	0.02	984.2	
	Block 2		0.06	0.05	< 0.01	949.6	-34.7
LDL-C	Block 1	831	0.00	0.00	0.21	2094.3	
	Block 2		0.01	0.00	0.12	2094.3	0.0
logTG	Block 1	831	0.01	0.00	0.11	956.4	
	Block 2		0.02	0.01	0.03	953.6	-2.8
logGlucose	Block 1	830	0.00	0.00	0.67	-1154.6	
	Block 2		0.01	0.01	0.01	-1160.0	-5.4

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Combined Estrogen-Progestosterone, Unopposed Estrogen usage entered

Block 2: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1;

Red bold text used to emphasize statistically significant changes in Block 2

Appendix Table 3b. Objective 2B.2 Unadjusted Model, Coefficients, Full Sample

Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	MVPA (mins)	-0.01 [-0.01, -0.01]	-0.17 [-0.25, -0.10]	*
	StaB (hours)	0.08 [0.02, 0.14]	0.11 [0.03, 0.19]	*
	Sleep duration (hours)	0.02 [-0.08, 0.12]	0.02 [-0.06, 0.09]	
	Controls (MHT reference group)			
	Combined Estrogen-Progesterone	0.55 [0.28, 0.82]	0.14 [0.07, 0.20]	*
AIx75	Unopposed Estrogen	0.04 [-0.19, 0.27]	0.01 [-0.06, 0.08]	
	MVPA (mins)	-0.04 [-0.08, -0.01]	-0.09 [-0.17, -0.01]	*
	StaB (hours)	0.34 [-0.20, 0.89]	0.05 [-0.03, 0.14]	
	Sleep duration (hours)	0.37 [-0.57, 1.30]	0.03 [-0.05, 0.11]	
	Controls (MHT reference group)			
SBP	Combined Estrogen-Progesterone	2.09 [-0.45, 4.62]	0.06 [-0.01, 0.12]	
	Unopposed Estrogen	-0.63 [-2.78, 1.53]	-0.02 [-0.09, 0.05]	
	MVPA (mins)	-0.09 [-0.14, -0.04]	-0.14 [-0.21, -0.06]	*
	StaB (hours)	-0.26 [-0.98, 0.46]	-0.03 [-0.12, 0.05]	
	Sleep duration (hours)	-0.16 [-1.41, 1.08]	-0.01 [-0.09, 0.07]	
DBP	Controls (MHT reference group)			
	Combined Estrogen-Progesterone	1.43 [-1.95, 4.80]	0.03 [-0.04, 0.10]	
	Unopposed Estrogen	-0.80 [-3.67, 2.07]	-0.02 [-0.09, 0.05]	
	MVPA (mins)	-0.05 [-0.08, -0.01]	-0.11 [-0.18, -0.03]	*
	StaB (hours)	-0.73 [-1.24, -0.21]	-0.12 [-0.21, -0.04]	*
logFRS	Sleep duration (hours)	-0.05 [-0.94, 0.84]	0.00 [-0.08, 0.07]	
	Controls (MHT reference group)			
	Combined Estrogen-Progesterone	-0.08 [-2.49, 2.34]	0.00 [-0.07, 0.07]	
	Unopposed Estrogen	-0.53 [-2.59, 1.52]	-0.02 [-0.09, 0.05]	
	MVPA (mins)	0.00 [-0.01, 0.00]	-0.17 [-0.24, -0.09]	*
WC	StaB (hours)	0.01 [-0.02, 0.04]	0.03 [-0.05, 0.12]	
	Sleep duration (hours)	0.01 [-0.04, 0.06]	0.01 [-0.06, 0.09]	
	Controls (MHT reference group)			
	Combined Estrogen-Progesterone	0.01 [-0.12, 0.14]	0.01 [-0.06, 0.07]	
	Unopposed Estrogen	-0.05 [-0.15, 0.06]	-0.03 [-0.10, 0.04]	
WC	MVPA (mins)	-0.15 [-0.19, -0.10]	-0.23 [-0.31, -0.16]	*
	StaB (hours)	0.15 [-0.53, 0.82]	0.02 [-0.07, 0.10]	
	Sleep duration (hours)	-1.06 [-2.23, 0.11]	-0.07 [-0.14, 0.01]	
	Controls (MHT reference group)			

HDL-C	Combined Estrogen-Progesterone	-3.44 [-6.62, -0.27]	-0.07 [-0.14, -0.01]	*
	Unopposed Estrogen	-0.41 [-3.11, 2.29]	-0.01 [-0.08, 0.06]	
	MVPA (mins)	0.00 [0.00, 0.00]	0.14 [0.06, 0.21]	*
	StaB (hours)	-0.03 [-0.06, -0.01]	-0.12 [-0.21, -0.04]	*
	Sleep duration (hours)	-0.01 [-0.05, 0.03]	-0.02 [-0.09, 0.06]	
LDL-C	Controls (MHT reference group)			
	Combined Estrogen-Progesterone	0.13 [0.03, 0.24]	0.08 [0.02, 0.15]	*
	Unopposed Estrogen	-0.06 [-0.14, 0.03]	-0.04 [-0.11, 0.03]	
	MVPA (mins)	0.00 [0.00, 0.01]	0.08 [0.01, 0.16]	*
	StaB (hours)	0.01 [-0.04, 0.05]	0.01 [-0.07, 0.10]	
logTG	Sleep duration (hours)	0.04 [-0.04, 0.11]	0.04 [-0.04, 0.11]	
	Controls (MHT reference group)			
	Combined Estrogen-Progesterone	-0.18 [-0.39, 0.03]	-0.06 [-0.13, 0.01]	
	Unopposed Estrogen	-0.03 [-0.21, 0.15]	-0.01 [-0.08, 0.06]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.09 [-0.16, -0.01]	*
logGlucose	StaB (hours)	0.01 [-0.01, 0.03]	0.03 [-0.05, 0.12]	
	Sleep duration (hours)	0.02 [-0.02, 0.06]	0.03 [-0.04, 0.11]	
	Controls (MHT reference group)			
	Combined Estrogen-Progesterone	-0.07 [-0.18, 0.03]	-0.05 [-0.12, 0.02]	
	Unopposed Estrogen	0.07 [-0.02, 0.16]	0.05 [-0.02, 0.12]	
logTG	MVPA (mins)	0.00 [0.00, 0.00]	-0.11 [-0.19, -0.04]	*
	StaB (hours)	0.00 [-0.01, 0.01]	0.00 [-0.08, 0.09]	
	Sleep duration (hours)	0.00 [-0.01, 0.01]	-0.01 [-0.09, 0.06]	
	Controls (MHT reference group)			
	Combined Estrogen-Progesterone	-0.02 [-0.05, 0.01]	-0.04 [-0.10, 0.03]	
logGlucose	Unopposed Estrogen	-0.01 [-0.03, 0.02]	-0.02 [-0.09, 0.05]	

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 3c. Objective 2B.2 Unadjusted Model Fit, MHT Users

Outcome	Block	N	R ²	MHT users Only	Sig. F Change	AIC	ΔAIC
				Adj. R ²			
aPWV	Block 1	153	0.04	0.04	0.01	542.1	
	Block 2		0.23	0.21	< 0.01	511.9	-30.1
AIx75	Block 1	153	0.01	0.01	0.14	1331.3	
	Block 2		0.04	0.01	0.24	1333.0	1.7
SBP	Block 1	153	0.01	0.00	0.32	1404.4	
	Block 2		0.06	0.04	0.02	1400.2	-4.2
DBP	Block 1	153	0.00	-0.01	0.71	1282.6	
	Block 2		0.01	-0.01	0.62	1286.8	4.2
logFRS	Block 1	153	0.00	0.00	0.50	266.9	
	Block 2		0.10	0.08	< 0.01	255.6	-11.3
WC	Block 1	153	0.02	0.01	0.09	1348.9	
	Block 2		0.05	0.03	0.13	1349.2	0.3
HDL-C	Block 1	153	0.05	0.05	< 0.01	180.7	
	Block 2		0.09	0.07	0.06	179.2	-1.5
LDL-C	Block 1	153	0.01	0.00	0.24	396.8	
	Block 2		0.06	0.04	0.03	393.4	-3.4
logTG	Block 1	153	0.03	0.02	0.03	178.5	
	Block 2		0.03	0.01	0.84	183.7	5.2
logGlucose	Block 1	153	0.00	0.00	0.62	-223.4	
	Block 2		0.03	0.00	0.24	-221.6	1.7

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Unopposed Estrogen usage entered

Block 2: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1;

Red bold text used to emphasize statistically significant changes in Block 2

Appendix Table 3d. Objective 2B.2 Unadjusted Model, Coefficients, MHT Users

Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	MVPA (mins)	-0.02 [-0.03, -0.01]	-0.36 [-0.52, -0.20]	*
	StaB (hours)	0.07 [-0.06, 0.20]	0.09 [-0.09, 0.27]	
	Sleep duration (hours)	-0.13 [-0.34, 0.08]	-0.09 [-0.25, 0.06]	
	Combined Estrogen-Progestosterone (MHT reference group)			
AIx75	Unopposed Estrogen	-0.54 [-0.86, -0.21]	-0.22 [-0.36, -0.09]	*
	MVPA (mins)	-0.06 [-0.18, 0.06]	-0.09 [-0.27, 0.09]	
	StaB (hours)	0.69 [-0.73, 2.12]	0.10 [-0.10, 0.29]	
	Sleep duration (hours)	0.66 [-1.68, 3.00]	0.05 [-0.12, 0.22]	
	Combined Estrogen-Progestosterone (MHT reference group)			
SBP	Unopposed Estrogen	-2.75 [-6.35, 0.86]	-0.12 [-0.27, 0.04]	*
	MVPA (mins)	-0.21 [-0.35, -0.07]	-0.26 [-0.44, -0.08]	
	StaB (hours)	-0.59 [-2.32, 1.15]	-0.07 [-0.26, 0.13]	
	Sleep duration (hours)	-1.64 [-4.49, 1.21]	-0.10 [-0.27, 0.07]	
DBP	Combined Estrogen-Progestosterone (MHT reference group)			
	Unopposed Estrogen	-2.40 [-6.78, 1.99]	-0.08 [-0.23, 0.07]	
	MVPA (mins)	-0.07 [-0.17, 0.03]	-0.12 [-0.31, 0.06]	
	StaB (hours)	-0.43 [-1.68, 0.81]	-0.07 [-0.27, 0.13]	
	Sleep duration (hours)	-0.33 [-2.37, 1.72]	-0.03 [-0.20, 0.15]	
logFRS	Combined Estrogen-Progestosterone (MHT reference group)			*
	Unopposed Estrogen	-0.56 [-3.71, 2.59]	-0.03 [-0.18, 0.13]	
	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.31 [-0.48, -0.13]	
	StaB (hours)	0.00 [-0.06, 0.06]	-0.01 [-0.20, 0.18]	
WC	Sleep duration (hours)	-0.04 [-0.14, 0.06]	-0.07 [-0.24, 0.09]	
	Combined Estrogen-Progestosterone (MHT reference group)			
	Unopposed Estrogen	-0.06 [-0.22, 0.09]	-0.06 [-0.21, 0.09]	
	MVPA (mins)	-0.10 [-0.22, 0.03]	-0.14 [-0.32, 0.04]	
	StaB (hours)	0.44 [-1.05, 1.94]	0.06 [-0.14, 0.25]	
HDL-C	Sleep duration (hours)	-0.26 [-2.72, 2.19]	-0.02 [-0.19, 0.15]	
	Combined Estrogen-Progestosterone (MHT reference group)			
	Unopposed Estrogen	3.10 [-0.68, 6.87]	0.12 [-0.03, 0.27]	
	MVPA (mins)	0.00 [0.00, 0.01]	0.07 [-0.10, 0.25]	
	StaB (hours)	-0.04 [-0.09, 0.01]	-0.17 [-0.36, 0.02]	
	Sleep duration (hours)	-0.03 [-0.11, 0.05]	-0.05 [-0.22, 0.11]	

Combined Estrogen-Progestosterone (MHT reference group)				
LDL-C	Unopposed Estrogen	-0.19 [-0.31, -0.06]	-0.22 [-0.37, -0.08]	*
	MVPA (mins)	0.01 [0.00, 0.01]	0.17 [-0.01, 0.35]	
	StaB (hours)	-0.02 [-0.12, 0.07]	-0.05 [-0.25, 0.14]	
	Sleep duration (hours)	0.09 [-0.06, 0.24]	0.10 [-0.07, 0.27]	
Combined Estrogen-Progestosterone (MHT reference group)				
logTG	Unopposed Estrogen	0.16 [-0.07, 0.39]	0.10 [-0.05, 0.25]	
	MVPA (mins)	0.00 [-0.01, 0.00]	-0.08 [-0.26, 0.11]	
	StaB (hours)	0.00 [-0.05, 0.05]	-0.02 [-0.21, 0.18]	
	Sleep duration (hours)	0.00 [-0.08, 0.08]	0.00 [-0.17, 0.18]	
Combined Estrogen-Progestosterone (MHT reference group)				
logGlucose	Unopposed Estrogen	0.14 [0.01, 0.26]	0.17 [0.02, 0.32]	*
	MVPA (mins)	0.00 [0.00, 0.00]	-0.18 [-0.37, 0.00]	*
	StaB (hours)	-0.01 [-0.02, 0.01]	-0.09 [-0.29, 0.11]	
	Sleep duration (hours)	0.00 [-0.03, 0.02]	-0.01 [-0.18, 0.16]	
Combined Estrogen-Progestosterone (MHT reference group)				
	Unopposed Estrogen	0.01 [-0.03, 0.05]	0.04 [-0.11, 0.19]	

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 4a. Objective 2B.3 Unadjusted Model Fit, Full Sample

Outcome	Block	N	R ²	Full Sample Adj. R ²	F change P-Value	AIC	ΔAIC
aPWV	Block 1	865	0.03	0.03	< 0.01	2656.3	
	Block 2		0.08	0.08	< 0.01	2615.6	-40.7
AIx75	Block 1	865	0.00	0.00	0.91	6497.7	
	Block 2		0.02	0.01	< 0.01	6489.9	-7.8
SBP	Block 1	865	0.00	0.00	0.32	7005.7	
	Block 2		0.02	0.01	< 0.01	6998.2	-7.5
DBP	Block 1	865	0.00	0.00	0.90	6432.1	
	Block 2		0.01	0.01	0.01	6425.7	-6.4
logFRS	Block 1	865	0.01	0.01	0.05	1324.4	
	Block 2		0.04	0.03	< 0.01	1302.0	-22.4
WC	Block 1	865	0.00	0.00	0.25	6937.7	
	Block 2		0.08	0.07	< 0.01	6875.2	-62.5
HDL-C	Block 1	865	0.00	0.00	0.72	1015.8	
	Block 2		0.04	0.04	< 0.01	986.2	-29.6
LDL-C	Block 1	865	0.00	0.00	0.60	2194.7	
	Block 2		0.01	0.00	0.17	2195.6	0.9
logTG	Block 1	865	0.00	0.00	1.00	990.3	
	Block 2		0.01	0.00	0.03	987.2	-3.1
logGlucose	Block 1	864	0.00	0.00	0.27	-1165.2	
	Block 2		0.02	0.01	0.02	-1169.0	-3.7

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Oral, Transdermal, Vaginal usage entered

Block 2: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1;

Red bold text used to emphasize statistically significant changes in Block 2

Appendix Table 4b. Objective 2B.3 Unadjusted Model, Coefficients, Full Sample

Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.16 [-0.23, -0.09]	*
	StaB (hours)	0.08 [0.02, 0.13]	0.11 [0.03, 0.19]	*
	Sleep duration (hours)	0.03 [-0.07, 0.13]	0.02 [-0.05, 0.09]	
	Controls (MHT reference group)			
	Oral	0.54 [0.31, 0.78]	0.15 [0.09, 0.22]	*
	Transdermal	0.21 [-0.12, 0.53]	0.04 [-0.02, 0.11]	
	Vaginal	-0.16 [-0.45, 0.12]	-0.04 [-0.10, 0.03]	
AIx75	MVPA (mins)	-0.05 [-0.08, -0.01]	-0.09 [-0.17, -0.02]	*
	StaB (hours)	0.37 [-0.16, 0.90]	0.06 [-0.03, 0.14]	
	Sleep duration (hours)	0.38 [-0.53, 1.29]	0.03 [-0.04, 0.11]	
	Controls (MHT reference group)			
	Oral	0.39 [-1.80, 2.59]	0.01 [-0.06, 0.08]	
	Transdermal	0.19 [-2.85, 3.23]	0.00 [-0.06, 0.07]	
	Vaginal	0.11 [-2.59, 2.80]	0.00 [-0.06, 0.07]	
SBP	MVPA (mins)	-0.09 [-0.14, -0.04]	-0.13 [-0.21, -0.06]	*
	StaB (hours)	-0.23 [-0.94, 0.48]	-0.03 [-0.11, 0.06]	
	Sleep duration (hours)	-0.26 [-1.49, 0.96]	-0.02 [-0.09, 0.06]	
	Controls (MHT reference group)			
	Oral	0.73 [-2.22, 3.68]	0.02 [-0.05, 0.08]	
	Transdermal	1.61 [-2.47, 5.69]	0.03 [-0.04, 0.09]	
	Vaginal	-2.44 [-6.05, 1.18]	-0.05 [-0.11, 0.02]	
DBP	MVPA (mins)	-0.05 [-0.09, -0.02]	-0.11 [-0.19, -0.04]	*
	StaB (hours)	-0.74 [-1.25, -0.23]	-0.12 [-0.21, -0.04]	*
	Sleep duration (hours)	-0.18 [-1.06, 0.69]	-0.02 [-0.09, 0.06]	
	Controls (MHT reference group)			
	Oral	-0.61 [-2.72, 1.51]	-0.02 [-0.09, 0.05]	
	Transdermal	-0.96 [-3.89, 1.97]	-0.02 [-0.09, 0.05]	
	Vaginal	0.47 [-2.12, 3.07]	0.01 [-0.05, 0.08]	
logFRS	MVPA (mins)	0.00 [-0.01, 0.00]	-0.16 [-0.24, -0.09]	*
	StaB (hours)	0.01 [-0.01, 0.04]	0.04 [-0.05, 0.12]	
	Sleep duration (hours)	0.01 [-0.04, 0.06]	0.02 [-0.06, 0.09]	
	Controls (MHT reference group)			
	Oral	0.02 [-0.09, 0.13]	0.01 [-0.05, 0.08]	
	Transdermal	0.03 [-0.12, 0.18]	0.01 [-0.05, 0.08]	

WC	Vaginal	-0.17 [-0.31, -0.04]	-0.08 [-0.15, -0.02]	*
	MVPA (mins)	-0.16 [-0.20, -0.11]	-0.25 [-0.32, -0.17]	*
	StaB (hours)	0.17 [-0.49, 0.83]	0.02 [-0.06, 0.10]	
	Sleep duration (hours)	-1.32 [-2.45, -0.18]	-0.08 [-0.16, -0.01]	*
	Controls (MHT reference group)			
	Oral	-3.39 [-6.14, -0.64]	-0.08 [-0.15, -0.02]	*
	Transdermal	0.80 [-3.00, 4.60]	0.01 [-0.05, 0.08]	
HDL-C	Vaginal	-1.66 [-5.02, 1.71]	-0.03 [-0.10, 0.03]	
	MVPA (mins)	0.00 [0.00, 0.00]	0.13 [0.05, 0.20]	*
	StaB (hours)	-0.03 [-0.05, -0.01]	-0.11 [-0.20, -0.03]	*
	Sleep duration (hours)	-0.01 [-0.05, 0.03]	-0.02 [-0.09, 0.06]	
	Controls (MHT reference group)			
	Oral	0.07 [-0.03, 0.16]	0.05 [-0.02, 0.11]	
	Transdermal	0.05 [-0.07, 0.18]	0.03 [-0.04, 0.09]	
LDL-C	Vaginal	-0.02 [-0.13, 0.10]	-0.01 [-0.08, 0.06]	
	MVPA (mins)	0.00 [0.00, 0.01]	0.08 [0.00, 0.15]	*
	StaB (hours)	0.01 [-0.03, 0.05]	0.02 [-0.07, 0.10]	
	Sleep duration (hours)	0.03 [-0.05, 0.11]	0.03 [-0.05, 0.11]	
	Controls (MHT reference group)			
	Oral	-0.11 [-0.29, 0.07]	-0.04 [-0.11, 0.03]	
	Transdermal	0.00 [-0.26, 0.25]	0.00 [-0.07, 0.07]	
logTG	Vaginal	0.00 [-0.22, 0.23]	0.00 [-0.07, 0.07]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.09 [-0.16, -0.01]	*
	StaB (hours)	0.01 [-0.01, 0.03]	0.03 [-0.05, 0.12]	
	Sleep duration (hours)	0.01 [-0.03, 0.05]	0.02 [-0.05, 0.10]	
	Controls (MHT reference group)			
	Oral	-0.02 [-0.11, 0.07]	-0.01 [-0.08, 0.05]	
	Transdermal	0.00 [-0.13, 0.12]	0.00 [-0.07, 0.07]	
logGlucose	Vaginal	-0.01 [-0.12, 0.10]	-0.01 [-0.07, 0.06]	
	MVPA (mins)	0.00 [0.00, 0.00]	-0.10 [-0.18, -0.03]	*
	StaB (hours)	0.00 [-0.01, 0.01]	0.00 [-0.08, 0.09]	
	Sleep duration (hours)	0.00 [-0.01, 0.01]	-0.01 [-0.08, 0.07]	
	Controls (MHT reference group)			
	Oral	0.00 [-0.03, 0.03]	0.00 [-0.07, 0.07]	
	Transdermal	0.01 [-0.02, 0.05]	0.03 [-0.04, 0.09]	
	Vaginal	-0.03 [-0.06, 0.00]	-0.06 [-0.12, 0.01]	

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 4c. Objective 2B.3 Unadjusted Model Fit, MHT Users

Outcome	Block	N	R ²	MHT users Only	Sig. F Change	AIC	ΔAIC
				Adj. R ²			
aPWV	Block 1	205	0.08	0.07	< 0.01	636.1	
	Block 2		0.20	0.17	< 0.01	614.8	-21.3
AIx75	Block 1	205	0.00	-0.01	0.95	1589.7	
	Block 2		0.03	0.01	0.09	1589.1	-0.6
SBP	Block 1	205	0.01	0.00	0.23	1692.5	
	Block 2		0.06	0.04	0.02	1688.4	-4.1
DBP	Block 1	205	0.00	-0.01	0.79	1554.1	
	Block 2		0.02	0.00	0.31	1556.4	2.3
logFRS	Block 1	205	0.04	0.03	0.02	305.7	
	Block 2		0.11	0.09	< 0.01	295.5	-10.1
WC	Block 1	205	0.01	0.00	0.23	1628.6	
	Block 2		0.10	0.08	< 0.01	1615.9	-12.7
HDL-C	Block 1	205	0.00	-0.01	0.62	211.0	
	Block 2		0.02	0.00	0.29	213.1	2.1
LDL-C	Block 1	205	0.01	0.00	0.57	500.2	
	Block 2		0.03	0.00	0.22	501.6	1.4
logTG	Block 1	205	0.00	-0.01	0.98	211.7	
	Block 2		0.01	-0.02	0.63	215.9	4.2
logGlucose	Block 1	205	0.02	0.01	0.20	-237.5	
	Block 2		0.03	0.00	0.49	-234.0	3.5

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Transdermal, Vaginal usage entered

Block 2: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1;

Red bold text used to emphasize statistically significant changes in Block 2

Appendix Table 4d. Objective 2B.3 Unadjusted Model, Coefficients, MHT Users

Outcome	Predictor	Unstandardized B [95% CI]	Standardized β [95% CI]	Sig.
aPWV	MVPA (mins)	-0.02 [-0.03, -0.01]	-0.27 [-0.42, -0.12]	*
	StaB (hours)	0.07 [-0.04, 0.19]	0.10 [-0.06, 0.26]	
	Sleep duration (hours)	-0.06 [-0.25, 0.13]	-0.05 [-0.19, 0.09]	
	Oral Usage (MHT reference group)			
	Transdermal	-0.32 [-0.69, 0.05]	-0.11 [-0.25, 0.02]	
AIx75	Vaginal	-0.66 [-1.00, -0.31]	-0.26 [-0.39, -0.12]	*
	MVPA (mins)	-0.07 [-0.17, 0.03]	-0.11 [-0.28, 0.05]	
	StaB (hours)	0.68 [-0.56, 1.92]	0.10 [-0.08, 0.28]	
	Sleep duration (hours)	0.61 [-1.44, 2.67]	0.05 [-0.11, 0.20]	
	Oral Usage (MHT reference group)			
SBP	Transdermal	-0.10 [-4.12, 3.92]	0.00 [-0.15, 0.14]	*
	Vaginal	-0.09 [-3.81, 3.63]	0.00 [-0.15, 0.14]	
	MVPA (mins)	-0.18 [-0.31, -0.05]	-0.22 [-0.38, -0.06]	
	StaB (hours)	-0.36 [-1.94, 1.23]	-0.04 [-0.22, 0.14]	
	Sleep duration (hours)	-1.74 [-4.36, 0.88]	-0.10 [-0.25, 0.05]	
DBP	Oral Usage (MHT reference group)			
	Transdermal	1.06 [-4.06, 6.18]	0.03 [-0.11, 0.18]	
	Vaginal	-2.65 [-7.39, 2.09]	-0.08 [-0.23, 0.06]	
	MVPA (mins)	-0.09 [-0.18, 0.01]	-0.15 [-0.32, 0.01]	
	StaB (hours)	-0.58 [-1.73, 0.57]	-0.09 [-0.27, 0.09]	
logFRS	Sleep duration (hours)	-0.89 [-2.79, 1.00]	-0.07 [-0.23, 0.08]	*
	Oral Usage (MHT reference group)			
	Transdermal	-0.23 [-3.94, 3.48]	-0.01 [-0.16, 0.14]	
	Vaginal	1.34 [-2.10, 4.77]	0.06 [-0.09, 0.21]	
	MVPA (mins)	-0.01 [-0.01, 0.00]	-0.25 [-0.41, -0.09]	
WC	StaB (hours)	0.01 [-0.04, 0.06]	0.03 [-0.14, 0.20]	*
	Sleep duration (hours)	-0.03 [-0.11, 0.06]	-0.04 [-0.19, 0.10]	
	Oral Usage (MHT reference group)			
	Transdermal	0.02 [-0.16, 0.19]	0.01 [-0.13, 0.15]	
	Vaginal	-0.18 [-0.34, -0.02]	-0.16 [-0.30, -0.02]	
WC	MVPA (mins)	-0.17 [-0.28, -0.06]	-0.24 [-0.40, -0.08]	*
	StaB (hours)	0.36 [-0.97, 1.68]	0.05 [-0.13, 0.22]	
	Sleep duration (hours)	-1.63 [-3.83, 0.56]	-0.11 [-0.26, 0.04]	
	Oral Usage (MHT reference group)			

	Transdermal	4.26 [-0.03, 8.55]	0.14 [0.00, 0.28]
	Vaginal	1.85 [-2.12, 5.82]	0.07 [-0.08, 0.21]
HDL-C	MVPA (mins)	0.00 [0.00, 0.00]	0.00 [-0.16, 0.17]
	StaB (hours)	-0.04 [-0.08, 0.01]	-0.15 [-0.32, 0.03]
	Sleep duration (hours)	-0.03 [-0.10, 0.04]	-0.06 [-0.21, 0.10]
	Oral Usage (MHT reference group)		
	Transdermal	-0.01 [-0.15, 0.13]	-0.01 [-0.16, 0.14]
	Vaginal	-0.07 [-0.20, 0.06]	-0.08 [-0.23, 0.07]
LDL-C	MVPA (mins)	0.01 [0.00, 0.01]	0.12 [-0.04, 0.29]
	StaB (hours)	-0.01 [-0.10, 0.08]	-0.02 [-0.20, 0.16]
	Sleep duration (hours)	0.05 [-0.10, 0.19]	0.05 [-0.10, 0.21]
	Oral Usage (MHT reference group)		
	Transdermal	0.10 [-0.19, 0.38]	0.05 [-0.10, 0.20]
	Vaginal	0.09 [-0.17, 0.36]	0.05 [-0.10, 0.20]
logTG	MVPA (mins)	0.00 [-0.01, 0.00]	-0.07 [-0.24, 0.09]
	StaB (hours)	0.00 [-0.04, 0.05]	0.01 [-0.17, 0.19]
	Sleep duration (hours)	-0.02 [-0.09, 0.05]	-0.05 [-0.20, 0.11]
	Oral Usage (MHT reference group)		
	Transdermal	0.02 [-0.13, 0.16]	0.02 [-0.13, 0.17]
	Vaginal	0.01 [-0.12, 0.14]	0.01 [-0.14, 0.16]
logGlucose	MVPA (mins)	0.00 [0.00, 0.00]	-0.12 [-0.29, 0.05]
	StaB (hours)	-0.01 [-0.02, 0.01]	-0.06 [-0.24, 0.11]
	Sleep duration (hours)	0.00 [-0.02, 0.03]	0.02 [-0.14, 0.17]
	Oral Usage (MHT reference group)		
	Transdermal	0.01 [-0.04, 0.06]	0.04 [-0.11, 0.19]
	Vaginal	-0.03 [-0.07, 0.01]	-0.10 [-0.25, 0.05]

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 5a. Sensitivity Analyses: Controlling for BMI, MHT History Exposure, Model Fit

Outcome	Block	Sensitivity Analysis				Objective 2B.1			
		Adj. R ²	Sig. F Change	AIC	ΔAIC	Adj. R ²	Sig. F Change	AIC	ΔAIC
aPWV	Block 1	0.02	< 0.01	2445.3		0.02	< 0.01	2443.3	
	Block 2	0.07	< 0.01	2404.8	-40.5	0.07	< 0.01	2403.0	-40.3
	Block 3	0.12	< 0.01	2368.7	-36.1	0.11	< 0.01	2370.3	-32.7
AIx75	Block 1	0.02	< 0.01	5932.83		0.01	0.08	5944.2	
	Block 2	0.02	0.24	5933.95	1.1	0.01	0.15	5944.4	0.2
	Block 3	0.03	0.05	5931.95	-2.0	0.02	0.01	5938.5	-5.9
SBP	Block 1	0.12	< 0.01	6356.84		0.02	< 0.01	6447.4	
	Block 2	0.13	0.25	6358.04	1.2	0.02	0.06	6445.6	-1.8
	Block 3	0.13	0.10	6357.57	-0.5	0.03	0.03	6442.2	-3.4
DBP	Block 1	0.08	< 0.01	5879.39		0.01	0.12	5943.7	
	Block 2	0.08	0.30	5880.98	1.6	0.01	0.11	5943.3	-0.4
	Block 3	0.10	< 0.01	5870.77	-10.2	0.02	0.01	5937.6	-5.7
logFRS	Block 1	0.09	< 0.01	1165.74		0.01	0.01	1226.2	
	Block 2	0.10	< 0.01	1156.38	-9.4	0.03	< 0.01	1213.6	-12.6
	Block 3	0.11	0.03	1152.96	-3.4	0.05	< 0.01	1199.9	-13.8
HDL-C	Block 1	0.14	< 0.01	854.27		0.03	< 0.01	947.5	
	Block 2	0.15	< 0.01	848.03	-6.2	0.03	0.92	951.3	3.8
	Block 3	0.14	0.84	857.91	9.9	0.07	< 0.01	922.6	-28.7
LDL-C	Block 1	0.01	0.01	2010.45		0.01	0.01	2008.6	
	Block 2	0.01	0.35	2016.38	5.9	0.01	0.71	2011.9	3.3
	Block 3	0.01	0.70	2013.72	-2.7	0.01	0.33	2014.4	2.5
logTG	Block 1	0.14	< 0.01	758.27		0.02	< 0.01	862.9	
	Block 2	0.14	0.76	761.72	3.4	0.02	0.87	866.6	3.7
	Block 3	0.14	0.68	766.17	4.5	0.03	0.03	863.5	-3.1
logGlucose	Block 1	0.10	< 0.01	-1153.25		0.02	< 0.01	-1086.7	
	Block 2	0.10	0.28	-1151.80	1.5	0.03	0.09	-1087.6	-0.9
	Block 3	0.10	0.59	-1147.73	4.1	0.03	0.13	-1087.3	0.3

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: Former, Current Usage entered

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 5b. Sensitivity Analyses: Controlling for BMI, MHT History Exposure, Coefficients

Outcome	Predictor	Sens.	Sig.	Objective 2B.1	Sig.
		Standardized β [95% CI]		Standardized β [95% CI]	
aPWV	BMI	-0.07 [-0.14, 0.00]		--	
	Age at menopause (years)	-0.05 [-0.13, 0.02]		-0.06 [-0.13, 0.01]	
	Spontaneous menopause	0.06 [-0.01, 0.13]		0.07 [0.00, 0.14]	
	History of VMS	-0.12 [-0.19, -0.05]	*	-0.12 [-0.18, -0.05]	*
	Postsecondary education	-0.04 [-0.11, 0.03]		-0.03 [-0.10, 0.04]	
	Primary earner status	0.02 [-0.04, 0.09]		0.02 [-0.05, 0.08]	
	MVPA (mins)	-0.18 [-0.26, -0.10]	*	-0.17 [-0.24, -0.09]	*
	StaB (hours)	0.09 [0.00, 0.17]	*	0.08 [0.00, 0.17]	*
	Sleep duration (hours)	0.03 [-0.05, 0.10]		0.03 [-0.04, 0.10]	
	Controls (MHT reference group)				
	Former Usage	0.20 [0.14, 0.27]	*	0.20 [0.13, 0.27]	*
	Current Usage	-0.04 [-0.11, 0.02]		-0.04 [-0.11, 0.03]	
AIx75	BMI	0.11 [0.04, 0.18]	*	--	
	Age at menopause (years)	-0.07 [-0.15, 0.01]		-0.06 [-0.14, 0.01]	
	Spontaneous menopause	0.03 [-0.04, 0.11]		0.02 [-0.06, 0.09]	
	History of VMS	-0.07 [-0.14, 0.00]	*	-0.08 [-0.15, -0.01]	*
	Postsecondary education	0.00 [-0.07, 0.07]		-0.01 [-0.08, 0.06]	
	Primary earner status	-0.04 [-0.11, 0.03]		-0.03 [-0.10, 0.04]	
	MVPA (mins)	-0.06 [-0.14, 0.02]		-0.08 [-0.16, 0.00]	*
	StaB (hours)	0.06 [-0.03, 0.15]		0.06 [-0.02, 0.15]	
	Sleep duration (hours)	0.03 [-0.04, 0.11]		0.03 [-0.05, 0.11]	
	Controls (MHT reference group)				
	Former Usage	0.02 [-0.05, 0.09]		0.02 [-0.05, 0.09]	
	Current Usage	-0.05 [-0.12, 0.02]		-0.06 [-0.13, 0.02]	
SBP	Age (years)	0.18 [0.11, 0.25]	*	0.11 [0.04, 0.19]	*
	BMI	0.34 [0.27, 0.41]	*	--	
	Age at menopause (years)	-0.03 [-0.10, 0.05]		-0.01 [-0.08, 0.07]	
	Spontaneous menopause	0.04 [-0.03, 0.11]		0.00 [-0.08, 0.07]	
	History of VMS	-0.01 [-0.08, 0.06]		-0.03 [-0.10, 0.04]	
	Postsecondary education	-0.01 [-0.08, 0.05]		-0.05 [-0.12, 0.02]	
	Primary earner status	-0.04 [-0.10, 0.03]		0.00 [-0.07, 0.07]	
	MVPA (mins)	-0.05 [-0.12, 0.03]		-0.12 [-0.20, -0.04]	*
	StaB (hours)	-0.10 [-0.18, -0.01]	*	-0.08 [-0.16, 0.01]	

	Sleep duration (hours)	0.00 [-0.08, 0.07]		-0.02 [-0.10, 0.06]	
	Controls (MHT reference group)				
	Former Usage	0.00 [-0.07, 0.07]		0.02 [-0.05, 0.10]	
	Current Usage	-0.06 [-0.13, 0.01]		-0.08 [-0.15, -0.01]	*
DBP	Age (years)	0.00 [-0.07, 0.07]		-0.06 [-0.14, 0.01]	
	BMI	0.31 [0.24, 0.38]	*	--	
	Age at menopause (years)	-0.07 [-0.14, 0.01]		-0.05 [-0.13, 0.02]	
	Spontaneous menopause	0.05 [-0.03, 0.12]		0.00 [-0.07, 0.08]	
	History of VMS	0.01 [-0.05, 0.08]		-0.01 [-0.08, 0.06]	
	Postsecondary education	-0.03 [-0.10, 0.03]		-0.07 [-0.14, 0.00]	*
	Primary earner status	-0.01 [-0.08, 0.06]		0.03 [-0.04, 0.10]	
	MVPA (mins)	-0.03 [-0.11, 0.04]		-0.10 [-0.18, -0.02]	*
	StaB (hours)	-0.15 [-0.24, -0.07]	*	-0.13 [-0.22, -0.05]	*
	Sleep duration (hours)	0.00 [-0.08, 0.07]		-0.02 [-0.10, 0.06]	
	Controls (MHT reference group)				
	Former Usage	-0.01 [-0.08, 0.06]		0.01 [-0.07, 0.08]	
	Current Usage	-0.06 [-0.13, 0.01]		-0.08 [-0.15, -0.01]	*
logFRS	BMI	0.25 [0.18, 0.32]	*	--	
	Age at menopause (years)	-0.05 [-0.12, 0.03]		-0.03 [-0.11, 0.04]	
	Spontaneous menopause	0.03 [-0.05, 0.10]		-0.01 [-0.09, 0.06]	
	History of VMS	-0.04 [-0.10, 0.03]		-0.05 [-0.12, 0.02]	
	Postsecondary education	-0.07 [-0.13, 0.00]	*	-0.10 [-0.16, -0.03]	*
	Primary earner status	-0.01 [-0.07, 0.06]		0.02 [-0.05, 0.09]	
	MVPA (mins)	-0.10 [-0.18, -0.02]	*	-0.15 [-0.23, -0.07]	*
	StaB (hours)	0.01 [-0.08, 0.09]		0.01 [-0.07, 0.10]	
	Sleep duration (hours)	0.03 [-0.05, 0.10]		0.01 [-0.06, 0.09]	
	Controls (MHT reference group)				
HDL-C	Former Usage	0.05 [-0.02, 0.12]		0.06 [-0.01, 0.13]	
	Current Usage	-0.10 [-0.17, -0.03]	*	-0.11 [-0.18, -0.04]	*
	Age (years)	0.08 [0.01, 0.15]	*	0.14 [0.07, 0.21]	*
	BMI	-0.32 [-0.38, -0.25]	*	--	
	Age at menopause (years)	-0.02 [-0.09, 0.05]		-0.04 [-0.11, 0.04]	
	Spontaneous menopause	0.07 [0.00, 0.14]	*	0.12 [0.04, 0.19]	*
	History of VMS	0.00 [-0.07, 0.06]		0.02 [-0.05, 0.08]	
	Postsecondary education	0.04 [-0.02, 0.11]		0.08 [0.01, 0.15]	*
	Primary earner status	-0.04 [-0.10, 0.03]		-0.07 [-0.14, 0.00]	*

	MVPA (mins)	0.04 [-0.03, 0.12]		0.11 [0.03, 0.19]	*
	StaB (hours)	-0.12 [-0.20, -0.04]	*	-0.14 [-0.22, -0.05]	*
	Sleep duration (hours)	-0.03 [-0.10, 0.04]		-0.01 [-0.09, 0.06]	
	Controls (MHT reference group)				
	Former Usage	0.01 [-0.06, 0.08]		0.00 [-0.08, 0.07]	
	Current Usage	-0.02 [-0.08, 0.05]		0.00 [-0.07, 0.07]	
LDL-C	Age (years)	-0.12 [-0.19, -0.04]	*	-0.12 [-0.19, -0.04]	*
	BMI	0.00 [-0.07, 0.08]		--	
	Age at menopause (years)	-0.01 [-0.09, 0.06]		-0.01 [-0.09, 0.06]	
	Spontaneous menopause	0.01 [-0.07, 0.08]		0.01 [-0.07, 0.08]	
	History of VMS	-0.03 [-0.10, 0.04]		-0.03 [-0.10, 0.04]	
	Postsecondary education	0.02 [-0.05, 0.09]		0.02 [-0.05, 0.09]	
	Primary earner status	-0.07 [-0.15, 0.00]	*	-0.07 [-0.14, 0.00]	*
	MVPA (mins)	0.07 [-0.01, 0.15]		0.07 [-0.01, 0.15]	
	StaB (hours)	0.03 [-0.06, 0.12]		0.03 [-0.06, 0.12]	
	Sleep duration (hours)	0.03 [-0.05, 0.11]		0.03 [-0.05, 0.11]	
	Controls (MHT reference group)				
	Former Usage	-0.01 [-0.08, 0.07]		-0.01 [-0.08, 0.07]	
	Current Usage	-0.03 [-0.10, 0.04]		-0.03 [-0.10, 0.04]	
logTG	Age (years)	-0.03 [-0.10, 0.04]		-0.11 [-0.18, -0.03]	*
	BMI	0.36 [0.29, 0.43]	*	--	
	Age at menopause (years)	-0.07 [-0.14, 0.00]		-0.05 [-0.13, 0.02]	
	Spontaneous menopause	-0.04 [-0.11, 0.03]		-0.09 [-0.16, -0.01]	*
	History of VMS	-0.02 [-0.09, 0.04]		-0.05 [-0.12, 0.02]	
	Postsecondary education	0.01 [-0.06, 0.07]		-0.04 [-0.11, 0.03]	
	Primary earner status	0.02 [-0.04, 0.09]		0.06 [-0.01, 0.13]	
	MVPA (mins)	0.00 [-0.08, 0.08]		-0.08 [-0.16, 0.00]	
	StaB (hours)	0.03 [-0.05, 0.11]		0.05 [-0.04, 0.14]	
	Sleep duration (hours)	0.04 [-0.03, 0.12]		0.03 [-0.05, 0.10]	
	Controls (MHT reference group)				
	Former Usage	-0.03 [-0.10, 0.04]		-0.01 [-0.08, 0.07]	
	Current Usage	0.00 [-0.06, 0.07]		-0.02 [-0.09, 0.05]	
logGlucose	Age (years)	0.10 [0.03, 0.18]	*	0.04 [-0.03, 0.12]	
	BMI	0.29 [0.22, 0.36]	*	--	
	Age at menopause (years)	0.09 [0.02, 0.17]	*	0.11 [0.03, 0.18]	*
	Spontaneous menopause	-0.09 [-0.16, -0.01]	*	-0.13 [-0.20, -0.05]	*

History of VMS	-0.03 [-0.10, 0.04]	-0.05 [-0.12, 0.02]	
Postsecondary education	-0.02 [-0.09, 0.05]	-0.05 [-0.12, 0.02]	
Primary earner status	0.02 [-0.05, 0.09]	0.05 [-0.02, 0.12]	
MVPA (mins)	-0.03 [-0.11, 0.05]	-0.10 [-0.17, -0.02]	*
StaB (hours)	-0.06 [-0.14, 0.03]	-0.04 [-0.13, 0.05]	
Sleep duration (hours)	-0.01 [-0.08, 0.07]	-0.02 [-0.10, 0.05]	
Controls (MHT reference group)			
Former Usage	0.00 [-0.07, 0.07]	0.02 [-0.06, 0.09]	
Current Usage	-0.06 [-0.12, 0.01]	-0.07 [-0.14, 0.00]	*

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 5c. Sensitivity Analyses: Controlling for BMI, MHT Type Exposure, Model Fit

Outcome	Block	Adj. R ²	Sensitivity Analysis			Adj. R ²	Objective 2B.2		
			Sig. F Change	AIC	ΔAIC		Sig. F Change	AIC	ΔAIC
aPWV	Block 1	0.02	< 0.01	2168.0		0.02	< 0.01	2166.2	
	Block 2	0.06	< 0.01	2145.4	-22.6	0.06	< 0.01	2143.6	-22.6
	Block 3	0.10	< 0.01	2115.1	-30.4	0.10	< 0.01	2115.5	-28.1
AIx75	Block 1	0.02	< 0.01	5329.4		0.01	0.07	5339.2	
	Block 2	0.02	0.17	5329.7	0.4	0.01	0.19	5339.9	0.7
	Block 3	0.03	0.11	5329.5	-0.2	0.02	0.02	5336.3	-3.6
SBP	Block 1	0.12	< 0.01	5689.7		0.01	0.02	5768.8	
	Block 2	0.12	0.63	5692.8	3.1	0.01	0.68	5772.0	3.2
	Block 3	0.12	0.20	5694.1	1.3	0.02	0.04999	5770.1	-1.9
DBP	Block 1	0.09	< 0.01	5235.3		0.00	0.25	5299.9	
	Block 2	0.09	0.54	5238.0	2.8	0.00	0.64	5303.0	3.1
	Block 3	0.10	0.01	5232.4	-5.6	0.01	0.03	5299.8	-3.3
logFRS	Block 1	0.09	< 0.01	1038.3		0.01	0.02	1093.6	
	Block 2	0.09	0.22	1039.2	0.9	0.01	0.32	1095.3	1.7
	Block 3	0.10	0.04	1036.9	-2.4	0.03	< 0.01	1084.0	-11.3
HDL-C	Block 1	0.15	< 0.01	739.2		0.04	< 0.01	827.3	
	Block 2	0.15	0.12	738.8	-0.4	0.04	0.13	827.2	-0.1
	Block 3	0.17	< 0.01	726.7	-12.1	0.08	< 0.01	798.3	-28.8
LDL-C	Block 1	0.02	0.01	1804.0		0.02	< 0.01	1802.0	
	Block 2	0.02	0.37	1806.0	2.0	0.02	0.38	1804.0	2.0
	Block 3	0.02	0.47	1809.4	3.4	0.02	0.50	1807.6	3.6
logTG	Block 1	0.13	< 0.01	696.8		0.02	< 0.01	782.7	
	Block 2	0.13	0.59	699.7	2.9	0.02	0.67	785.9	3.2
	Block 3	0.13	0.77	704.6	4.8	0.02	0.11	785.7	-0.2
logGlucose	Block 1	0.11	< 0.01	-1059.9		0.03	< 0.01	-998.3	
	Block 2	0.11	0.83	-1056.3	3.6	0.03	0.95	-994.4	3.9
	Block 3	0.11	0.56	-1052.4	3.9	0.03	0.16	-993.7	0.7

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: Combined Estrogen-Progestosterone, Unopposed Estrogen Usage entered

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 5d. Sensitivity Analyses: Controlling for BMI, MHT Type Exposure, Coefficients

Outcome	Predictor	SENS1.2		Objective 2B.2	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	BMI	-0.06 [-0.13, 0.02]		--	
	Age at menopause (years)	-0.05 [-0.12, 0.03]		-0.05 [-0.13, 0.03]	
	Spontaneous menopause	0.03 [-0.04, 0.11]		0.04 [-0.03, 0.12]	
	History of VMS	-0.15 [-0.22, -0.08]	*	-0.14 [-0.21, -0.07]	*
	Postsecondary education	-0.04 [-0.11, 0.04]		-0.03 [-0.10, 0.04]	
	Primary earner status	0.02 [-0.05, 0.10]		0.02 [-0.05, 0.09]	
	MVPA (mins)	-0.18 [-0.26, -0.10]	*	-0.17 [-0.25, -0.09]	*
	StaB (hours)	0.08 [0.00, 0.17]		0.08 [-0.01, 0.17]	
	Sleep duration (hours)	0.02 [-0.06, 0.10]		0.02 [-0.06, 0.10]	
	Controls (MHT reference group)				
	Combined Estrogen-Progestosterone	0.17 [0.10, 0.25]	*	0.17 [0.10, 0.25]	*
	Unopposed Estrogen	0.01 [-0.07, 0.08]		0.00 [-0.07, 0.08]	
AIx75	BMI	0.12 [0.04, 0.19]	*	--	
	Age at menopause (years)	-0.08 [-0.16, 0.00]	*	-0.08 [-0.16, 0.01]	
	Spontaneous menopause	0.04 [-0.04, 0.12]		0.02 [-0.06, 0.10]	
	History of VMS	-0.08 [-0.15, 0.00]	*	-0.09 [-0.16, -0.01]	*
	Postsecondary education	0.01 [-0.06, 0.09]		0.00 [-0.07, 0.07]	
	Primary earner status	-0.06 [-0.13, 0.02]		-0.05 [-0.12, 0.03]	
	MVPA (mins)	-0.06 [-0.15, 0.02]		-0.08 [-0.17, 0.00]	*
	StaB (hours)	0.05 [-0.04, 0.14]		0.05 [-0.04, 0.15]	
	Sleep duration (hours)	0.02 [-0.07, 0.10]		0.01 [-0.07, 0.09]	
	Controls (MHT reference group)				
	Combined Estrogen-Progestosterone	0.05 [-0.02, 0.13]		0.05 [-0.02, 0.13]	
	Unopposed Estrogen	-0.04 [-0.11, 0.04]		-0.04 [-0.11, 0.04]	
SBP	Age (years)	0.17 [0.09, 0.24]	*	0.10 [0.02, 0.18]	*
	BMI	0.34 [0.27, 0.42]	*	--	
	Age at menopause (years)	0.00 [-0.08, 0.07]		0.02 [-0.06, 0.10]	
	Spontaneous menopause	0.04 [-0.03, 0.12]		-0.01 [-0.09, 0.07]	
	History of VMS	-0.02 [-0.09, 0.05]		-0.05 [-0.12, 0.02]	
	Postsecondary education	-0.01 [-0.08, 0.06]		-0.05 [-0.12, 0.03]	
	Primary earner status	-0.03 [-0.11, 0.04]		0.00 [-0.07, 0.08]	
	MVPA (mins)	-0.05 [-0.13, 0.03]		-0.12 [-0.20, -0.04]	*
	StaB (hours)	-0.08 [-0.17, 0.01]		-0.07 [-0.16, 0.03]	

	Sleep duration (hours)	0.00 [-0.08, 0.08]		-0.01 [-0.10, 0.07]	
	Controls (MHT reference group)				
	Combined Estrogen-Progestosterone	0.01 [-0.06, 0.08]		0.02 [-0.06, 0.10]	
	Unopposed Estrogen	-0.03 [-0.10, 0.05]		-0.02 [-0.10, 0.06]	
DBP	Age (years)	-0.01 [-0.08, 0.07]		-0.07 [-0.15, 0.01]	
	BMI	0.32 [0.25, 0.40]	*	--	
	Age at menopause (years)	-0.04 [-0.11, 0.04]		-0.02 [-0.10, 0.06]	
	Spontaneous menopause	0.05 [-0.02, 0.13]		0.00 [-0.08, 0.08]	
	History of VMS	0.01 [-0.06, 0.08]		-0.02 [-0.09, 0.06]	
	Postsecondary education	-0.04 [-0.11, 0.03]		-0.07 [-0.15, 0.00]	
	Primary earner status	-0.01 [-0.08, 0.06]		0.03 [-0.05, 0.10]	
	MVPA (mins)	-0.04 [-0.12, 0.04]		-0.10 [-0.19, -0.02]	*
	StaB (hours)	-0.13 [-0.22, -0.04]	*	-0.12 [-0.21, -0.02]	*
	Sleep duration (hours)	0.01 [-0.07, 0.09]		-0.01 [-0.09, 0.08]	
	Controls (MHT reference group)				
	Combined Estrogen-Progestosterone	0.01 [-0.07, 0.08]		0.01 [-0.06, 0.09]	
	Unopposed Estrogen	-0.04 [-0.11, 0.04]		-0.03 [-0.11, 0.05]	
logFRS	BMI	0.27 [0.19, 0.34]	*	--	
	Age at menopause (years)	-0.04 [-0.11, 0.04]		-0.02 [-0.10, 0.06]	
	Spontaneous menopause	0.02 [-0.06, 0.10]		-0.02 [-0.10, 0.06]	
	History of VMS	-0.05 [-0.12, 0.03]		-0.06 [-0.14, 0.01]	
	Postsecondary education	-0.07 [-0.14, 0.00]		-0.09 [-0.17, -0.02]	*
	Primary earner status	-0.01 [-0.08, 0.06]		0.02 [-0.06, 0.09]	
	MVPA (mins)	-0.10 [-0.18, -0.02]	*	-0.15 [-0.23, -0.07]	*
	StaB (hours)	0.01 [-0.08, 0.10]		0.01 [-0.08, 0.11]	
	Sleep duration (hours)	0.02 [-0.06, 0.10]		0.01 [-0.07, 0.09]	
	Controls (MHT reference group)				
	Combined Estrogen-Progestosterone	0.02 [-0.05, 0.10]		0.02 [-0.05, 0.09]	
	Unopposed Estrogen	-0.06 [-0.13, 0.02]		-0.05 [-0.13, 0.03]	
HDL-C	Age (years)	0.09 [0.02, 0.17]	*	0.16 [0.08, 0.23]	*
	BMI	-0.32 [-0.39, -0.25]	*	--	
	Age at menopause (years)	-0.02 [-0.09, 0.06]		-0.04 [-0.12, 0.04]	
	Spontaneous menopause	0.04 [-0.03, 0.12]		0.09 [0.01, 0.17]	*
	History of VMS	-0.01 [-0.08, 0.06]		0.02 [-0.05, 0.09]	
	Postsecondary education	0.05 [-0.02, 0.12]		0.08 [0.01, 0.16]	*
	Primary earner status	-0.04 [-0.11, 0.03]		-0.08 [-0.15, -0.01]	*

	MVPA (mins)	0.05 [-0.02, 0.13]		0.12 [0.04, 0.20]	*
	StaB (hours)	-0.13 [-0.22, -0.05]	*	-0.15 [-0.24, -0.06]	*
	Sleep duration (hours)	-0.04 [-0.12, 0.04]		-0.02 [-0.10, 0.06]	
	Controls (MHT reference group)				
	Combined Estrogen-Progestosterone	0.05 [-0.02, 0.12]		0.04 [-0.03, 0.11]	
	Unopposed Estrogen	-0.05 [-0.12, 0.03]		-0.05 [-0.13, 0.02]	
LDL-C	Age (years)	-0.11 [-0.19, -0.03]	*	-0.12 [-0.19, -0.04]	*
	BMI	0.02 [-0.06, 0.10]		--	
	Age at menopause (years)	-0.02 [-0.10, 0.06]		-0.02 [-0.10, 0.06]	
	Spontaneous menopause	0.02 [-0.06, 0.10]		0.02 [-0.06, 0.10]	
	History of VMS	-0.02 [-0.10, 0.05]		-0.02 [-0.10, 0.05]	
	Postsecondary education	0.03 [-0.05, 0.10]		0.03 [-0.05, 0.10]	
	Primary earner status	-0.09 [-0.17, -0.02]	*	-0.09 [-0.17, -0.02]	*
	MVPA (mins)	0.07 [-0.02, 0.16]		0.07 [-0.02, 0.15]	
	StaB (hours)	0.04 [-0.06, 0.13]		0.04 [-0.05, 0.13]	
	Sleep duration (hours)	0.02 [-0.06, 0.11]		0.02 [-0.06, 0.11]	
	Controls (MHT reference group)				
	Combined Estrogen-Progestosterone	-0.05 [-0.13, 0.03]		-0.05 [-0.13, 0.03]	
	Unopposed Estrogen	-0.02 [-0.09, 0.06]		-0.02 [-0.09, 0.06]	
logTG	Age (years)	-0.04 [-0.12, 0.03]		-0.11 [-0.19, -0.03]	*
	BMI	0.35 [0.28, 0.43]	*	--	
	Age at menopause (years)	-0.08 [-0.15, 0.00]	*	-0.05 [-0.13, 0.03]	
	Spontaneous menopause	-0.03 [-0.10, 0.05]		-0.08 [-0.16, 0.00]	
	History of VMS	-0.01 [-0.08, 0.06]		-0.04 [-0.12, 0.03]	
	Postsecondary education	0.01 [-0.06, 0.08]		-0.02 [-0.10, 0.05]	
	Primary earner status	0.01 [-0.06, 0.08]		0.05 [-0.03, 0.12]	
	MVPA (mins)	0.01 [-0.07, 0.09]		-0.06 [-0.15, 0.02]	
	StaB (hours)	0.03 [-0.05, 0.12]		0.05 [-0.04, 0.15]	
	Sleep duration (hours)	0.04 [-0.04, 0.12]		0.02 [-0.06, 0.11]	
	Controls (MHT reference group)				
	Combined Estrogen-Progestosterone	-0.04 [-0.11, 0.04]		-0.03 [-0.10, 0.05]	
	Unopposed Estrogen	0.01 [-0.06, 0.08]		0.02 [-0.06, 0.09]	
logGlucose	Age (years)	0.10 [0.02, 0.17]	*	0.04 [-0.04, 0.11]	
	BMI	0.30 [0.23, 0.38]	*	--	
	Age at menopause (years)	0.09 [0.01, 0.17]	*	0.11 [0.03, 0.19]	*
	Spontaneous menopause	-0.08 [-0.16, -0.01]	*	-0.13 [-0.21, -0.05]	*

History of VMS	-0.03 [-0.11, 0.04]	-0.06 [-0.14, 0.01]	
Postsecondary education	-0.03 [-0.10, 0.04]	-0.06 [-0.14, 0.01]	
Primary earner status	0.03 [-0.04, 0.10]	0.06 [-0.01, 0.14]	
MVPA (mins)	-0.04 [-0.12, 0.05]	-0.10 [-0.18, -0.01]	*
StaB (hours)	-0.06 [-0.15, 0.03]	-0.04 [-0.14, 0.05]	
Sleep duration (hours)	0.00 [-0.08, 0.08]	-0.02 [-0.10, 0.07]	
Controls (MHT reference group)			
Combined Estrogen-Progestosterone	-0.02 [-0.10, 0.05]	-0.02 [-0.09, 0.06]	
Unopposed Estrogen	-0.01 [-0.09, 0.06]	-0.01 [-0.09, 0.07]	

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 5e. Sensitivity Analyses: Controlling for BMI, MHT Route Exposure, Model Fit

Outcome	Block	Adj. R ²	Sensitivity Analysis			Adj. R ²	Objective 2B.3		
			Sig. F Change	AIC	ΔAIC		Sig. F Change	AIC	ΔAIC
aPWV	Block 1	0.02	< 0.01	2259.4		0.02	< 0.01	2257.6	
	Block 2	0.06	< 0.01	2233.6	-25.9	0.06	< 0.01	2231.7	-25.9
	Block 3	0.10	< 0.01	2204.6	-29.0	0.10	< 0.01	2205.2	-26.5
AIx75	Block 1	0.02	< 0.01	5555.39		0.00	0.14	5566.2	
	Block 2	0.02	0.95	5561.06	5.7	0.00	0.95	5571.9	5.7
	Block 3	0.02	0.09	5560.55	-0.5	0.01	0.02	5567.6	-4.3
SBP	Block 1	0.13	< 0.01	5933.49		0.01	0.02	6024.4	
	Block 2	0.12	0.71	5938.10	4.6	0.01	0.52	6028.2	3.7
	Block 3	0.13	0.20	5939.42	1.3	0.02	0.04	6025.5	-2.7
DBP	Block 1	0.09	< 0.01	5466.55		0.00	0.15	5535.4	
	Block 2	0.09	0.77	5471.39	4.8	0.00	0.91	5540.9	5.4
	Block 3	0.10	0.01	5464.56	-6.8	0.01	0.01	5536.2	-4.7
logFRS	Block 1	0.09	< 0.01	1079.26		0.01	0.02	1137.8	
	Block 2	0.09	0.04	1077.05	-2.2	0.02	0.04	1135.6	-2.2
	Block 3	0.10	0.06	1075.33	-1.7	0.04	< 0.01	1124.2	-11.4
HDL-C	Block 1	0.14	< 0.01	756.02		0.04	< 0.01	843.6	
	Block 2	0.14	0.39	758.94	2.9	0.03	0.66	848.0	4.4
	Block 3	0.16	< 0.01	748.21	-10.7	0.07	< 0.01	819.8	-28.2
LDL-C	Block 1	0.02	< 0.01	1881.89		0.02	0.01	1879.9	
	Block 2	0.01	0.73	1886.58	4.7	0.01	0.73	1884.6	4.7
	Block 3	0.01	0.37	1889.41	2.8	0.01	0.37	1887.4	2.8
logTG	Block 1	0.14	< 0.01	712.68		0.02	< 0.01	803.4	
	Block 2	0.13	0.82	717.73	5.1	0.02	0.97	809.1	5.8
	Block 3	0.13	0.80	722.70	5.0	0.02	0.10	808.8	-0.3
logGlucose	Block 1	0.10	< 0.01	-1061.31		0.03	< 0.01	-1000.2	
	Block 2	0.10	0.61	-1057.17	4.1	0.02	0.46	-996.9	3.4
	Block 3	0.10	0.52	-1053.50	3.7	0.03	0.18	-995.8	1.0

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: Oral, Transdermal, Vaginal Usage entered

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 5f. Sensitivity Analyses: Controlling for BMI, MHT Route Exposure, Coefficients

Outcome	Predictor	Sensitivity Analyses		Objective 2B.3	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	BMI	-0.06 [-0.13, 0.01]		--	
	Age at menopause (years)	-0.03 [-0.11, 0.04]		-0.04 [-0.11, 0.04]	
	Spontaneous menopause	0.07 [0.00, 0.15]		0.08 [0.01, 0.16]	*
	History of VMS	-0.14 [-0.21, -0.07]	*	-0.14 [-0.21, -0.07]	*
	Postsecondary education	-0.02 [-0.09, 0.05]		-0.01 [-0.08, 0.05]	
	Primary earner status	0.02 [-0.05, 0.09]		0.01 [-0.06, 0.08]	
	MVPA (mins)	-0.17 [-0.25, -0.09]	*	-0.16 [-0.24, -0.08]	*
	StaB (hours)	0.08 [-0.01, 0.16]		0.07 [-0.01, 0.16]	
	Sleep duration (hours)	0.02 [-0.06, 0.10]		0.03 [-0.05, 0.10]	
	Controls (MHT reference group)				
	Oral	0.17 [0.09, 0.24]	*	0.17 [0.10, 0.24]	*
	Transdermal	0.07 [0.00, 0.14]	*	0.07 [0.00, 0.14]	
	Vaginal	-0.04 [-0.11, 0.03]		-0.04 [-0.11, 0.03]	
AIx75	BMI	0.12 [0.04, 0.19]	*	--	
	Age at menopause (years)	-0.07 [-0.15, 0.01]		-0.07 [-0.14, 0.01]	
	Spontaneous menopause	0.05 [-0.03, 0.13]		0.03 [-0.05, 0.11]	
	History of VMS	-0.07 [-0.14, 0.01]		-0.07 [-0.14, 0.00]	
	Postsecondary education	0.01 [-0.06, 0.08]		0.00 [-0.07, 0.07]	
	Primary earner status	-0.05 [-0.12, 0.03]		-0.03 [-0.11, 0.04]	
	MVPA (mins)	-0.07 [-0.15, 0.02]		-0.09 [-0.17, 0.00]	*
	StaB (hours)	0.05 [-0.04, 0.14]		0.05 [-0.04, 0.14]	
	Sleep duration (hours)	0.02 [-0.06, 0.10]		0.02 [-0.07, 0.10]	
	Controls (MHT reference group)				
	Oral	0.01 [-0.07, 0.08]		0.00 [-0.07, 0.08]	
	Transdermal	0.01 [-0.07, 0.08]		0.01 [-0.07, 0.08]	
	Vaginal	0.00 [-0.08, 0.07]		-0.01 [-0.08, 0.07]	
SBP	Age (years)	0.17 [0.09, 0.24]	*	0.09 [0.02, 0.17]	*
	BMI	0.36 [0.28, 0.43]	*	--	
	Age at menopause (years)	-0.01 [-0.09, 0.06]		0.01 [-0.07, 0.09]	
	Spontaneous menopause	0.06 [-0.01, 0.14]		0.01 [-0.06, 0.09]	
	History of VMS	-0.02 [-0.08, 0.05]		-0.04 [-0.12, 0.03]	
	Postsecondary education	-0.01 [-0.08, 0.06]		-0.05 [-0.12, 0.02]	
	Primary earner status	-0.04 [-0.11, 0.03]		0.00 [-0.07, 0.07]	

	MVPA (mins)	-0.05 [-0.13, 0.03]		-0.12 [-0.21, -0.04]	*
	StaB (hours)	-0.08 [-0.17, 0.00]		-0.07 [-0.16, 0.02]	
	Sleep duration (hours)	0.00 [-0.08, 0.07]		-0.02 [-0.11, 0.06]	
	Controls (MHT reference group)				
	Oral	0.00 [-0.07, 0.07]		0.00 [-0.08, 0.07]	
	Transdermal	0.02 [-0.05, 0.09]		0.03 [-0.04, 0.11]	
	Vaginal	-0.03 [-0.10, 0.04]		-0.04 [-0.11, 0.03]	
DBP	Age (years)	0.00 [-0.07, 0.08]		-0.07 [-0.14, 0.01]	
	BMI	0.33 [0.25, 0.40]	*	--	
	Age at menopause (years)	-0.05 [-0.13, 0.02]		-0.03 [-0.11, 0.05]	
	Spontaneous menopause	0.06 [-0.01, 0.14]		0.02 [-0.06, 0.10]	
	History of VMS	0.02 [-0.05, 0.09]		-0.01 [-0.08, 0.06]	
	Postsecondary education	-0.04 [-0.11, 0.03]		-0.08 [-0.15, 0.00]	*
	Primary earner status	-0.01 [-0.08, 0.06]		0.03 [-0.04, 0.10]	
	MVPA (mins)	-0.04 [-0.12, 0.04]		-0.11 [-0.20, -0.03]	*
	StaB (hours)	-0.14 [-0.23, -0.06]	*	-0.13 [-0.22, -0.03]	*
	Sleep duration (hours)	0.00 [-0.08, 0.07]		-0.02 [-0.10, 0.06]	
	Controls (MHT reference group)				
	Oral	-0.03 [-0.10, 0.04]		-0.03 [-0.11, 0.04]	
	Transdermal	-0.03 [-0.10, 0.04]		-0.01 [-0.09, 0.06]	
	Vaginal	0.01 [-0.06, 0.08]		0.01 [-0.07, 0.08]	
logFRS	BMI	0.27 [0.19, 0.34]	*	--	
	Age at menopause (years)	-0.03 [-0.11, 0.04]		-0.01 [-0.09, 0.06]	
	Spontaneous menopause	0.05 [-0.03, 0.12]		0.00 [-0.07, 0.08]	
	History of VMS	-0.05 [-0.12, 0.02]		-0.06 [-0.13, 0.01]	
	Postsecondary education	-0.06 [-0.13, 0.01]		-0.09 [-0.16, -0.02]	*
	Primary earner status	-0.01 [-0.08, 0.06]		0.02 [-0.06, 0.09]	
	MVPA (mins)	-0.10 [-0.18, -0.02]	*	-0.15 [-0.23, -0.07]	*
	StaB (hours)	0.00 [-0.09, 0.09]		0.01 [-0.08, 0.10]	
	Sleep duration (hours)	0.02 [-0.06, 0.10]		0.01 [-0.08, 0.09]	
	Controls (MHT reference group)				
	Oral	0.02 [-0.05, 0.09]		0.01 [-0.06, 0.08]	
	Transdermal	0.02 [-0.05, 0.09]		0.02 [-0.05, 0.10]	
	Vaginal	-0.09 [-0.16, -0.02]	*	-0.09 [-0.16, -0.02]	*
	Age (years)	0.10 [0.03, 0.17]	*	0.16 [0.09, 0.24]	*
HDL-C	BMI	-0.32 [-0.39, -0.25]	*	--	

LDL-C	Age at menopause (years)	-0.02 [-0.10, 0.05]		-0.04 [-0.12, 0.03]	
	Spontaneous menopause	0.07 [-0.01, 0.14]		0.11 [0.04, 0.19]	*
	History of VMS	-0.01 [-0.08, 0.06]		0.02 [-0.05, 0.09]	
	Postsecondary education	0.05 [-0.02, 0.12]		0.08 [0.01, 0.15]	*
	Primary earner status	-0.04 [-0.11, 0.03]		-0.07 [-0.14, 0.00]	*
	MVPA (mins)	0.04 [-0.03, 0.12]		0.11 [0.03, 0.19]	*
	StaB (hours)	-0.13 [-0.21, -0.05]	*	-0.15 [-0.23, -0.06]	*
	Sleep duration (hours)	-0.05 [-0.12, 0.03]		-0.03 [-0.11, 0.05]	
	Controls (MHT reference group)				
	Oral	0.00 [-0.07, 0.07]		0.00 [-0.07, 0.07]	
	Transdermal	0.04 [-0.03, 0.11]		0.03 [-0.04, 0.10]	
	Vaginal	-0.04 [-0.11, 0.03]		-0.03 [-0.11, 0.04]	
	Age (years)	-0.11 [-0.19, -0.03]	*	-0.11 [-0.19, -0.04]	*
	BMI	0.01 [-0.07, 0.08]		--	
logTG	Age at menopause (years)	-0.02 [-0.10, 0.06]		-0.02 [-0.10, 0.06]	
	Spontaneous menopause	0.01 [-0.07, 0.09]		0.01 [-0.07, 0.09]	
	History of VMS	-0.03 [-0.10, 0.04]		-0.03 [-0.10, 0.04]	
	Postsecondary education	0.02 [-0.05, 0.09]		0.02 [-0.05, 0.09]	
	Primary earner status	-0.09 [-0.16, -0.02]	*	-0.09 [-0.16, -0.02]	*
	MVPA (mins)	0.08 [-0.01, 0.16]		0.07 [-0.01, 0.16]	
	StaB (hours)	0.03 [-0.06, 0.12]		0.03 [-0.06, 0.12]	
	Sleep duration (hours)	0.02 [-0.06, 0.10]		0.02 [-0.06, 0.10]	
	Controls (MHT reference group)				
	Oral	-0.03 [-0.11, 0.04]		-0.03 [-0.11, 0.04]	
	Transdermal	0.00 [-0.08, 0.07]		0.00 [-0.08, 0.07]	
	Vaginal	-0.02 [-0.10, 0.05]		-0.02 [-0.10, 0.05]	
	Age (years)	-0.04 [-0.11, 0.03]	*	-0.11 [-0.19, -0.04]	*
	BMI	0.36 [0.28, 0.43]		--	
	Age at menopause (years)	-0.07 [-0.15, 0.00]		-0.05 [-0.13, 0.03]	
	Spontaneous menopause	-0.04 [-0.12, 0.03]		-0.09 [-0.17, -0.02]	*
	History of VMS	-0.03 [-0.09, 0.04]		-0.05 [-0.13, 0.02]	
	Postsecondary education	0.01 [-0.06, 0.08]		-0.03 [-0.10, 0.04]	
	Primary earner status	0.01 [-0.06, 0.08]		0.05 [-0.02, 0.12]	
	MVPA (mins)	0.01 [-0.06, 0.09]		-0.06 [-0.15, 0.02]	
	StaB (hours)	0.03 [-0.05, 0.12]		0.05 [-0.04, 0.14]	
	Sleep duration (hours)	0.04 [-0.04, 0.11]		0.02 [-0.06, 0.10]	

Controls (MHT reference group)					
logGlucose	Oral	-0.01 [-0.09, 0.06]		-0.02 [-0.09, 0.06]	
	Transdermal	-0.03 [-0.10, 0.04]		-0.02 [-0.09, 0.05]	
	Vaginal	0.00 [-0.07, 0.07]		0.00 [-0.08, 0.07]	
	Age (years)	0.11 [0.03, 0.18]	*	0.05 [-0.03, 0.12]	
	BMI	0.30 [0.22, 0.37]	*	--	
	Age at menopause (years)	0.09 [0.02, 0.17]	*	0.11 [0.03, 0.19]	*
	Spontaneous menopause	-0.08 [-0.15, 0.00]	*	-0.12 [-0.20, -0.04]	*
	History of VMS	-0.03 [-0.11, 0.04]		-0.06 [-0.13, 0.01]	
	Postsecondary education	-0.02 [-0.09, 0.05]		-0.05 [-0.12, 0.02]	
	Primary earner status	0.03 [-0.04, 0.10]		0.06 [-0.01, 0.13]	
	MVPA (mins)	-0.03 [-0.11, 0.05]		-0.09 [-0.18, -0.01]	*
	StaB (hours)	-0.06 [-0.14, 0.03]		-0.04 [-0.13, 0.05]	
	Sleep duration (hours)	0.01 [-0.07, 0.09]		-0.01 [-0.09, 0.07]	
	Controls (MHT reference group)				
Oral	0.02 [-0.05, 0.09]		0.02 [-0.05, 0.10]		
Transdermal	0.02 [-0.05, 0.09]		0.03 [-0.04, 0.11]		
Vaginal	-0.03 [-0.10, 0.04]		-0.04 [-0.11, 0.03]		
Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose					

Appendix Table 6a. Sensitivity Analyses: Group Comparisons by MHT History, Age 55-64

Variable	Controls (N=393)	Former MHT Usage (N=61)	Current MHT Usage (N=57)	Omnibus p-value	Effect size
Age (years)	60 [58, 62]	61 [59, 63]	59 [57, 62]	0.15	$\epsilon^2=0.00$
BMI (kg/m ²)	25.8 [23.2, 30.2]	27.0 [24.8, 30.8]	26.3 [22.8, 29.0]	0.06	$\epsilon^2=0.01$
Mean arterial pressure (mmHg)	97 (11)	100 (10)	95 (13)	0.08	$\eta^2=0.01$
Age at menopause (years)	53 [51, 56]	52 [45, 55]	52 [48, 54]	0.02	$\epsilon^2=0.01$
MVPA (avg. mins/day)	23.1 [11.5, 41.1]	25.8 [14.3, 43.0]	22.6 [14.0, 42.2]	0.55	$\epsilon^2=0.00$
StaB (avg. hours/day)	11.9 (1.6)	11.5 (1.4)	11.9 (1.7)	0.19	$\eta^2=0.01$
Sleep (avg. hours/day)	6.5 (0.9)	6.6 (0.8)	6.5 (0.8)	0.69	$\eta^2=0.00$
aPWV (m/s)	8.4 [8.0, 8.8]	8.4 [8.1, 8.8]	8.3 [7.8, 8.7]	0.16	$\epsilon^2=0.00$
AIx75 (%)	20.0 [12.7, 27.0]	21.0 [13.7, 26.0]	21.3 [12.7, 27.7]	0.97	$\epsilon^2=0.00$
SBP (mmHg)	120 (13)	123 (12)	119 (16)	0.19	$\eta^2=0.01$
DBP (mmHg)	77 (10)	81 (10) *	76 (11) †	0.02	$\eta^2=0.02$
FRS (%)	5.3 [3.9, 7.3]	4.5 [3.9, 7.3]	4.5 [3.3, 6.3]	0.17	$\epsilon^2=0.00$
WC (cm)	92.5 [85.0, 102.5]	95.0 [88.5, 104.8]	91.5 [85.0, 98.5]	0.13	$\epsilon^2=0.00$
HDL-C (mmol/L)	1.65 [1.39, 1.97]	1.66 [1.47, 2.02]	1.68 [1.40, 1.92]	0.72	$\epsilon^2=0.00$
LDL-C (mmol/L)	3.33 [2.86, 3.94]	3.59 [2.84, 4.05]	3.31 [2.70, 3.94]	0.58	$\epsilon^2=0.00$
TG (mmol/L)	1.01 [0.77, 1.37]	0.95 [0.81, 1.41]	1.03 [0.74, 1.29]	0.87	$\epsilon^2=0.00$
Glucose (mmol/L)	5.64 [5.33, 6.01]	5.61 [5.28, 5.93]	5.53 [5.39, 5.77]	0.29	$\epsilon^2=0.00$

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Total N = 511

Age at menopause: N = 351 (never); 52 (former); 56 (current)

DBP tested using Welch's ANOVA

Post-hoc tests for age at menopause non-significant

Outcomes reported as Mean (SD) or Median [IQR]

*p < 0.05 compared to controls

†p < 0.05 compared to former users

Red bold text used to emphasize statistically significant findings.

Appendix Table 6b. Sensitivity Analyses: Group Comparisons by MHT History, Age 65 and Older

Variable	Controls (N=267)	Former MHT Usage (N=112)	Current MHT Usage (N=39)	Omnibus p-value	Effect size
Age (years)	69 [66, 72]	70 [67, 74] *	68 [66, 71] †	< 0.01	$\epsilon^2=0.02$
BMI (kg/m ²)	25.4 [23.2, 29.0]	25.3 [22.8, 27.9]	24.6 [22.6, 28.2]	0.53	$\epsilon^2=0.00$
Mean arterial pressure (mmHg)	98 (11)	98 (12)	97 (13)	0.83	$\eta^2=0.00$
Age at menopause (years)	52 [51, 55]	51 [47, 53] *	51 [46, 53] *	< 0.01	$\epsilon^2=0.06$
MVPA (avg. mins/day)	18.9 [7.3, 35.0]	13.0 [5.0, 24.5] *	17.7 [5.3, 35.0]	0.02	$\epsilon^2=0.01$
StaB (avg. hours/day)	12.3 (1.6)	12.6 (1.6)	12.2 (1.8)	0.44	$\eta^2=0.00$
Sleep (avg. hours/day)	6.4 (0.8)	6.5 (0.9)	6.4 (0.9)	0.76	$\eta^2=0.00$
aPWV (m/s)	9.8 [9.3, 10.4]	10.0 [9.5, 10.9]	9.6 [9.2, 10.2]	0.03	$\epsilon^2=0.01$
AIx75 (%)	22.7 [16.3, 30.5]	24.8 [12.8, 32.0]	21.7 [14.3, 25.8]	0.41	$\epsilon^2=0.00$
SBP (mmHg)	123 (14)	124 (16)	121 (15)	0.52	$\eta^2=0.00$
DBP (mmHg)	77 (10)	75 (11)	76 (12)	0.46	$\eta^2=0.00$
FRS (%)	7.3 [5.3, 10.9]	7.3 [5.3, 10.0]	6.3 [4.9, 8.0]	0.13	$\epsilon^2=0.01$
WC (cm)	92.8 [85.0, 103.4]	91.3 [82.2, 99.6]	91.5 [85.0, 102.7]	0.22	$\epsilon^2=0.00$
HDL-C (mmol/L)	1.74 [1.45, 2.09]	1.75 [1.52, 2.04]	1.79 [1.56, 1.99]	0.83	$\epsilon^2=0.00$
LDL-C (mmol/L)	3.21 [2.48, 3.84]	3.19 [2.77, 3.77]	3.20 [2.72, 3.71]	0.96	$\epsilon^2=0.00$
TG (mmol/L)	0.98 [0.74, 1.29]	0.96 [0.80, 1.25]	0.97 [0.74, 1.37]	0.95	$\epsilon^2=0.00$
Glucose (mmol/L)	5.69 [5.37, 6.03]	5.69 [5.39, 6.05]	5.53 [5.21, 5.90]	0.09	$\epsilon^2=0.01$

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Total N = 418

Age at menopause: N = 234 (never); 104 (former); 33 (current)

DBP tested using Welch's ANOVA

aPWV post-hoc tests non-significant

Outcomes reported as Mean (SD) or Median [IQR]

*p < 0.05 compared to controls

†p < 0.05 compared to former users

Red bold text used to emphasize statistically significant findings.

Appendix Table 6c. Sensitivity Analyses: Group Comparisons by MHT Type, Age 55-64

Variable	Controls N=393	Combined Estrogen- Progesterone N=30	Unopposed Estrogen N=52	Omnibus p- value	Effect size
Age (years)	60 [58, 62]	61 [59, 64]	60 [58, 62]	0.33	$\epsilon^2=0.00$
BMI (kg/m ²)	25.8 [23.2, 30.2]	27.8 [24.9, 30.7]	27.0 [24.7, 30.1]	0.06	$\epsilon^2=0.01$
Mean arterial pressure (mmHg)	97 (11)	99 (10)	98 (12)	0.53	$\eta^2=0.00$
Age at menopause (years)	53 [51, 55]	53 [51, 55]	50 [44, 53] *	< 0.01	$\epsilon^2=0.03$
MVPA (avg. mins/day)	23.1 [11.5, 41.1]	27.3 [16.9, 45.3]	22.3 [13.1, 38.0]	0.48	$\epsilon^2=0.00$
StaB (avg. hours/day)	11.9 (1.6)	11.2 (1.7)	11.9 (1.5)	0.06	$\eta^2=0.01$
Sleep (avg. hours/day)	6.5 (0.9)	6.7 (0.9)	6.6 (0.8)	0.40	$\eta^2=0.00$
aPWV (m/s)	8.4 [8.0, 8.8]	8.4 [8.2, 8.9]	8.4 [7.9, 8.8]	0.51	$\epsilon^2=0.00$
AIx75 (%)	20.0 [12.7, 27.0]	20.8 [12.2, 25.6]	23.0 [14.0, 28.8]	0.42	$\epsilon^2=0.00$
SBP (mmHg)	120 (13)	122 (13)	121 (15)	0.66	$\eta^2=0.00$
DBP (mmHg)	76 [71, 84]	81 [71, 86]	78 [70, 85]	0.32	$\epsilon^2=0.00$
FRS (%)	5.3 [3.9, 7.3]	4.5 [3.9, 7.3]	4.9 [3.9, 7.3]	0.97	$\epsilon^2=0.00$
WC (cm)	92.5 [85.0, 102.5]	95.9 [89.0, 104.3]	96.0 [88.5, 104.5]	0.33	$\epsilon^2=0.00$
HDL-C (mmol/L)	1.65 [1.39, 1.97]	1.82 [1.51, 2.15]	1.65 [1.34, 1.85]	0.08	$\epsilon^2=0.01$
LDL-C (mmol/L)	3.33 [2.86, 3.94]	3.44 [2.66, 3.84]	3.57 [2.94, 3.96]	0.56	$\eta^2=0.00$
TG (mmol/L)	1.01 [0.77, 1.37]	0.94 [0.76, 1.39]	1.09 [0.85, 1.53]	0.34	$\epsilon^2=0.00$
Glucose (mmol/L)	5.64 [5.33, 6.01]	5.51 [5.31, 5.71]	5.66 [5.40, 5.86]	0.30	$\epsilon^2=0.00$

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Total N = 475

Age at menopause: N = 351 (never); 25 (combined); 47 (unopposed estrogen)

LDL tested with Welch's ANOVA

Outcomes reported as Mean (SD) or Median [IQR]

*p < 0.05 compared to controls

†p < 0.05 compared to combined estrogen-progesterone users

Red bold text used to emphasize statistically significant findings.

Appendix Table 6d. Sensitivity Analyses: Group Comparisons by MHT Type, Age 65 and Older

Variable	Controls N=267	Combined Estrogen- Progesterone N=40	Unopposed Estrogen N=49	Omnibus p- value	Effect size
Age (years)	69 [66, 72]	71 [68, 75] *	69 [66, 72]	0.01	$\varepsilon^2=0.02$
BMI (kg/m ²)	25.4 [23.2, 29.0]	24.7 [22.0, 26.5]	25.5 [23.3, 27.7]	0.13	$\varepsilon^2=0.01$
Mean arterial pressure (mmHg)	98 (11)	98 (12)	96 (10)	0.51	$\eta^2=0.00$
Age at menopause (years)	52 [51, 55]	51 [47, 53]	50 [45, 52] *	< 0.01	$\varepsilon^2=0.05$
MVPA (avg. mins/day)	18.9 [7.3, 35.0]	10.9 [4.0, 21.6] *	14.4 [6.8, 28.4]	0.02	$\varepsilon^2=0.02$
StaB (avg. hours/day)	12.3 (1.6)	12.6 (1.6)	12.5 (1.5)	0.62	$\eta^2=0.00$
Sleep (avg. hours/day)	6.4 (0.8)	6.5 (1.0)	6.3 (0.8)	0.39	$\eta^2=0.01$
aPWV (m/s)	9.8 [9.3, 10.4]	10.2 [9.7, 11.2] *	9.8 [9.3, 10.4]	0.03	$\varepsilon^2=0.01$
AIx75 (%)	22.7 [16.3, 30.5]	26.0 [15.2, 36.0]	22.0 [11.0, 28.0]	0.08	$\varepsilon^2=0.01$
SBP (mmHg)	123 (14)	124 (16)	121 (14)	0.52	$\eta^2=0.00$
DBP (mmHg)	76 [70, 83]	75 [70, 82]	74 [68, 80]	0.26	$\varepsilon^2=0.00$
FRS (%)	7.3 [5.3, 10.9]	7.3 [5.3, 10.0]	6.3 [4.5, 8.6]	0.16	$\varepsilon^2=0.00$
WC (cm)	92.8 [85.0, 103.4]	89.8 [79.6, 96.8]	89.8 [83.0, 99.0]	0.09	$\varepsilon^2=0.01$
HDL-C (mmol/L)	1.74 [1.45, 2.09]	1.74 [1.56, 2.13]	1.71 [1.47, 1.96]	0.60	$\varepsilon^2=0.00$
LDL-C (mmol/L)	3.22 (0.91)	3.04 (0.74)	3.08 (0.75)	0.27	$\eta^2=0.01$
TG (mmol/L)	0.98 [0.74, 1.29]	0.85 [0.73, 1.11]	1.04 [0.88, 1.33]	0.14	$\varepsilon^2=0.01$
Glucose (mmol/L)	5.69 [5.37, 6.03]	5.69 [5.34, 6.05]	5.63 [5.39, 5.99]	0.86	$\varepsilon^2=0.00$

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Total N = 356

Age at menopause: N = 234 (never); 40 (combined); 43 (unopposed estrogen)

LDL tested with Welch's ANOVA

Outcomes reported as Mean (SD) or Median [IQR]

*p < 0.05 compared to controls

†p < 0.05 compared to combined estrogen-progesterone users

Red bold text used to emphasize statistically significant findings.

Appendix Table 6e. Sensitivity Analyses: Group Comparisons by MHT Route, Age 55-64

Variable	Controls (N=393)	Oral (N=35)	Transdermal (N=21)	Vaginal (N=35)	Omnibus p-value	Effect size
Age (years)	60 [58, 62]	61 [59, 62]	60 [58, 63]	60 [58, 63]	0.96	$\varepsilon^2=0.00$
BMI (kg/m ²)	25.8 [23.2, 30.2]	27.9 [24.9, 30.3]	26.8 [23.1, 31.2]	27.0 [25.2, 29.3]	0.34	$\varepsilon^2=0.00$
Mean arterial pressure (mmHg)	97 (11)	98 (10)	99 (11)	97 (13)	0.77	$\eta^2=0.00$
Age at menopause (years)	53 [51, 55]	52 [46, 55]	48 [45, 55]	51 [45, 53]	0.01	$\varepsilon^2=0.02$
MVPA (avg. mins/day)	23.1 [11.5, 41.1]	21.0 [14.2, 36.0]	27.5 [14.3, 39.8]	22.8 [13.5, 42.6]	0.94	$\varepsilon^2=0.00$
StaB (avg. hours/day)	11.9 (1.6)	11.7 (1.5)	11.6 (2.0)	11.8 (1.6)	0.75	$\eta^2=0.00$
Sleep (avg. hours/day)	6.5 (0.9)	6.4 (1.0)	6.7 (0.6)	6.7 (0.6)	0.36	$\eta^2=0.01$
aPWV (m/s)	8.4 [8.0, 8.8]	8.4 [7.9, 8.9]	8.4 [8.2, 8.8]	8.3 [8.0, 8.7]	0.75	$\varepsilon^2=0.00$
AIx75 (%)	20.0 [12.7, 27.0]	21.0 [12.8, 26.7]	14.0 [9.7, 25.3]	23.2 [15.3, 27.8]	0.26	$\varepsilon^2=0.00$
SBP (mmHg)	120 (13)	121 (13)	124 (15)	119 (16)	0.64	$\eta^2=0.00$
DBP (mmHg)	76 [71, 84]	80 [72, 85]	78 [70, 84]	79 [70, 87]	0.62	$\varepsilon^2=0.00$
FRS (%)	5.3 [3.9, 7.3]	4.5 [3.6, 7.3]	6.3 [3.9, 8.6]	4.5 [3.3, 5.3]	0.23	$\varepsilon^2=0.00$
WC (cm)	92.5 [85.0, 102.5]	94.8 [89.1, 104.0]	96.3 [88.5, 107.5]	94.5 [87.5, 101.5]	0.72	$\varepsilon^2=0.00$
HDL-C (mmol/L)	1.65 [1.39, 1.97]	1.64 [1.47, 1.89]	1.67 [1.40, 2.05]	1.66 [1.40, 1.90]	0.92	$\varepsilon^2=0.00$
LDL-C (mmol/L)	3.40 (0.84)	3.23 (0.82)	3.70 (0.75)	3.28 (0.79)	0.15	$\eta^2=0.01$
TG (mmol/L)	1.01 [0.77, 1.37]	0.97 [0.74, 1.63]	0.93 [0.79, 1.41]	1.03 [0.82, 1.28]	0.95	$\varepsilon^2=0.00$
Glucose (mmol/L)	5.64 [5.33, 6.01]	5.58 [5.41, 5.87]	5.54 [5.28, 5.93]	5.64 [5.42, 5.82]	0.91	$\varepsilon^2=0.00$

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Total N = 484

Age at menopause: N = 351 (never); 32 (oral estrogen); 18 (transdermal estrogen); 33 (vaginal estrogen)

LDL tested with Welch's ANOVA

Post-hoc tests non-significant

Outcomes reported as Mean (SD) or Median [IQR]

*p < 0.05 compared to controls

†p < 0.05 compared to oral users

Red bold text used to emphasize statistically significant findings.

Appendix Table 6f. Sensitivity Analyses: Group Comparisons by MHT Route, Age 65 and Older

Variable	Controls (N=267)	Oral (N=62)	Transdermal (N=26)	Vaginal (N=26)	Omnibus p-value	Effect size
Age (years)	69 [66, 72]	72 [67, 75] *	70 [67, 71]	68 [66, 71]	0.01	$\varepsilon^2=0.02$
BMI (kg/m ²)	25.4 [23.2, 29.0]	24.4 [22.2, 27.7]	26.5 [25.1, 27.8]	23.8 [22.2, 26.9]	0.10	$\varepsilon^2=0.01$
Mean arterial pressure (mmHg)	98 (11)	98 (13)	97 (9)	96 (13)	0.81	$\eta^2=0.00$
Age at menopause (years)	52 [51, 55]	51 [45, 53] *	50 [44, 53] *	53 [51, 55]	< 0.01	$\varepsilon^2=0.05$
MVPA (avg. mins/day)	18.9 [7.3, 35.0]	12.9 [5.6, 20.8] *	11.1 [4.2, 22.6]	19.5 [6.9, 33.1]	0.01	$\varepsilon^2=0.02$
StaB (avg. hours/day)	12.3 (1.6)	12.6 (1.5)	12.5 (1.6)	12.3 (1.6)	0.74	$\eta^2=0.00$
Sleep (avg. hours/day)	6.4 (0.8)	6.5 (0.9)	6.4 (0.8)	6.3 (1.1)	0.67	$\eta^2=0.00$
aPWV (m/s)	9.8 [9.3, 10.4]	10.2 [9.5, 11.1]	9.8 [9.3, 10.2]	9.3 [9.1, 9.9] †	< 0.01	$\varepsilon^2=0.03$
AIx75 (%)	22.7 [16.3, 30.5]	22.2 [12.1, 31.0]	26.5 [21.6, 30.6]	19.7 [14.3, 28.6]	0.27	$\varepsilon^2=0.00$
SBP (mmHg)	123 (14)	124 (16)	124 (13)	119 (15)	0.49	$\eta^2=0.01$
DBP (mmHg)	76 [70, 83]	74 [68, 82]	75 [69, 80]	74 [67, 81]	0.36	$\varepsilon^2=0.00$
FRS (%)	7.3 [5.3, 10.9]	7.3 [5.3, 10.0]	7.3 [5.3, 7.3]	5.3 [4.5, 8.6]	0.048	$\varepsilon^2=0.01$
WC (cm)	92.8 [85.0, 103.4]	89.3 [78.8, 98.8]	95.3 [87.8, 102.7]	88.4 [83.6, 96.9]	0.10	$\varepsilon^2=0.01$
HDL-C (mmol/L)	1.74 [1.45, 2.09]	1.74 [1.52, 2.11]	1.79 [1.56, 1.99]	1.83 [1.60, 2.02]	0.80	$\varepsilon^2=0.00$
LDL-C (mmol/L)	3.22 (0.91)	3.18 (0.71)	2.99 (0.73)	3.39 (1.03)	0.38	$\eta^2=0.01$
TG (mmol/L)	0.98 [0.74, 1.29]	0.96 [0.77, 1.28]	0.96 [0.82, 1.23]	0.91 [0.77, 1.23]	0.99	$\varepsilon^2=0.00$
Glucose (mmol/L)	5.69 [5.37, 6.03]	5.69 [5.35, 6.14]	5.74 [5.48, 6.02]	5.53 [5.21, 5.74]	0.11	$\varepsilon^2=0.01$

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Total N = 381

Age at menopause: N = 234 (never); 55 (oral estrogen); 25 (transdermal estrogen); 23 (vaginal estrogen)

LDL tested with Welch's ANOVA

Post-hoc tests for FRS non-significant

Outcomes reported as Mean (SD) or Median [IQR]

*p < 0.05 compared to controls

†p < 0.05 compared to oral users

Red bold text used to emphasize statistically significant findings.

Appendix Table 7a. Sensitivity Analyses: Controlling for Age, MHT History Exposure, Model Fit

Outcome	Block	Sensitivity Analysis				Objective 2B.1			
		Adj. R ²	Sig. F Change	AIC	ΔAIC	Adj. R ²	Sig. F Change	AIC	ΔAIC
aPWV	Block 1	0.81	< 0.01	1154.9		0.02	< 0.01	2443.3	
	Block 2	0.81	0.18	1155.5	0.6	0.07	< 0.01	2403.0	-40.3
	Block 3	0.81	0.01	1148.6	-6.9	0.11	< 0.01	2370.3	-32.7
AIx75	Block 1	0.03	< 0.01	5926.27		0.01	0.08	5944.2	
	Block 2	0.03	0.32	5927.98	1.7	0.01	0.15	5944.4	0.2
	Block 3	0.03	0.08	5926.99	-1.0	0.02	0.01	5938.5	-5.9
logFRS	Block 1	0.15	< 0.01	1107.17		0.01	0.01	1226.2	
	Block 2	0.16	0.01	1101.08	-6.1	0.03	< 0.01	1213.6	-12.6
	Block 3	0.17	0.04	1098.40	-2.7	0.05	< 0.01	1199.9	-13.8

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: Former, Current Usage entered

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 7b. Sensitivity Analyses: Controlling for Age, MHT History Exposure, Coefficients

Outcome	Predictor	Sens.	Sig.	Objective 2B.1	Sig.
		Standardized β [95% CI]		Standardized β [95% CI]	
aPWV	Age	0.89 [0.85, 0.92]	*	--	
	Age at menopause (years)	-0.02 [-0.05, 0.01]		-0.06 [-0.13, 0.01]	
	Spontaneous menopause	0.00 [-0.03, 0.03]		0.07 [0.00, 0.14]	
	History of VMS	-0.01 [-0.04, 0.02]		-0.12 [-0.18, -0.05]	*
	Postsecondary education	-0.02 [-0.05, 0.01]		-0.03 [-0.10, 0.04]	
	Primary earner status	0.00 [-0.03, 0.03]		0.02 [-0.05, 0.08]	
	MVPA (mins)	-0.06 [-0.10, -0.03]	*	-0.17 [-0.24, -0.09]	*
	StaB (hours)	-0.04 [-0.07, 0.00]		0.08 [0.00, 0.17]	*
	Sleep duration (hours)	-0.01 [-0.04, 0.03]		0.03 [-0.04, 0.10]	
	Controls (MHT reference group)				
	Former Usage	0.00 [-0.03, 0.04]		0.20 [0.13, 0.27]	*
	Current Usage	-0.03 [-0.06, 0.00]		-0.04 [-0.11, 0.03]	
AIx75	Age	0.14 [0.06, 0.21]	*	--	
	Age at menopause (years)	-0.06 [-0.13, 0.02]		-0.06 [-0.14, 0.01]	
	Spontaneous menopause	0.00 [-0.07, 0.08]		0.02 [-0.06, 0.09]	
	History of VMS	-0.06 [-0.13, 0.01]		-0.08 [-0.15, -0.01]	*
	Postsecondary education	-0.01 [-0.08, 0.06]		-0.01 [-0.08, 0.06]	
	Primary earner status	-0.03 [-0.10, 0.04]		-0.03 [-0.10, 0.04]	
	MVPA (mins)	-0.07 [-0.15, 0.01]		-0.08 [-0.16, 0.00]	*
	StaB (hours)	0.05 [-0.04, 0.13]		0.06 [-0.02, 0.15]	
	Sleep duration (hours)	0.02 [-0.05, 0.10]		0.03 [-0.05, 0.11]	
	Controls (MHT reference group)				
	Former Usage	-0.01 [-0.09, 0.06]		0.02 [-0.05, 0.09]	
	Current Usage	-0.05 [-0.12, 0.02]		-0.06 [-0.13, 0.02]	
logFRS	Age	0.36 [0.29, 0.43]	*	--	
	Age at menopause (years)	-0.02 [-0.09, 0.05]		-0.03 [-0.11, 0.04]	
	Spontaneous menopause	-0.04 [-0.11, 0.03]		-0.01 [-0.09, 0.06]	
	History of VMS	0.00 [-0.07, 0.06]		-0.05 [-0.12, 0.02]	
	Postsecondary education	-0.09 [-0.16, -0.03]	*	-0.10 [-0.16, -0.03]	*
	Primary earner status	0.02 [-0.05, 0.08]		0.02 [-0.05, 0.09]	
	MVPA (mins)	-0.11 [-0.18, -0.03]	*	-0.15 [-0.23, -0.07]	*
	StaB (hours)	-0.03 [-0.11, 0.05]		0.01 [-0.07, 0.10]	
	Sleep duration (hours)	0.00 [-0.07, 0.07]		0.01 [-0.06, 0.09]	

Controls (MHT reference group)

Former Usage	-0.02 [-0.09, 0.04]		0.06 [-0.01, 0.13]	
Current Usage	-0.11 [-0.17, -0.04]	*	-0.11 [-0.18, -0.04]	*

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 7c. Sensitivity Analyses: Controlling for Age, MHT Type Exposure, Model Fit

Outcome	Block	Adj. R ²	Sensitivity Analysis			Adj. R ²	Objective 2B.2		
			Sig. F Change	AIC	ΔAIC		Sig. F Change	AIC	ΔAIC
aPWV	Block 1	0.80	< 0.01	1042.3		0.02	< 0.01	2166.2	
	Block 2	0.80	0.37	1044.3	2.0	0.06	< 0.01	2143.6	-22.6
	Block 3	0.80	< 0.01	1038.0	-6.3	0.10	< 0.01	2115.5	-28.1
AIx75	Block 1	0.03	< 0.01	5326.8		0.01	0.07	5339.2	
	Block 2	0.03	0.44	5329.1	2.3	0.01	0.19	5339.9	0.7
	Block 3	0.03	0.12	5329.1	0.0	0.02	0.02	5336.3	-3.6
logFRS	Block 1	0.13	< 0.01	1002.6		0.01	0.02	1093.6	
	Block 2	0.13	0.25	1003.8	1.2	0.01	0.32	1095.3	1.7
	Block 3	0.14	0.05	1001.7	-2.1	0.03	< 0.01	1084.0	-11.3

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: Combined Estrogen-Progestosterone, Unopposed Estrogen Usage entered

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 7d. Sensitivity Analyses: Controlling for Age, MHT Type Exposure, Coefficients

Outcome	Predictor	SENS2.2		Objective 2B.2	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	Age	0.88 [0.84, 0.91]	*	--	
	Age at menopause (years)	-0.01 [-0.05, 0.02]		-0.05 [-0.13, 0.03]	
	Spontaneous menopause	0.00 [-0.04, 0.03]		0.04 [-0.03, 0.12]	
	History of VMS	-0.02 [-0.05, 0.02]		-0.14 [-0.21, -0.07]	*
	Postsecondary education	-0.02 [-0.05, 0.01]		-0.03 [-0.10, 0.04]	
	Primary earner status	0.00 [-0.03, 0.04]		0.02 [-0.05, 0.09]	
	MVPA (mins)	-0.07 [-0.11, -0.03]	*	-0.17 [-0.25, -0.09]	*
	StaB (hours)	-0.03 [-0.07, 0.01]		0.08 [-0.01, 0.17]	
	Sleep duration (hours)	-0.01 [-0.04, 0.03]		0.02 [-0.06, 0.10]	
	Controls (MHT reference group)				
	Combined Estrogen-Progestosterone	0.01 [-0.02, 0.05]		0.17 [0.10, 0.25]	*
	Unopposed Estrogen	-0.02 [-0.05, 0.02]		0.00 [-0.07, 0.08]	
AIx75	Age	0.12 [0.04, 0.19]	*	--	
	Age at menopause (years)	-0.07 [-0.15, 0.01]		-0.08 [-0.16, 0.01]	
	Spontaneous menopause	0.01 [-0.07, 0.09]		0.02 [-0.06, 0.10]	
	History of VMS	-0.07 [-0.14, 0.01]		-0.09 [-0.16, -0.01]	*
	Postsecondary education	0.00 [-0.07, 0.08]		0.00 [-0.07, 0.07]	
	Primary earner status	-0.05 [-0.12, 0.03]		-0.05 [-0.12, 0.03]	
	MVPA (mins)	-0.07 [-0.16, 0.01]		-0.08 [-0.17, 0.00]	*
	StaB (hours)	0.04 [-0.05, 0.13]		0.05 [-0.04, 0.15]	
	Sleep duration (hours)	0.01 [-0.08, 0.09]		0.01 [-0.07, 0.09]	
	Controls (MHT reference group)				
	Combined Estrogen-Progestosterone	0.03 [-0.05, 0.10]		0.05 [-0.02, 0.13]	
	Unopposed Estrogen	-0.04 [-0.12, 0.04]		-0.04 [-0.11, 0.04]	
logFRS	Age	0.34 [0.27, 0.42]	*	--	
	Age at menopause (years)	0.00 [-0.08, 0.07]		-0.02 [-0.10, 0.06]	
	Spontaneous menopause	-0.04 [-0.12, 0.03]		-0.02 [-0.10, 0.06]	
	History of VMS	-0.01 [-0.08, 0.06]		-0.06 [-0.14, 0.01]	
	Postsecondary education	-0.09 [-0.16, -0.02]	*	-0.09 [-0.17, -0.02]	*
	Primary earner status	0.01 [-0.06, 0.08]		0.02 [-0.06, 0.09]	
	MVPA (mins)	-0.11 [-0.19, -0.03]	*	-0.15 [-0.23, -0.07]	*
	StaB (hours)	-0.03 [-0.12, 0.06]		0.01 [-0.08, 0.11]	
	Sleep duration (hours)	0.00 [-0.08, 0.08]		0.01 [-0.07, 0.09]	

Controls (MHT reference group)

Combined Estrogen-Progesterone	-0.04 [-0.11, 0.03]	0.02 [-0.05, 0.09]
Unopposed Estrogen	-0.06 [-0.13, 0.01]	-0.05 [-0.13, 0.03]

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 7e. Sensitivity Analyses: Controlling for Age, MHT Route Exposure, Model Fit

Outcome	Block	Sensitivity Analysis				Objective 2B.3			
		Adj. R ²	Sig. F Change	AIC	ΔAIC	Adj. R ²	Sig. F Change	AIC	ΔAIC
aPWV	Block 1	0.80	< 0.01	1088.9		0.02	< 0.01	2257.6	
	Block 2	0.80	0.27	1090.9	2.1	0.06	< 0.01	2231.7	-25.9
	Block 3	0.80	0.01	1084.2	-6.7	0.10	< 0.01	2205.2	-26.5
AIx75	Block 1	0.02	< 0.01	5552.36		0.00	0.14	5566.2	
	Block 2	0.02	0.98	5558.19	5.8	0.00	0.95	5571.9	5.7
	Block 3	0.02	0.10	5557.79	-0.4	0.01	0.02	5567.6	-4.3
logFRS	Block 1	0.13	< 0.01	1043.31		0.01	0.02	1137.8	
	Block 2	0.14	0.05	1041.54	-1.8	0.02	0.04	1135.6	-2.2
	Block 3	0.14	0.04	1038.92	-2.6	0.04	< 0.01	1124.2	-11.4

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: Oral, Transdermal, Vaginal Usage entered

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 7f. Sensitivity Analyses: Controlling for Age, MHT Route Exposure, Coefficients

Outcome	Predictor	Sensitivity Analyses		Objective 2B.3	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	Age	0.88 [0.85, 0.91]	*	--	
	Age at menopause (years)	-0.02 [-0.05, 0.02]		-0.04 [-0.11, 0.04]	
	Spontaneous menopause	0.01 [-0.03, 0.04]		0.08 [0.01, 0.16]	*
	History of VMS	-0.02 [-0.05, 0.02]		-0.14 [-0.21, -0.07]	*
	Postsecondary education	-0.02 [-0.05, 0.01]		-0.01 [-0.08, 0.05]	
	Primary earner status	0.00 [-0.03, 0.03]		0.01 [-0.06, 0.08]	
	MVPA (mins)	-0.07 [-0.11, -0.03]	*	-0.16 [-0.24, -0.08]	*
	StaB (hours)	-0.04 [-0.08, 0.01]		0.07 [-0.01, 0.16]	
	Sleep duration (hours)	-0.01 [-0.05, 0.02]		0.03 [-0.05, 0.10]	
	Controls (MHT reference group)				
	Oral	0.01 [-0.03, 0.04]		0.17 [0.10, 0.24]	*
	Transdermal	0.01 [-0.02, 0.04]		0.07 [0.00, 0.14]	
	Vaginal	-0.03 [-0.06, 0.01]		-0.04 [-0.11, 0.03]	
AIx75	Age	0.13 [0.06, 0.21]	*	--	
	Age at menopause (years)	-0.06 [-0.14, 0.02]		-0.07 [-0.14, 0.01]	
	Spontaneous menopause	0.02 [-0.06, 0.10]		0.03 [-0.05, 0.11]	
	History of VMS	-0.05 [-0.13, 0.02]		-0.07 [-0.14, 0.00]	
	Postsecondary education	0.00 [-0.07, 0.07]		0.00 [-0.07, 0.07]	
	Primary earner status	-0.04 [-0.11, 0.04]		-0.03 [-0.11, 0.04]	
	MVPA (mins)	-0.07 [-0.16, 0.01]		-0.09 [-0.17, 0.00]	*
	StaB (hours)	0.04 [-0.05, 0.13]		0.05 [-0.04, 0.14]	
	Sleep duration (hours)	0.01 [-0.07, 0.09]		0.02 [-0.07, 0.10]	
	Controls (MHT reference group)				
	Oral	-0.02 [-0.10, 0.05]		0.00 [-0.07, 0.08]	
	Transdermal	0.00 [-0.07, 0.07]		0.01 [-0.07, 0.08]	
	Vaginal	0.00 [-0.08, 0.07]		-0.01 [-0.08, 0.07]	
logFRS	Age	0.34 [0.27, 0.41]	*	--	
	Age at menopause (years)	-0.01 [-0.08, 0.07]		-0.01 [-0.09, 0.06]	
	Spontaneous menopause	-0.03 [-0.10, 0.05]		0.00 [-0.07, 0.08]	
	History of VMS	-0.01 [-0.08, 0.06]		-0.06 [-0.13, 0.01]	
	Postsecondary education	-0.09 [-0.16, -0.02]	*	-0.09 [-0.16, -0.02]	*
	Primary earner status	0.01 [-0.06, 0.08]		0.02 [-0.06, 0.09]	
	MVPA (mins)	-0.11 [-0.19, -0.04]	*	-0.15 [-0.23, -0.07]	*

StaB (hours)	-0.04 [-0.12, 0.05]	0.01 [-0.08, 0.10]
Sleep duration (hours)	-0.01 [-0.09, 0.07]	0.01 [-0.08, 0.09]
Controls (MHT reference group)		
Oral	-0.05 [-0.12, 0.02]	0.01 [-0.06, 0.08]
Transdermal	0.00 [-0.07, 0.07]	0.02 [-0.05, 0.10]
Vaginal	-0.09 [-0.16, -0.02]	* -0.09 [-0.16, -0.02] *

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 8a. Sensitivity Analysis: Controlling for MHT duration, history exposure, model fit

Outcome	Block	Sensitivity Analysis: Duration				Objective 2B.1			
		Adj. R ²	Sig. F Change	AIC	ΔAIC	Adj. R ²	Sig. F Change	AIC	ΔAIC
aPWV	Block 1	-0.02	0.95	701.6		-0.01	0.89	769.9	
	Block 2	0.11	< 0.01	675.5	-26.1	0.08	< 0.01	747.4	-22.6
	Block 3	0.20	< 0.01	655.0	-20.5	0.17	< 0.01	725.9	-21.5
AIx75	Block 1	-0.01	0.82	1660.44		-0.01	0.77	1814.6	
	Block 2	-0.01	0.23	1661.42	1.0	0.00	0.07	1813.2	-1.4
	Block 3	0.01	0.09	1660.68	-0.7	0.01	0.10	1812.7	-0.4
SBP	Block 1	0.01	0.21	1762.76		0.02	0.08	1939.3	
	Block 2	0.03	0.03	1759.66	-3.1	0.03	0.06	1937.7	-1.7
	Block 3	0.06	0.04	1757.06	-2.6	0.06	0.02	1933.1	-4.5
DBP	Block 1	-0.01	0.79	1630.55		-0.01	0.65	1798.9	
	Block 2	0.01	0.04	1628.01	-2.5	0.00	0.05	1797.0	-1.9
	Block 3	0.02	0.17	1628.67	0.7	0.02	0.13	1797.2	0.1
logFRS	Block 1	-0.01	0.76	342.81		0.00	0.47	378.9	
	Block 2	0.05	< 0.01	332.47	-10.3	0.06	< 0.01	365.5	-13.4
	Block 3	0.11	< 0.01	320.27	-12.2	0.11	< 0.01	355.4	-10.1
WC	Block 1	0.07	< 0.01	1710.80		0.06	< 0.01	1869.3	
	Block 2	0.09	0.06	1708.79	-2.0	0.08	0.02	1865.7	-3.6
	Block 3	0.18	< 0.01	1690.08	-18.7	0.18	< 0.01	1840.9	-24.8
HDL-C	Block 1	0.02	0.11	274.02		0.03	0.04	284.5	
	Block 2	0.03	0.10	273.15	-0.9	0.03	0.96	286.5	2.0
	Block 3	0.05	0.08	271.94	-1.2	0.04	0.09	285.7	-0.8
LDL-C	Block 1	0.03	0.04	505.17		0.02	0.08	568.6	
	Block 2	0.03	0.69	508.38	3.2	0.02	0.48	570.1	1.5
	Block 3	0.02	0.55	512.13	3.7	0.03	0.24	571.7	1.6
logTG	Block 1	0.04	0.03	214.93		0.05	0.01	242.1	
	Block 2	0.04	0.22	215.76	0.8	0.04	0.86	244.1	2.0
	Block 3	0.06	0.09	214.82	-0.9	0.05	0.11	243.8	-0.3
logGlucose	Block 1	0.03	0.04	-241.41		0.03	0.03	-282.5	
	Block 2	0.04	0.21	-240.71	0.7	0.04	0.19	-282.3	0.2
	Block 3	0.03	0.60	-236.71	4.0	0.04	0.41	-279.3	3.0

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-

transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: Current usage, MHT duration entered (Former usage = reference)

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 8b. Sensitivity Analysis: Controlling for MHT duration, history exposure, coefficients

Outcome	Predictor	Sensitivity Analysis: Duration		Objective 2B.1	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	0.04 [-0.09, 0.18]		-0.03 [-0.16, 0.10]	
	Spontaneous menopause	0.02 [-0.11, 0.16]		0.07 [-0.06, 0.20]	
	History of VMS	-0.05 [-0.18, 0.07]		-0.05 [-0.17, 0.07]	
	Postsecondary education	-0.01 [-0.14, 0.11]		0.00 [-0.12, 0.12]	
	Primary earner status	0.02 [-0.11, 0.14]		0.00 [-0.12, 0.12]	
	MVPA (mins)	-0.27 [-0.42, -0.13]	*	-0.26 [-0.40, -0.12]	*
	StaB (hours)	0.08 [-0.09, 0.24]		0.09 [-0.06, 0.24]	
	Sleep duration (hours)	-0.02 [-0.16, 0.12]		-0.01 [-0.15, 0.12]	
	Former Usage (MHT reference group)				
	Current Usage	-0.25 [-0.37, -0.12]	*	-0.28 [-0.39, -0.16]	*
	MHT Duration (years)	0.20 [0.07, 0.33]	*	--	--
AIx75	Age at menopause (years)	-0.07 [-0.22, 0.09]		-0.08 [-0.22, 0.06]	
	Spontaneous menopause	0.01 [-0.14, 0.16]		0.01 [-0.13, 0.15]	
	History of VMS	-0.04 [-0.18, 0.10]		-0.02 [-0.15, 0.11]	
	Postsecondary education	-0.03 [-0.17, 0.11]		-0.03 [-0.16, 0.10]	
	Primary earner status	0.04 [-0.10, 0.17]		0.04 [-0.09, 0.17]	
	MVPA (mins)	-0.13 [-0.29, 0.03]		-0.11 [-0.27, 0.04]	
	StaB (hours)	0.07 [-0.11, 0.25]		0.08 [-0.09, 0.24]	
	Sleep duration (hours)	0.04 [-0.11, 0.20]		0.06 [-0.09, 0.20]	
	Former Usage (MHT reference group)				
	Current Usage	-0.10 [-0.24, 0.04]		-0.10 [-0.23, 0.03]	
	MHT Duration (years)	0.01 [-0.13, 0.16]		--	--
SBP	Age (years)	0.14 [-0.01, 0.29]		0.13 [-0.01, 0.27]	
	Age at menopause (years)	-0.01 [-0.16, 0.14]		-0.02 [-0.15, 0.12]	
	Spontaneous menopause	-0.03 [-0.17, 0.12]		-0.02 [-0.16, 0.12]	
	History of VMS	0.04 [-0.10, 0.17]		0.05 [-0.07, 0.18]	
	Postsecondary education	0.00 [-0.13, 0.14]		0.01 [-0.12, 0.14]	
	Primary earner status	-0.04 [-0.17, 0.09]		-0.07 [-0.19, 0.06]	
	MVPA (mins)	-0.23 [-0.39, -0.07]	*	-0.24 [-0.39, -0.09]	*
	StaB (hours)	-0.17 [-0.34, 0.01]		-0.18 [-0.35, -0.02]	*
	Sleep duration (hours)	-0.04 [-0.20, 0.11]		-0.07 [-0.21, 0.07]	
	Former Usage (MHT reference group)				
	Current Usage	-0.17 [-0.31, -0.03]	*	-0.13 [-0.27, 0.00]	*

DBP	MHT Duration (years)	-0.10 [-0.25, 0.04]		--	--
	Age (years)	-0.15 [-0.31, 0.00]		-0.14 [-0.28, 0.01]	
	Age at menopause (years)	-0.05 [-0.20, 0.10]		-0.07 [-0.21, 0.07]	
	Spontaneous menopause	0.05 [-0.10, 0.20]		0.06 [-0.08, 0.20]	
	History of VMS	0.01 [-0.12, 0.15]		0.02 [-0.11, 0.15]	
	Postsecondary education	-0.03 [-0.17, 0.11]		-0.02 [-0.15, 0.12]	
	Primary earner status	0.03 [-0.10, 0.17]		0.01 [-0.12, 0.14]	
	MVPA (mins)	-0.16 [-0.33, 0.00]		-0.16 [-0.31, 0.00]	
	StaB (hours)	-0.17 [-0.35, 0.01]		-0.18 [-0.35, -0.01]	*
	Sleep duration (hours)	-0.03 [-0.19, 0.13]		-0.04 [-0.18, 0.10]	
	Former Usage (MHT reference group)				
logFRS	Current Usage	-0.19 [-0.33, -0.05]	*	-0.14 [-0.28, 0.00]	*
	MHT Duration (years)	-0.03 [-0.18, 0.11]		--	--
	Age at menopause (years)	-0.07 [-0.21, 0.08]		-0.10 [-0.23, 0.03]	
	Spontaneous menopause	0.00 [-0.14, 0.14]		0.02 [-0.12, 0.15]	
	History of VMS	0.01 [-0.12, 0.14]		0.02 [-0.11, 0.14]	
	Postsecondary education	-0.03 [-0.16, 0.10]		-0.03 [-0.15, 0.10]	
	Primary earner status	-0.06 [-0.19, 0.07]		-0.06 [-0.18, 0.06]	
	MVPA (mins)	-0.28 [-0.43, -0.12]	*	-0.25 [-0.40, -0.11]	*
	StaB (hours)	0.00 [-0.17, 0.17]		-0.01 [-0.17, 0.15]	
	Sleep duration (hours)	-0.01 [-0.16, 0.14]		-0.01 [-0.15, 0.13]	
	Former Usage (MHT reference group)				
WC	Current Usage	-0.23 [-0.36, -0.10]	*	-0.23 [-0.35, -0.10]	*
	MHT Duration (years)	0.02 [-0.12, 0.16]		--	--
	Age (years)	-0.34 [-0.48, -0.20]	*	-0.33 [-0.46, -0.20]	*
	Age at menopause (years)	-0.04 [-0.18, 0.10]		-0.04 [-0.16, 0.09]	
	Spontaneous menopause	-0.09 [-0.22, 0.05]		-0.07 [-0.20, 0.06]	
	History of VMS	0.05 [-0.08, 0.17]		0.04 [-0.08, 0.16]	
	Postsecondary education	-0.13 [-0.25, 0.00]	*	-0.12 [-0.24, 0.00]	*
	Primary earner status	0.15 [0.02, 0.27]	*	0.14 [0.02, 0.26]	*
	MVPA (mins)	-0.28 [-0.43, -0.13]	*	-0.31 [-0.45, -0.17]	*
	StaB (hours)	0.07 [-0.10, 0.23]		0.05 [-0.11, 0.20]	
	Sleep duration (hours)	-0.06 [-0.20, 0.08]		-0.09 [-0.22, 0.04]	
	Former Usage (MHT reference group)				
	Current Usage	-0.16 [-0.29, -0.03]	*	-0.15 [-0.27, -0.03]	*
	MHT Duration (years)	-0.03 [-0.16, 0.11]		--	--

HDL-C	Age (years)	0.02 [-0.14, 0.17]		0.06 [-0.08, 0.20]	
	Age at menopause (years)	0.06 [-0.08, 0.21]		0.01 [-0.12, 0.15]	
	Spontaneous menopause	0.15 [0.01, 0.30]	*	0.18 [0.04, 0.32]	*
	History of VMS	-0.02 [-0.16, 0.11]		-0.04 [-0.17, 0.09]	
	Postsecondary education	0.08 [-0.06, 0.21]		0.09 [-0.04, 0.22]	
	Primary earner status	-0.05 [-0.18, 0.09]		-0.06 [-0.18, 0.07]	
	MVPA (mins)	0.09 [-0.07, 0.25]		0.08 [-0.07, 0.24]	
	StaB (hours)	-0.13 [-0.30, 0.05]		-0.12 [-0.28, 0.05]	
	Sleep duration (hours)	0.00 [-0.15, 0.15]		0.01 [-0.13, 0.15]	
	Former Usage (MHT reference group)				
	Current Usage	0.01 [-0.13, 0.15]		-0.01 [-0.14, 0.12]	
	MHT Duration (years)	0.14 [-0.01, 0.28]		--	--
LDL-C	Age (years)	-0.20 [-0.35, -0.04]	*	-0.15 [-0.29, -0.01]	*
	Age at menopause (years)	-0.06 [-0.22, 0.09]		-0.09 [-0.22, 0.05]	
	Spontaneous menopause	0.09 [-0.06, 0.24]		0.07 [-0.08, 0.21]	
	History of VMS	-0.04 [-0.18, 0.09]		-0.05 [-0.18, 0.08]	
	Postsecondary education	0.04 [-0.10, 0.18]		0.03 [-0.10, 0.16]	
	Primary earner status	-0.06 [-0.20, 0.08]		-0.06 [-0.19, 0.07]	
	MVPA (mins)	0.03 [-0.13, 0.20]		0.08 [-0.07, 0.24]	
	StaB (hours)	-0.09 [-0.27, 0.09]		-0.06 [-0.23, 0.10]	
	Sleep duration (hours)	0.00 [-0.15, 0.16]		0.04 [-0.10, 0.19]	
	Former Usage (MHT reference group)				
	Current Usage	-0.06 [-0.21, 0.08]		-0.05 [-0.19, 0.08]	
	MHT Duration (years)	0.01 [-0.14, 0.15]		--	--
logTG	Age (years)	-0.07 [-0.22, 0.08]		-0.08 [-0.22, 0.06]	
	Age at menopause (years)	-0.22 [-0.37, -0.07]	*	-0.18 [-0.32, -0.05]	*
	Spontaneous menopause	-0.06 [-0.21, 0.08]		-0.08 [-0.22, 0.06]	
	History of VMS	0.03 [-0.11, 0.16]		-0.01 [-0.14, 0.12]	
	Postsecondary education	-0.04 [-0.17, 0.09]		-0.07 [-0.20, 0.06]	
	Primary earner status	0.01 [-0.13, 0.14]		0.06 [-0.06, 0.19]	
	MVPA (mins)	-0.17 [-0.33, 0.00]	*	-0.16 [-0.31, -0.01]	*
	StaB (hours)	0.03 [-0.15, 0.20]		0.01 [-0.16, 0.17]	
	Sleep duration (hours)	0.03 [-0.12, 0.18]		0.03 [-0.11, 0.17]	
	Former Usage (MHT reference group)				
	Current Usage	-0.01 [-0.15, 0.13]		-0.01 [-0.14, 0.12]	
	MHT Duration (years)	-0.11 [-0.25, 0.04]		--	--

logGlucose	Age (years)	0.18 [0.03, 0.34]	*	0.16 [0.01, 0.30]	*
	Age at menopause (years)	0.13 [-0.02, 0.28]		0.15 [0.01, 0.29]	*
	Spontaneous menopause	-0.09 [-0.24, 0.05]		-0.12 [-0.26, 0.02]	
	History of VMS	-0.03 [-0.16, 0.11]		-0.03 [-0.16, 0.10]	
	Postsecondary education	0.02 [-0.12, 0.16]		0.03 [-0.10, 0.16]	
	Primary earner status	0.02 [-0.11, 0.16]		0.04 [-0.09, 0.17]	
	MVPA (mins)	-0.11 [-0.27, 0.06]		-0.12 [-0.27, 0.03]	
	StaB (hours)	-0.10 [-0.28, 0.08]		-0.12 [-0.28, 0.05]	
	Sleep duration (hours)	-0.04 [-0.20, 0.11]		-0.06 [-0.20, 0.09]	
	Former Usage (MHT reference group)				
	Current Usage	-0.09 [-0.23, 0.06]		-0.09 [-0.23, 0.04]	
	MHT Duration (years)	-0.10 [-0.25, 0.05]		--	--

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 8c. Sensitivity Analysis: Controlling for MHT duration, type exposure, model fit

Outcome	Block	Sensitivity Analysis: Duration				Objective 2B.2			
		Adj. R ²	Sig. F Change	AIC	ΔAIC	Adj. R ²	Sig. F Change	AIC	ΔAIC
aPWV	Block 1	-0.02	0.92	500.0		-0.02	0.92	500.0	
	Block 2	0.07	< 0.01	487.0	-13.0	0.05	< 0.01	489.5	-10.5
	Block 3	0.24	< 0.01	460.1	-27.0	0.21	< 0.01	464.9	-24.6
AIx75	Block 1	-0.02	0.88	1206.02		-0.02	0.88	1206.0	
	Block 2	-0.02	0.40	1208.08	2.1	-0.02	0.17	1206.1	0.1
	Block 3	-0.01	0.24	1209.61	1.5	-0.01	0.24	1207.6	1.5
SBP	Block 1	0.00	0.36	1262.05		0.00	0.36	1262.0	
	Block 2	0.01	0.20	1262.62	0.6	0.00	0.61	1263.8	1.7
	Block 3	0.06	0.02	1258.28	-4.3	0.05	0.01	1258.3	-5.5
DBP	Block 1	0.00	0.39	1154.44		0.00	0.39	1154.4	
	Block 2	-0.01	0.76	1157.87	3.4	0.00	0.49	1155.9	1.5
	Block 3	0.01	0.12	1157.60	-0.3	0.02	0.12	1155.6	-0.3
logFRS	Block 1	-0.01	0.67	246.74		-0.01	0.67	246.7	
	Block 2	-0.01	0.40	248.82	2.1	-0.01	0.18	246.9	0.1
	Block 3	0.09	< 0.01	235.59	-13.2	0.09	< 0.01	233.6	-13.3
WC	Block 1	0.08	< 0.01	1211.51		0.08	< 0.01	1211.5	
	Block 2	0.07	0.75	1214.89	3.4	0.08	0.70	1213.4	
	Block 3	0.14	< 0.01	1206.73	-8.2	0.14	< 0.01	1204.7	
HDL-C	Block 1	0.03	0.11	165.59		0.03	0.11	165.6	
	Block 2	0.07	0.02	161.37	-4.2	0.06	0.02	162.2	-3.4
	Block 3	0.09	0.09	160.35	-1.0	0.08	0.07	160.5	-1.6
LDL-C	Block 1	0.07	0.01	355.72		0.07	0.01	355.7	
	Block 2	0.06	0.72	359.01	3.3	0.07	0.42	357.0	1.3
	Block 3	0.05	0.70	363.48	4.5	0.06	0.71	361.5	4.5
logTG	Block 1	0.05	0.03	160.98		0.05	0.03	161.0	
	Block 2	0.07	0.07	159.46	-1.5	0.05	0.24	161.5	0.5
	Block 3	0.07	0.60	163.46	4.0	0.05	0.53	165.1	3.6
logGlucose	Block 1	0.04	0.06	-188.66		0.04	0.06	-188.7	
	Block 2	0.04	0.40	-186.61	2.0	0.04	0.37	-187.5	1.1
	Block 3	0.04	0.29	-184.66	2.0	0.04	0.27	-185.7	1.8

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed

Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: Unopposed Estrogen, MHT duration entered (Combined Estrogen-Progestosterone= reference)

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 8d. Sensitivity Analysis: Controlling for MHT duration, type exposure, coefficients

Outcome	Predictor	Sensitivity Analysis: Duration		Objective 2B.2	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	0.04 [-0.12, 0.21]		-0.02 [-0.18, 0.14]	
	Spontaneous menopause	0.03 [-0.13, 0.19]		0.02 [-0.14, 0.18]	
	History of VMS	-0.09 [-0.24, 0.05]		-0.11 [-0.26, 0.03]	
	Postsecondary education	-0.02 [-0.16, 0.13]		-0.01 [-0.16, 0.14]	
	Primary earner status	-0.02 [-0.16, 0.12]		-0.02 [-0.17, 0.13]	
	MVPA (mins)	-0.38 [-0.56, -0.20]	*	-0.37 [-0.55, -0.19]	*
	StaB (hours)	0.03 [-0.17, 0.23]		0.05 [-0.15, 0.26]	
	Sleep duration (hours)	-0.12 [-0.29, 0.05]		-0.09 [-0.26, 0.08]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	-0.20 [-0.36, -0.04]	*	-0.28 [-0.43, -0.12]	*
	MHT Duration (years)	0.20 [0.05, 0.36]	*	--	--
AIx75	Age at menopause (years)	-0.13 [-0.31, 0.06]		-0.13 [-0.31, 0.05]	
	Spontaneous menopause	0.05 [-0.13, 0.23]		0.05 [-0.13, 0.23]	
	History of VMS	-0.03 [-0.19, 0.14]		-0.03 [-0.19, 0.13]	
	Postsecondary education	-0.01 [-0.17, 0.16]		0.00 [-0.17, 0.16]	
	Primary earner status	0.00 [-0.16, 0.17]		0.00 [-0.16, 0.17]	
	MVPA (mins)	-0.15 [-0.36, 0.05]		-0.15 [-0.36, 0.05]	
	StaB (hours)	0.03 [-0.20, 0.26]		0.03 [-0.20, 0.25]	
	Sleep duration (hours)	-0.01 [-0.21, 0.18]		-0.01 [-0.20, 0.18]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	-0.11 [-0.29, 0.08]		-0.11 [-0.28, 0.06]	
	MHT Duration (years)	0.01 [-0.17, 0.19]		--	--
SBP	Age (years)	0.10 [-0.08, 0.29]		0.07 [-0.11, 0.25]	
	Age at menopause (years)	0.00 [-0.18, 0.18]		0.04 [-0.13, 0.21]	
	Spontaneous menopause	0.02 [-0.16, 0.19]		0.02 [-0.16, 0.20]	
	History of VMS	0.01 [-0.15, 0.17]		0.02 [-0.14, 0.18]	
	Postsecondary education	0.06 [-0.10, 0.22]		0.06 [-0.11, 0.22]	
	Primary earner status	-0.12 [-0.28, 0.04]		-0.12 [-0.28, 0.04]	
	MVPA (mins)	-0.32 [-0.53, -0.12]	*	-0.34 [-0.55, -0.14]	*
	StaB (hours)	-0.19 [-0.41, 0.03]		-0.20 [-0.42, 0.02]	
	Sleep duration (hours)	-0.08 [-0.27, 0.11]		-0.10 [-0.29, 0.09]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	-0.07 [-0.25, 0.11]		-0.04 [-0.21, 0.13]	

DBP	MHT Duration (years)	-0.12 [-0.30, 0.06]		--	--
	Age (years)	-0.23 [-0.42, -0.04]	*	-0.23 [-0.41, -0.05]	*
	Age at menopause (years)	0.02 [-0.16, 0.21]		0.02 [-0.15, 0.20]	
	Spontaneous menopause	0.13 [-0.05, 0.31]		0.13 [-0.05, 0.31]	
	History of VMS	-0.03 [-0.19, 0.14]		-0.03 [-0.19, 0.14]	
	Postsecondary education	-0.01 [-0.17, 0.16]		-0.01 [-0.17, 0.16]	
	Primary earner status	0.00 [-0.16, 0.16]		0.00 [-0.16, 0.16]	
	MVPA (mins)	-0.25 [-0.46, -0.04]	*	-0.25 [-0.46, -0.05]	*
	StaB (hours)	-0.13 [-0.36, 0.09]		-0.13 [-0.36, 0.09]	
	Sleep duration (hours)	-0.04 [-0.23, 0.16]		-0.04 [-0.23, 0.15]	
	Combined Estrogen-Progesterone Usage (MHT reference group)				
logFRS	Unopposed Estrogen Usage	-0.06 [-0.24, 0.13]		-0.06 [-0.23, 0.12]	
	MHT Duration (years)	0.00 [-0.18, 0.19]		--	--
	Age at menopause (years)	-0.11 [-0.28, 0.07]		-0.11 [-0.27, 0.06]	
	Spontaneous menopause	0.05 [-0.12, 0.23]		0.05 [-0.12, 0.23]	
	History of VMS	0.00 [-0.16, 0.16]		0.00 [-0.16, 0.15]	
	Postsecondary education	0.01 [-0.14, 0.17]		0.01 [-0.14, 0.17]	
	Primary earner status	-0.15 [-0.31, 0.01]		-0.15 [-0.31, 0.01]	
	MVPA (mins)	-0.37 [-0.56, -0.17]	*	-0.37 [-0.56, -0.17]	*
	StaB (hours)	-0.06 [-0.28, 0.16]		-0.06 [-0.27, 0.16]	
	Sleep duration (hours)	-0.08 [-0.27, 0.10]		-0.08 [-0.27, 0.10]	
	Combined Estrogen-Progesterone Usage (MHT reference group)				
WC	Unopposed Estrogen Usage	-0.09 [-0.27, 0.08]		-0.09 [-0.25, 0.07]	
	MHT Duration (years)	0.00 [-0.17, 0.17]		--	--
	Age (years)	-0.39 [-0.57, -0.22]	*	-0.40 [-0.57, -0.23]	*
	Age at menopause (years)	-0.03 [-0.20, 0.15]		-0.02 [-0.19, 0.14]	
	Spontaneous menopause	-0.09 [-0.26, 0.08]		-0.09 [-0.26, 0.08]	
	History of VMS	0.00 [-0.16, 0.15]		0.00 [-0.15, 0.15]	
	Postsecondary education	-0.07 [-0.22, 0.09]		-0.07 [-0.22, 0.09]	
	Primary earner status	0.11 [-0.04, 0.27]		0.11 [-0.04, 0.27]	
	MVPA (mins)	-0.25 [-0.45, -0.05]	*	-0.25 [-0.44, -0.06]	*
	StaB (hours)	0.06 [-0.15, 0.27]		0.06 [-0.15, 0.27]	
	Sleep duration (hours)	-0.10 [-0.28, 0.08]		-0.10 [-0.28, 0.08]	
	Combined Estrogen-Progesterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	0.00 [-0.17, 0.18]		0.01 [-0.16, 0.17]	
	MHT Duration (years)	-0.01 [-0.18, 0.16]		--	--

HDL-C	Age (years)	0.07 [-0.11, 0.25]	0.11 [-0.07, 0.28]	
	Age at menopause (years)	0.08 [-0.10, 0.26]	0.04 [-0.13, 0.21]	
	Spontaneous menopause	0.11 [-0.07, 0.28]	0.10 [-0.07, 0.28]	
	History of VMS	-0.04 [-0.20, 0.12]	-0.05 [-0.21, 0.11]	
	Postsecondary education	0.11 [-0.04, 0.27]	0.12 [-0.04, 0.28]	
	Primary earner status	-0.08 [-0.23, 0.08]	-0.08 [-0.23, 0.08]	
	MVPA (mins)	0.10 [-0.10, 0.30]	0.12 [-0.08, 0.32]	
	StaB (hours)	-0.16 [-0.38, 0.06]	-0.15 [-0.37, 0.07]	
	Sleep duration (hours)	-0.04 [-0.23, 0.14]	-0.02 [-0.21, 0.16]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)			
	Unopposed Estrogen Usage	-0.14 [-0.32, 0.04]	-0.18 [-0.35, -0.01]	*
	MHT Duration (years)	0.13 [-0.05, 0.30]	--	--
LDL-C	Age (years)	-0.17 [-0.35, 0.02]	-0.17 [-0.35, 0.01]	
	Age at menopause (years)	-0.15 [-0.33, 0.03]	-0.14 [-0.31, 0.03]	
	Spontaneous menopause	0.15 [-0.03, 0.32]	0.15 [-0.03, 0.32]	
	History of VMS	-0.03 [-0.19, 0.13]	-0.03 [-0.19, 0.13]	
	Postsecondary education	0.10 [-0.06, 0.26]	0.10 [-0.06, 0.26]	
	Primary earner status	-0.13 [-0.29, 0.03]	-0.13 [-0.29, 0.03]	
	MVPA (mins)	0.05 [-0.15, 0.26]	0.05 [-0.15, 0.25]	
	StaB (hours)	-0.07 [-0.29, 0.16]	-0.07 [-0.29, 0.15]	
	Sleep duration (hours)	0.00 [-0.19, 0.19]	0.00 [-0.19, 0.19]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)			
	Unopposed Estrogen Usage	0.08 [-0.10, 0.26]	0.08 [-0.09, 0.25]	
	MHT Duration (years)	-0.02 [-0.20, 0.16]	--	--
logTG	Age (years)	-0.02 [-0.21, 0.16]	-0.07 [-0.25, 0.11]	
	Age at menopause (years)	-0.31 [-0.48, -0.13]	-0.25 [-0.43, -0.08]	*
	Spontaneous menopause	-0.03 [-0.20, 0.15]	-0.02 [-0.20, 0.16]	
	History of VMS	0.05 [-0.12, 0.21]	0.06 [-0.10, 0.22]	
	Postsecondary education	-0.01 [-0.17, 0.15]	-0.02 [-0.18, 0.14]	
	Primary earner status	-0.02 [-0.18, 0.14]	-0.02 [-0.18, 0.14]	
	MVPA (mins)	-0.10 [-0.31, 0.10]	-0.13 [-0.33, 0.07]	
	StaB (hours)	0.00 [-0.22, 0.23]	-0.01 [-0.23, 0.21]	
	Sleep duration (hours)	0.04 [-0.15, 0.23]	0.01 [-0.18, 0.20]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)			
	Unopposed Estrogen Usage	0.05 [-0.13, 0.23]	0.10 [-0.07, 0.27]	
	MHT Duration (years)	-0.17 [-0.35, 0.01]	--	--

logGlucose	Age (years)	0.23 [0.04, 0.41]	*	0.20 [0.02, 0.38]	*
	Age at menopause (years)	0.16 [-0.02, 0.34]		0.18 [0.01, 0.36]	*
	Spontaneous menopause	-0.10 [-0.28, 0.08]		-0.10 [-0.27, 0.08]	
	History of VMS	-0.06 [-0.23, 0.10]		-0.06 [-0.22, 0.10]	
	Postsecondary education	0.02 [-0.15, 0.18]		0.01 [-0.15, 0.17]	
	Primary earner status	0.07 [-0.09, 0.23]		0.07 [-0.09, 0.23]	
	MVPA (mins)	-0.15 [-0.35, 0.06]		-0.16 [-0.37, 0.04]	
	StaB (hours)	-0.19 [-0.41, 0.03]		-0.20 [-0.42, 0.03]	
	Sleep duration (hours)	-0.02 [-0.21, 0.17]		-0.03 [-0.22, 0.15]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	0.07 [-0.11, 0.25]		0.10 [-0.08, 0.27]	
	MHT Duration (years)	-0.09 [-0.27, 0.10]		--	--

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 8e. Sensitivity Analysis: Controlling for MHT duration, route exposure, model fit

Outcome	Block	Sensitivity Analysis: Duration				Objective 2B.3			
		Adj. R ²	Sig. F Change	AIC	ΔAIC	Adj. R ²	Sig. F Change	AIC	ΔAIC
aPWV	Block 1	-0.02	0.84	542.1		-0.02	0.82	589.9	
	Block 2	0.11	< 0.01	522.7	-19.5	0.07	< 0.01	575.8	-14.1
	Block 3	0.22	< 0.01	503.8	-18.9	0.16	< 0.01	559.5	-16.2
AIx75	Block 1	-0.02	0.86	1321.7		-0.02	0.85	1432.1	
	Block 2	-0.04	0.96	1327.4	5.7	-0.03	0.93	1436.0	3.8
	Block 3	-0.02	0.11	1326.9	-0.4	-0.02	0.19	1437.0	1.0
SBP	Block 1	-0.02	0.79	1387.1		-0.01	0.56	1517.5	
	Block 2	0.00	0.10	1386.6	-0.5	0.00	0.32	1519.1	1.6
	Block 3	0.03	0.05	1384.4	-2.3	0.04	0.01	1513.6	-5.4
DBP	Block 1	0.01	0.33	1263.6		0.00	0.35	1389.9	
	Block 2	-0.01	0.97	1269.3	5.7	-0.01	0.96	1393.8	3.9
	Block 3	0.01	0.08	1268.0	-1.3	0.02	0.06	1392.1	-1.8
logFRS	Block 1	-0.02	0.88	264.5		-0.01	0.63	290.3	
	Block 2	0.03	0.01	259.3	-5.2	0.03	0.01	285.2	-5.1
	Block 3	0.10	< 0.01	249.8	-9.5	0.09	< 0.01	276.0	-9.2
WC	Block 1	0.11	< 0.01	1335.7		0.09	< 0.01	1451.0	
	Block 2	0.12	0.31	1337.9	2.2	0.09	0.36	1452.9	
	Block 3	0.20	< 0.01	1323.4	-14.5	0.20	< 0.01	1430.1	
HDL-C	Block 1	0.02	0.15	175.6		0.03	0.06	178.7	
	Block 2	0.05	0.07	174.0	-1.6	0.04	0.21	179.3	0.7
	Block 3	0.06	0.12	173.7	-0.2	0.06	0.10	178.6	-0.7
LDL-C	Block 1	0.06	0.02	391.6		0.04	0.04	437.5	
	Block 2	0.04	0.89	396.9	5.3	0.03	0.77	440.9	3.4
	Block 3	0.04	0.43	399.9	3.0	0.04	0.22	442.3	1.3
logTG	Block 1	0.05	0.03	167.4		0.05	0.01	182.5	
	Block 2	0.06	0.24	169.0	1.5	0.05	0.81	186.1	3.6
	Block 3	0.05	0.68	173.3	4.4	0.04	0.47	189.4	3.3
logGlucose	Block 1	0.04	0.06	-171.3		0.04	0.04	-199.4	
	Block 2	0.05	0.20	-170.2	1.1	0.04	0.38	-197.4	2.0
	Block 3	0.04	0.51	-166.7	3.5	0.04	0.48	-194.0	3.4

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed

Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: Transdermal, Vaginal, MHT duration entered (Oral = reference)

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 8f. Sensitivity Analysis: Controlling for MHT duration, route exposure, coefficients

Outcome	Predictor	Sensitivity Analysis: Duration		Objective 2B.3	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	0.09 [-0.07, 0.24]		0.01 [-0.14, 0.16]	
	Spontaneous menopause	0.07 [-0.08, 0.23]		0.12 [-0.03, 0.28]	
	History of VMS	-0.10 [-0.23, 0.04]		-0.09 [-0.23, 0.04]	
	Postsecondary education	0.02 [-0.12, 0.16]		0.05 [-0.09, 0.19]	
	Primary earner status	0.01 [-0.13, 0.15]		-0.02 [-0.16, 0.12]	
	MVPA (mins)	-0.31 [-0.48, -0.14]	*	-0.27 [-0.44, -0.11]	*
	StaB (hours)	0.03 [-0.16, 0.22]		0.07 [-0.11, 0.25]	
	Sleep duration (hours)	-0.11 [-0.27, 0.05]		-0.06 [-0.21, 0.10]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	-0.11 [-0.26, 0.03]		-0.08 [-0.23, 0.07]	
	Vaginal Usage	-0.24 [-0.40, -0.09]	*	-0.28 [-0.42, -0.13]	*
	MHT Duration (years)	0.21 [0.07, 0.36]	*	--	--
AIx75	Age at menopause (years)	-0.09 [-0.27, 0.08]		-0.09 [-0.26, 0.07]	
	Spontaneous menopause	0.07 [-0.11, 0.24]		0.07 [-0.10, 0.23]	
	History of VMS	-0.02 [-0.17, 0.14]		0.01 [-0.14, 0.16]	
	Postsecondary education	-0.01 [-0.17, 0.15]		-0.01 [-0.16, 0.14]	
	Primary earner status	0.04 [-0.11, 0.20]		0.05 [-0.10, 0.20]	
	MVPA (mins)	-0.20 [-0.39, 0.00]	*	-0.15 [-0.34, 0.03]	
	StaB (hours)	0.00 [-0.21, 0.21]		0.02 [-0.18, 0.22]	
	Sleep duration (hours)	-0.02 [-0.21, 0.17]		0.01 [-0.16, 0.18]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.01 [-0.16, 0.18]		0.02 [-0.14, 0.18]	
	Vaginal Usage	0.01 [-0.17, 0.18]		0.01 [-0.16, 0.17]	
	MHT Duration (years)	0.04 [-0.13, 0.21]		--	--
SBP	Age (years)	0.05 [-0.12, 0.23]		0.05 [-0.11, 0.21]	
	Age at menopause (years)	0.02 [-0.15, 0.19]		0.02 [-0.14, 0.17]	
	Spontaneous menopause	0.04 [-0.13, 0.21]		0.06 [-0.10, 0.22]	
	History of VMS	-0.01 [-0.17, 0.14]		0.03 [-0.12, 0.18]	
	Postsecondary education	0.06 [-0.10, 0.21]		0.04 [-0.11, 0.19]	
	Primary earner status	-0.05 [-0.20, 0.11]		-0.09 [-0.23, 0.06]	
	MVPA (mins)	-0.27 [-0.47, -0.08]	*	-0.30 [-0.48, -0.12]	*
	StaB (hours)	-0.15 [-0.36, 0.06]		-0.17 [-0.36, 0.03]	
	Sleep duration (hours)	-0.09 [-0.27, 0.09]		-0.12 [-0.29, 0.04]	

Oral Usage (MHT reference group)				
DBP	Transdermal Usage	0.04 [-0.13, 0.20]		0.06 [-0.10, 0.22]
	Vaginal Usage	-0.12 [-0.30, 0.05]		-0.05 [-0.22, 0.11]
	MHT Duration (years)	-0.13 [-0.30, 0.04]		--
	Age (years)	-0.24 [-0.41, -0.06]	*	-0.19 [-0.35, -0.03]
	Age at menopause (years)	0.01 [-0.16, 0.19]		-0.02 [-0.17, 0.14]
	Spontaneous menopause	0.12 [-0.06, 0.29]		0.13 [-0.03, 0.30]
	History of VMS	-0.04 [-0.20, 0.12]		0.00 [-0.15, 0.15]
	Postsecondary education	-0.01 [-0.17, 0.14]		-0.02 [-0.17, 0.13]
	Primary earner status	0.05 [-0.10, 0.21]		0.02 [-0.12, 0.17]
	MVPA (mins)	-0.26 [-0.45, -0.06]	*	-0.25 [-0.43, -0.07]
logFRS	StaB (hours)	-0.15 [-0.36, 0.06]		-0.17 [-0.37, 0.03]
	Sleep duration (hours)	-0.07 [-0.25, 0.11]		-0.08 [-0.25, 0.08]
	Oral Usage (MHT reference group)			
	Transdermal Usage	-0.01 [-0.18, 0.16]		0.02 [-0.14, 0.18]
	Vaginal Usage	-0.02 [-0.19, 0.16]		0.03 [-0.14, 0.19]
	MHT Duration (years)	0.01 [-0.16, 0.19]		--
	Age at menopause (years)	-0.07 [-0.24, 0.09]		-0.09 [-0.24, 0.06]
	Spontaneous menopause	0.07 [-0.10, 0.23]		0.10 [-0.06, 0.25]
	History of VMS	-0.03 [-0.18, 0.12]		-0.01 [-0.15, 0.14]
	Postsecondary education	0.02 [-0.13, 0.17]		0.01 [-0.13, 0.16]
WC	Primary earner status	-0.09 [-0.24, 0.06]		-0.11 [-0.26, 0.03]
	MVPA (mins)	-0.31 [-0.49, -0.12]	*	-0.29 [-0.47, -0.12]
	StaB (hours)	-0.04 [-0.24, 0.16]		-0.05 [-0.24, 0.14]
	Sleep duration (hours)	-0.07 [-0.24, 0.11]		-0.07 [-0.23, 0.09]
	Oral Usage (MHT reference group)			
	Transdermal Usage	0.00 [-0.16, 0.16]		0.04 [-0.11, 0.20]
	Vaginal Usage	-0.22 [-0.38, -0.05]	*	-0.16 [-0.31, 0.00]
	MHT Duration (years)	-0.04 [-0.20, 0.12]		--
	Age (years)	-0.40 [-0.56, -0.24]	*	-0.38 [-0.52, -0.23]
	Age at menopause (years)	-0.05 [-0.21, 0.10]		-0.05 [-0.20, 0.09]
	Spontaneous menopause	-0.05 [-0.21, 0.11]		-0.03 [-0.18, 0.11]
	History of VMS	0.01 [-0.13, 0.15]		0.01 [-0.13, 0.14]
	Postsecondary education	-0.11 [-0.25, 0.03]		-0.09 [-0.23, 0.04]
	Primary earner status	0.17 [0.03, 0.31]	*	0.14 [0.00, 0.27]
	MVPA (mins)	-0.30 [-0.47, -0.12]	*	-0.33 [-0.49, -0.16]

	StaB (hours)	0.03 [-0.16, 0.22]		0.04 [-0.14, 0.22]	
	Sleep duration (hours)	-0.12 [-0.29, 0.04]		-0.13 [-0.28, 0.02]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.08 [-0.07, 0.23]		0.09 [-0.06, 0.23]	
	Vaginal Usage	-0.04 [-0.20, 0.12]		-0.01 [-0.16, 0.14]	
	MHT Duration (years)	-0.02 [-0.18, 0.13]		--	--
HDL-C	Age (years)	0.08 [-0.10, 0.25]		0.11 [-0.04, 0.27]	
	Age at menopause (years)	0.08 [-0.09, 0.25]		0.02 [-0.13, 0.18]	
	Spontaneous menopause	0.17 [0.00, 0.34]	*	0.20 [0.04, 0.36]	*
	History of VMS	-0.04 [-0.19, 0.11]		-0.07 [-0.22, 0.08]	
	Postsecondary education	0.11 [-0.05, 0.26]		0.12 [-0.02, 0.27]	
	Primary earner status	-0.06 [-0.21, 0.10]		-0.06 [-0.20, 0.09]	
	MVPA (mins)	0.09 [-0.10, 0.28]		0.08 [-0.10, 0.26]	
	StaB (hours)	-0.14 [-0.35, 0.07]		-0.14 [-0.34, 0.05]	
	Sleep duration (hours)	-0.07 [-0.25, 0.11]		-0.04 [-0.20, 0.12]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.05 [-0.11, 0.21]		0.06 [-0.09, 0.22]	
	Vaginal Usage	-0.10 [-0.27, 0.08]		-0.10 [-0.27, 0.06]	
	MHT Duration (years)	0.14 [-0.03, 0.31]		--	--
LDL-C	Age (years)	-0.20 [-0.37, -0.02]	*	-0.14 [-0.30, 0.02]	
	Age at menopause (years)	-0.12 [-0.29, 0.05]		-0.13 [-0.28, 0.03]	
	Spontaneous menopause	0.12 [-0.05, 0.29]		0.11 [-0.06, 0.27]	
	History of VMS	-0.05 [-0.20, 0.11]		-0.06 [-0.21, 0.09]	
	Postsecondary education	0.08 [-0.08, 0.23]		0.05 [-0.09, 0.20]	
	Primary earner status	-0.12 [-0.27, 0.04]		-0.12 [-0.27, 0.03]	
	MVPA (mins)	0.06 [-0.13, 0.25]		0.11 [-0.07, 0.29]	
	StaB (hours)	-0.10 [-0.31, 0.11]		-0.07 [-0.27, 0.12]	
	Sleep duration (hours)	-0.02 [-0.20, 0.16]		0.01 [-0.16, 0.18]	
	Oral Usage (MHT reference group)				
	Vaginal Usage	-0.07 [-0.25, 0.10]		0.05 [-0.11, 0.21]	
	Transdermal Usage	0.01 [-0.16, 0.17]		-0.02 [-0.18, 0.15]	
	MHT Duration (years)	-0.03 [-0.21, 0.14]		--	--
logTG	Age (years)	-0.06 [-0.24, 0.11]		-0.08 [-0.24, 0.08]	
	Age at menopause (years)	-0.27 [-0.44, -0.10]	*	-0.22 [-0.38, -0.06]	*
	Spontaneous menopause	-0.07 [-0.24, 0.10]		-0.09 [-0.26, 0.07]	
	History of VMS	0.04 [-0.12, 0.19]		0.00 [-0.15, 0.15]	

	Postsecondary education	-0.02 [-0.18, 0.13]		-0.07 [-0.22, 0.08]	
	Primary earner status	-0.03 [-0.18, 0.13]		0.01 [-0.13, 0.16]	
	MVPA (mins)	-0.10 [-0.29, 0.10]		-0.12 [-0.30, 0.06]	
	StaB (hours)	0.00 [-0.21, 0.21]		0.00 [-0.20, 0.19]	
	Sleep duration (hours)	0.02 [-0.16, 0.20]		-0.01 [-0.17, 0.16]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	-0.01 [-0.18, 0.15]		-0.01 [-0.17, 0.15]	
	Vaginal Usage	0.03 [-0.14, 0.21]		0.06 [-0.11, 0.22]	
	MHT Duration (years)	-0.14 [-0.32, 0.03]		--	--
logGlucose	Age (years)	0.23 [0.05, 0.40]	*	0.18 [0.02, 0.34]	*
	Age at menopause (years)	0.12 [-0.05, 0.29]		0.16 [0.00, 0.31]	*
	Spontaneous menopause	-0.06 [-0.23, 0.11]		-0.08 [-0.25, 0.08]	
	History of VMS	-0.07 [-0.22, 0.09]		-0.05 [-0.20, 0.10]	
	Postsecondary education	0.04 [-0.12, 0.19]		0.04 [-0.11, 0.19]	
	Primary earner status	0.07 [-0.09, 0.22]		0.07 [-0.08, 0.21]	
	MVPA (mins)	-0.07 [-0.26, 0.12]		-0.11 [-0.29, 0.07]	
	StaB (hours)	-0.11 [-0.32, 0.09]		-0.13 [-0.33, 0.06]	
	Sleep duration (hours)	0.03 [-0.15, 0.22]		-0.01 [-0.17, 0.16]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.07 [-0.10, 0.23]		0.05 [-0.11, 0.21]	
	Vaginal Usage	-0.08 [-0.26, 0.09]		-0.06 [-0.23, 0.10]	
	MHT Duration (years)	-0.16 [-0.33, 0.02]		--	--

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 9. Sensitivity Analysis: Group Differences by MHT Timing

Variable	Controls (N=660)	Delayed MHT Initiation (≥ 10 years) (N=31)	Initiated MHT Within 10 Years (N=185)	Omnibus p- value	Effect size
Age (years)	63 [60, 67]	66 [60, 70]	66 [60, 70] *	< 0.01	$\epsilon^2=0.01$
BMI (kg/m ²)	25.8 [23.2, 29.7]	26.1 [23.7, 30.9]	25.6 [23.1, 28.6]	0.53	$\epsilon^2=0.00$
Mean arterial pressure (mmHg)	97 (11)	99 (14)	97 (11)	0.62	$\eta^2=0.00$
Age at menopause (years)	53 [51, 55]	45 [41, 51] *	51 [47, 54] *†	< 0.01	$\epsilon^2=0.06$
MVPA (avg. mins/day)	21.2 [9.7, 38.4]	14.2 [5.9, 30.5]	18.4 [8.5, 34.7]	0.26	$\epsilon^2=0.00$
StaB (avg. hours/day)	12.1 (1.6)	12.2 (1.5)	12.0 (1.6)	0.85	$\eta^2=0.00$
Sleep (avg. hours/day)	6.5 (0.9)	6.6 (0.7)	6.6 (0.8)	0.26	$\eta^2=0.00$
aPWV (m/s)	8.8 [8.2, 9.7]	8.9 [8.4, 9.8]	9.1 [8.4, 10.0] *	< 0.01	$\epsilon^2=0.01$
AIx75 (%)	21.3 [13.7, 28.7]	23.3 [16.7, 29.7]	21.3 [13.0, 28.0]	0.65	$\epsilon^2=0.00$
SBP (mmHg)	122 (14)	123 (18)	121 (14)	0.67	$\eta^2=0.00$
DBP (mmHg)	76 [70, 84]	78 [69, 84]	76 [68, 83]	0.59	$\epsilon^2=0.00$
FRS (%)	6.3 [3.9, 8.6]	5.3 [3.9, 8.6]	5.3 [3.9, 8.6]	0.67	$\epsilon^2=0.00$
WC (cm)	92.6 [85, 102.5]	94.0 [85.5, 100.1]	91.0 [83.5, 101.8]	0.44	$\epsilon^2=0.00$
HDL-C (mmol/L)	1.67 [1.40, 2.03]	1.54 [1.48, 1.94]	1.72 [1.50, 2.01]	0.23	$\epsilon^2=0.00$
LDL-C (mmol/L)	3.30 [2.69, 3.91]	3.59 [2.70, 4.02]	3.27 [2.72, 3.81]	0.51	$\epsilon^2=0.00$
TG (mmol/L)	0.99 [0.75, 1.33]	0.96 [0.78, 1.61]	0.95 [0.76, 1.24]	0.36	$\epsilon^2=0.00$
Glucose (mmol/L)	5.67 [5.35, 6.02]	5.64 [5.49, 5.81]	5.63 [5.30, 5.93]	0.53	$\epsilon^2=0.00$

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; FRS, Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Age at menopause: N = 585 (never)

Glucose: N=659 (controls)

Outcomes reported as Mean (SD) or Median [IQR]

*p < 0.05 compared to controls

†p < 0.05 compared to delayed initiation (≥10 years)

Red text used to emphasize statistically significant findings.

Appendix Table 10a. Sensitivity Analysis: Controlling for MHT timing, history exposure, model fit

Outcome	Block	Sensitivity Analysis: Timing				Objective 2B.1			
		Adj. R ²	Sig. F Change	AIC	ΔAIC	Adj. R ²	Sig. F Change	AIC	ΔAIC
aPWV	Block 1	0.00	0.44	681.6		-0.01	0.89	769.9	
	Block 2	0.07	< 0.01	666.9	-14.7	0.08	< 0.01	747.4	-22.6
	Block 3	0.19	< 0.01	642.3	-24.6	0.17	< 0.01	725.9	-21.5
AIx75	Block 1	0.00	0.53	1650.92		-0.01	0.77	1814.6	
	Block 2	0.00	0.32	1652.55	1.6	0.00	0.07	1813.2	-1.4
	Block 3	0.00	0.23	1654.05	1.5	0.01	0.10	1812.7	-0.4
SBP	Block 1	0.02	0.14	1760.07		0.02	0.08	1939.3	
	Block 2	0.03	0.12	1759.61	-0.5	0.03	0.06	1937.7	-1.7
	Block 3	0.06	0.03	1756.36	-3.3	0.06	0.02	1933.1	-4.5
DBP	Block 1	0.01	0.29	1632.15		-0.01	0.65	1798.9	
	Block 2	0.02	0.15	1632.19	0.0	0.00	0.05	1797.0	-1.9
	Block 3	0.02	0.24	1633.74	1.5	0.02	0.13	1797.2	0.1
logFRS	Block 1	0.03	0.06	331.70		0.00	0.47	378.9	
	Block 2	0.07	< 0.01	324.02	-7.7	0.06	< 0.01	365.5	-13.4
	Block 3	0.12	< 0.01	315.63	-8.4	0.11	< 0.01	355.4	-10.1
WC	Block 1	0.07	< 0.01	1703.17		0.06	< 0.01	1869.3	
	Block 2	0.08	0.09	1702.15	-1.0	0.08	0.02	1865.7	-3.6
	Block 3	0.20	< 0.01	1675.64	-26.5	0.18	< 0.01	1840.9	-24.8
HDL-C	Block 1	0.04	0.02	265.29		0.03	0.04	284.5	
	Block 2	0.04	0.48	267.75	2.5	0.03	0.96	286.5	2.0
	Block 3	0.05	0.13	267.77	0.0	0.04	0.09	285.7	-0.8
LDL-C	Block 1	0.03	0.07	517.40		0.02	0.08	568.6	
	Block 2	0.02	0.68	520.59	3.2	0.02	0.48	570.1	1.5
	Block 3	0.03	0.16	521.15	0.6	0.03	0.24	571.7	1.6
logTG	Block 1	0.07	< 0.01	219.26		0.05	0.01	242.1	
	Block 2	0.06	0.92	223.08	3.8	0.04	0.86	244.1	2.0
	Block 3	0.08	0.10	222.40	-0.7	0.05	0.11	243.8	-0.3
logGlucose	Block 1	0.00	0.53	-315.40		0.03	0.03	-282.5	
	Block 2	-0.01	0.52	-312.76	2.6	0.04	0.19	-282.3	0.2
	Block 3	-0.02	0.74	-308.08	4.7	0.04	0.41	-279.3	3.0

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Sensitivity Analysis N=214

Block 1: Covariates entered

Block 2: Current usage, delayed MHT initiation entered (Former usage = reference)

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 10b. Sensitivity Analysis: Controlling for MHT timing, history exposure, coefficients

Outcome	Predictor	Sensitivity Analysis: Timing		Objective 2B.1	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	-0.08 [-0.23, 0.06]		-0.03 [-0.16, 0.10]	
	Spontaneous menopause	0.15 [0.01, 0.29]	*	0.07 [-0.06, 0.20]	
	History of VMS	0.01 [-0.12, 0.13]		-0.05 [-0.17, 0.07]	
	Postsecondary education	0.00 [-0.13, 0.12]		0.00 [-0.12, 0.12]	
	Primary earner status	0.01 [-0.12, 0.13]		0.00 [-0.12, 0.12]	
	MVPA (mins)	-0.28 [-0.43, -0.13]	*	-0.26 [-0.40, -0.12]	*
	StaB (hours)	0.09 [-0.07, 0.25]		0.09 [-0.06, 0.24]	
	Sleep duration (hours)	-0.06 [-0.20, 0.08]		-0.01 [-0.15, 0.12]	
	Former Usage (MHT reference group)				
	Current Usage	-0.25 [-0.38, -0.13]	*	-0.28 [-0.39, -0.16]	*
	Delayed MHT Initiation	0.00 [-0.13, 0.13]		--	--
AIx75	Age at menopause (years)	-0.12 [-0.28, 0.04]		-0.08 [-0.22, 0.06]	
	Spontaneous menopause	0.09 [-0.06, 0.24]		0.01 [-0.13, 0.15]	
	History of VMS	0.01 [-0.13, 0.15]		-0.02 [-0.15, 0.11]	
	Postsecondary education	0.01 [-0.13, 0.15]		-0.03 [-0.16, 0.10]	
	Primary earner status	0.03 [-0.11, 0.16]		0.04 [-0.09, 0.17]	
	MVPA (mins)	-0.11 [-0.28, 0.05]		-0.11 [-0.27, 0.04]	
	StaB (hours)	0.05 [-0.13, 0.22]		0.08 [-0.09, 0.24]	
	Sleep duration (hours)	0.03 [-0.12, 0.19]		0.06 [-0.09, 0.20]	
	Former Usage (MHT reference group)				
	Current Usage	-0.09 [-0.23, 0.05]		-0.10 [-0.23, 0.03]	
	Delayed MHT Initiation	0.01 [-0.13, 0.16]		--	--
SBP	Age (years)	0.07 [-0.08, 0.21]		0.13 [-0.01, 0.27]	
	Age at menopause (years)	-0.03 [-0.19, 0.12]		-0.02 [-0.15, 0.12]	
	Spontaneous menopause	0.05 [-0.10, 0.20]		-0.02 [-0.16, 0.12]	
	History of VMS	0.11 [-0.03, 0.24]		0.05 [-0.07, 0.18]	
	Postsecondary education	0.00 [-0.13, 0.14]		0.01 [-0.12, 0.14]	
	Primary earner status	-0.06 [-0.19, 0.07]		-0.07 [-0.19, 0.06]	
	MVPA (mins)	-0.23 [-0.39, -0.07]	*	-0.24 [-0.39, -0.09]	*
	StaB (hours)	-0.14 [-0.32, 0.03]		-0.18 [-0.35, -0.02]	*
	Sleep duration (hours)	-0.12 [-0.27, 0.04]		-0.07 [-0.21, 0.07]	
	Former Usage (MHT reference group)				
	Current Usage	-0.15 [-0.29, -0.01]	*	-0.13 [-0.27, 0.00]	*

DBP	Delayed MHT Initiation	0.08 [-0.07, 0.22]		--	--
	Age (years)	-0.17 [-0.32, -0.02]	*	-0.14 [-0.28, 0.01]	
	Age at menopause (years)	-0.07 [-0.23, 0.09]		-0.07 [-0.21, 0.07]	
	Spontaneous menopause	0.11 [-0.04, 0.26]		0.06 [-0.08, 0.20]	
	History of VMS	0.06 [-0.08, 0.20]		0.02 [-0.11, 0.15]	
	Postsecondary education	0.00 [-0.14, 0.14]		-0.02 [-0.15, 0.12]	
	Primary earner status	0.02 [-0.11, 0.16]		0.01 [-0.12, 0.14]	
	MVPA (mins)	-0.14 [-0.31, 0.02]		-0.16 [-0.31, 0.00]	
	StaB (hours)	-0.16 [-0.34, 0.01]		-0.18 [-0.35, -0.01]	*
	Sleep duration (hours)	-0.08 [-0.23, 0.07]		-0.04 [-0.18, 0.10]	
logFRS	Former Usage (MHT reference group)				
	Current Usage	-0.15 [-0.29, 0.00]	*	-0.14 [-0.28, 0.00]	*
	Delayed MHT Initiation	0.06 [-0.08, 0.21]		--	--
	Age at menopause (years)	-0.15 [-0.30, 0.00]	*	-0.10 [-0.23, 0.03]	
	Spontaneous menopause	0.10 [-0.04, 0.24]		0.02 [-0.12, 0.15]	
	History of VMS	0.10 [-0.03, 0.23]		0.02 [-0.11, 0.14]	
	Postsecondary education	-0.01 [-0.14, 0.12]		-0.03 [-0.15, 0.10]	
	Primary earner status	-0.05 [-0.18, 0.07]		-0.06 [-0.18, 0.06]	
	MVPA (mins)	-0.25 [-0.40, -0.10]	*	-0.25 [-0.40, -0.11]	*
	StaB (hours)	-0.03 [-0.20, 0.14]		-0.01 [-0.17, 0.15]	
WC	Sleep duration (hours)	-0.07 [-0.22, 0.07]		-0.01 [-0.15, 0.13]	
	Former Usage (MHT reference group)				
	Current Usage	-0.21 [-0.34, -0.08]	*	-0.23 [-0.35, -0.10]	*
	Delayed MHT Initiation	0.04 [-0.10, 0.18]		--	--
	Age (years)	-0.38 [-0.52, -0.25]	*	-0.33 [-0.46, -0.20]	*
	Age at menopause (years)	-0.09 [-0.23, 0.05]		-0.04 [-0.16, 0.09]	
	Spontaneous menopause	-0.02 [-0.16, 0.11]		-0.07 [-0.20, 0.06]	
	History of VMS	0.06 [-0.07, 0.18]		0.04 [-0.08, 0.16]	
	Postsecondary education	-0.13 [-0.25, -0.01]	*	-0.12 [-0.24, 0.00]	*
	Primary earner status	0.12 [0.00, 0.25]	*	0.14 [0.02, 0.26]	*
	MVPA (mins)	-0.34 [-0.49, -0.19]	*	-0.31 [-0.45, -0.17]	*
	StaB (hours)	0.03 [-0.13, 0.19]		0.05 [-0.11, 0.20]	
	Sleep duration (hours)	-0.10 [-0.24, 0.04]		-0.09 [-0.22, 0.04]	
	Former Usage (MHT reference group)				
	Current Usage	-0.16 [-0.28, -0.03]	*	-0.15 [-0.27, -0.03]	*
	Delayed MHT Initiation	0.00 [-0.13, 0.13]		--	--

HDL-C	Age (years)	0.08 [-0.07, 0.23]		0.06 [-0.08, 0.20]	
	Age at menopause (years)	0.02 [-0.14, 0.17]		0.01 [-0.12, 0.15]	
	Spontaneous menopause	0.20 [0.05, 0.35]	*	0.18 [0.04, 0.32]	*
	History of VMS	-0.03 [-0.17, 0.10]		-0.04 [-0.17, 0.09]	
	Postsecondary education	0.10 [-0.04, 0.23]		0.09 [-0.04, 0.22]	
	Primary earner status	-0.04 [-0.18, 0.09]		-0.06 [-0.18, 0.07]	
	MVPA (mins)	0.09 [-0.07, 0.26]		0.08 [-0.07, 0.24]	
	StaB (hours)	-0.10 [-0.27, 0.08]		-0.12 [-0.28, 0.05]	
	Sleep duration (hours)	0.01 [-0.14, 0.16]		0.01 [-0.13, 0.15]	
	Former Usage (MHT reference group)				
	Current Usage	-0.02 [-0.16, 0.12]		-0.01 [-0.14, 0.12]	
	Delayed MHT Initiation	-0.07 [-0.22, 0.07]		--	--
LDL-C	Age (years)	-0.14 [-0.29, 0.01]		-0.15 [-0.29, -0.01]	*
	Age at menopause (years)	-0.05 [-0.21, 0.10]		-0.09 [-0.22, 0.05]	
	Spontaneous menopause	0.07 [-0.08, 0.22]		0.07 [-0.08, 0.21]	
	History of VMS	-0.02 [-0.16, 0.12]		-0.05 [-0.18, 0.08]	
	Postsecondary education	0.05 [-0.09, 0.18]		0.03 [-0.10, 0.16]	
	Primary earner status	-0.07 [-0.21, 0.06]		-0.06 [-0.19, 0.07]	
	MVPA (mins)	0.07 [-0.09, 0.24]		0.08 [-0.07, 0.24]	
	StaB (hours)	-0.11 [-0.29, 0.06]		-0.06 [-0.23, 0.10]	
	Sleep duration (hours)	0.01 [-0.14, 0.16]		0.04 [-0.10, 0.19]	
	Former Usage (MHT reference group)				
	Current Usage	-0.04 [-0.18, 0.11]		-0.05 [-0.19, 0.08]	
	Delayed MHT Initiation	0.07 [-0.07, 0.22]		--	--
logTG	Age (years)	-0.11 [-0.26, 0.03]		-0.08 [-0.22, 0.06]	
	Age at menopause (years)	-0.24 [-0.39, -0.08]	*	-0.18 [-0.32, -0.05]	*
	Spontaneous menopause	-0.07 [-0.21, 0.08]		-0.08 [-0.22, 0.06]	
	History of VMS	0.02 [-0.12, 0.15]		-0.01 [-0.14, 0.12]	
	Postsecondary education	-0.07 [-0.20, 0.07]		-0.07 [-0.20, 0.06]	
	Primary earner status	0.05 [-0.08, 0.18]		0.06 [-0.06, 0.19]	
	MVPA (mins)	-0.18 [-0.34, -0.02]	*	-0.16 [-0.31, -0.01]	*
	StaB (hours)	-0.02 [-0.19, 0.16]		0.01 [-0.16, 0.17]	
	Sleep duration (hours)	-0.02 [-0.17, 0.13]		0.03 [-0.11, 0.17]	
	Former Usage (MHT reference group)				
	Current Usage	0.01 [-0.13, 0.15]		-0.01 [-0.14, 0.12]	
	Delayed MHT Initiation	0.02 [-0.12, 0.16]		--	--

logGlucose	Age (years)	0.11 [-0.05, 0.26]	0.16 [0.01, 0.30]	*
	Age at menopause (years)	0.02 [-0.14, 0.18]	0.15 [0.01, 0.29]	*
	Spontaneous menopause	-0.02 [-0.17, 0.14]	-0.12 [-0.26, 0.02]	
	History of VMS	-0.02 [-0.16, 0.12]	-0.03 [-0.16, 0.10]	
	Postsecondary education	0.03 [-0.11, 0.17]	0.03 [-0.10, 0.16]	
	Primary earner status	0.03 [-0.11, 0.17]	0.04 [-0.09, 0.17]	
	MVPA (mins)	-0.09 [-0.26, 0.08]	-0.12 [-0.27, 0.03]	
	StaB (hours)	-0.06 [-0.24, 0.13]	-0.12 [-0.28, 0.05]	
	Sleep duration (hours)	-0.05 [-0.21, 0.11]	-0.06 [-0.20, 0.09]	
	Former Usage (MHT reference group)			
	Current Usage	-0.08 [-0.23, 0.06]	-0.09 [-0.23, 0.04]	
	Delayed MHT Initiation	-0.01 [-0.15, 0.14]	--	--

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 10c. Sensitivity Analysis: Controlling for MHT timing, type exposure, model fit

Outcome	Block	Sensitivity Analysis: Timing				Objective 2B.2			
		Adj. R ²	Sig. F Change	AIC	ΔAIC	Adj. R ²	Sig. F Change	AIC	ΔAIC
aPWV	Block 1	-0.03	0.92	462.1		-0.02	0.92	500.0	
	Block 2	0.04	< 0.01	454.5	-7.6	0.05	< 0.01	489.5	-10.5
	Block 3	0.24	< 0.01	423.4	-31.1	0.21	< 0.01	464.9	-24.6
AIx75	Block 1	-0.01	0.69	1123.71		-0.02	0.88	1206.0	
	Block 2	-0.02	0.60	1126.62	2.9	-0.02	0.17	1206.1	0.1
	Block 3	-0.02	0.35	1129.10	2.5	-0.01	0.24	1207.6	1.5
SBP	Block 1	-0.01	0.57	1179.18		0.00	0.36	1262.0	
	Block 2	-0.02	0.74	1182.54	3.4	0.00	0.61	1263.8	1.7
	Block 3	0.03	0.03	1178.57	-4.0	0.05	0.01	1258.3	-5.5
DBP	Block 1	0.02	0.21	1080.64		0.00	0.39	1154.4	
	Block 2	0.01	0.79	1084.14	3.5	0.00	0.49	1155.9	1.5
	Block 3	0.01	0.26	1085.76	1.6	0.02	0.12	1155.6	-0.3
logFRS	Block 1	0.00	0.48	226.72		-0.01	0.67	246.7	
	Block 2	-0.01	0.46	229.07	2.4	-0.01	0.18	246.9	0.1
	Block 3	0.09	< 0.01	217.71	-11.4	0.09	< 0.01	233.6	-13.3
WC	Block 1	0.10	< 0.01	1132.81		0.08	< 0.01	1211.5	
	Block 2	0.09	0.74	1136.17	3.4	0.08	0.70	1213.4	
	Block 3	0.16	< 0.01	1126.81	-9.4	0.14	< 0.01	1204.7	
HDL-C	Block 1	0.05	0.05	154.55		0.03	0.11	165.6	
	Block 2	0.08	0.045	151.95	-2.6	0.06	0.02	162.2	-3.4
	Block 3	0.11	0.06	150.00	-1.9	0.08	0.07	160.5	-1.6
LDL-C	Block 1	0.07	0.02	333.29		0.07	0.01	355.7	
	Block 2	0.06	0.74	336.64	3.4	0.07	0.42	357.0	1.3
	Block 3	0.05	0.61	340.68	4.0	0.06	0.71	361.5	4.5
logTG	Block 1	0.08	0.01	148.00		0.05	0.03	161.0	
	Block 2	0.08	0.49	150.50	2.5	0.05	0.24	161.5	0.5
	Block 3	0.07	0.55	154.21	3.7	0.05	0.53	165.1	3.6
logGlucose	Block 1	-0.02	0.72	-256.92		0.04	0.06	-188.7	
	Block 2	-0.03	0.77	-253.47	3.5	0.04	0.37	-187.5	1.1
	Block 3	-0.03	0.36	-251.00	2.5	0.04	0.27	-185.7	1.8

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed

Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: Unopposed Estrogen, Delayed MHT initiation entered (Combined Estrogen-Progestosterone= reference)

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 10d. Sensitivity Analysis: Controlling for MHT timing, type exposure, coefficients

Outcome	Predictor	Sensitivity Analysis: Duration		Objective 2B.2	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	-0.10 [-0.26, 0.07]		-0.02 [-0.18, 0.14]	
	Spontaneous menopause	0.11 [-0.05, 0.28]		0.02 [-0.14, 0.18]	
	History of VMS	-0.08 [-0.23, 0.07]		-0.11 [-0.26, 0.03]	
	Postsecondary education	-0.01 [-0.16, 0.14]		-0.01 [-0.16, 0.14]	
	Primary earner status	-0.03 [-0.18, 0.12]		-0.02 [-0.17, 0.13]	
	MVPA (mins)	-0.39 [-0.57, -0.21]	*	-0.37 [-0.55, -0.19]	*
	StaB (hours)	0.08 [-0.13, 0.28]		0.05 [-0.15, 0.26]	
	Sleep duration (hours)	-0.11 [-0.29, 0.06]		-0.09 [-0.26, 0.08]	
	Combined Estrogen-Progesterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	-0.26 [-0.42, -0.10]	*	-0.28 [-0.43, -0.12]	*
	Delayed MHT Initiation	-0.08 [-0.24, 0.08]		--	--
AIx75	Age at menopause (years)	-0.17 [-0.36, 0.03]		-0.13 [-0.31, 0.05]	
	Spontaneous menopause	0.11 [-0.08, 0.31]		0.05 [-0.13, 0.23]	
	History of VMS	-0.01 [-0.18, 0.17]		-0.03 [-0.19, 0.13]	
	Postsecondary education	0.03 [-0.14, 0.20]		0.00 [-0.17, 0.16]	
	Primary earner status	-0.03 [-0.20, 0.15]		0.00 [-0.16, 0.17]	
	MVPA (mins)	-0.14 [-0.35, 0.07]		-0.15 [-0.36, 0.05]	
	StaB (hours)	0.03 [-0.21, 0.26]		0.03 [-0.20, 0.25]	
	Sleep duration (hours)	-0.02 [-0.22, 0.19]		-0.01 [-0.20, 0.18]	
	Combined Estrogen-Progesterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	-0.09 [-0.27, 0.09]		-0.11 [-0.28, 0.06]	
	Delayed MHT Initiation	0.01 [-0.18, 0.19]		--	--
SBP	Age (years)	0.01 [-0.18, 0.20]		0.07 [-0.11, 0.25]	
	Age at menopause (years)	0.02 [-0.18, 0.21]		0.04 [-0.13, 0.21]	
	Spontaneous menopause	0.08 [-0.11, 0.27]		0.02 [-0.16, 0.20]	
	History of VMS	0.05 [-0.12, 0.22]		0.02 [-0.14, 0.18]	
	Postsecondary education	0.05 [-0.12, 0.22]		0.06 [-0.11, 0.22]	
	Primary earner status	-0.11 [-0.28, 0.05]		-0.12 [-0.28, 0.04]	
	MVPA (mins)	-0.32 [-0.54, -0.11]	*	-0.34 [-0.55, -0.14]	*
	StaB (hours)	-0.16 [-0.40, 0.07]		-0.20 [-0.42, 0.02]	
	Sleep duration (hours)	-0.15 [-0.34, 0.05]		-0.10 [-0.29, 0.09]	
	Combined Estrogen-Progesterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	-0.08 [-0.27, 0.11]		-0.04 [-0.21, 0.13]	

DBP	Delayed MHT Initiation	0.06 [-0.13, 0.24]		--	--
	Age (years)	-0.26 [-0.45, -0.06]	*	-0.23 [-0.41, -0.05]	*
	Age at menopause (years)	0.01 [-0.19, 0.20]		0.02 [-0.15, 0.20]	
	Spontaneous menopause	0.17 [-0.02, 0.36]		0.13 [-0.05, 0.31]	
	History of VMS	0.00 [-0.17, 0.17]		-0.03 [-0.19, 0.14]	
	Postsecondary education	0.01 [-0.16, 0.18]		-0.01 [-0.17, 0.16]	
	Primary earner status	0.00 [-0.17, 0.17]		0.00 [-0.16, 0.16]	
	MVPA (mins)	-0.22 [-0.44, 0.00]	*	-0.25 [-0.46, -0.05]	*
	StaB (hours)	-0.12 [-0.36, 0.11]		-0.13 [-0.36, 0.09]	
	Sleep duration (hours)	-0.06 [-0.26, 0.14]		-0.04 [-0.23, 0.15]	
Combined Estrogen-Progestosterone Usage (MHT reference group)					
	Unopposed Estrogen Usage	-0.07 [-0.25, 0.12]		-0.06 [-0.23, 0.12]	
	Delayed MHT Initiation	0.04 [-0.14, 0.23]		--	--
logFRS	Age at menopause (years)	-0.16 [-0.34, 0.03]		-0.11 [-0.27, 0.06]	
	Spontaneous menopause	0.13 [-0.06, 0.31]		0.05 [-0.12, 0.23]	
	History of VMS	0.04 [-0.12, 0.20]		0.00 [-0.16, 0.15]	
	Postsecondary education	0.04 [-0.13, 0.20]		0.01 [-0.14, 0.17]	
	Primary earner status	-0.14 [-0.31, 0.02]		-0.15 [-0.31, 0.01]	
	MVPA (mins)	-0.33 [-0.53, -0.13]	*	-0.37 [-0.56, -0.17]	*
	StaB (hours)	-0.04 [-0.26, 0.19]		-0.06 [-0.27, 0.16]	
	Sleep duration (hours)	-0.13 [-0.32, 0.06]		-0.08 [-0.27, 0.10]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	-0.11 [-0.28, 0.07]		-0.09 [-0.25, 0.07]	
	Delayed MHT Initiation	0.00 [-0.18, 0.17]		--	--
WC	Age (years)	-0.43 [-0.61, -0.25]	*	-0.40 [-0.57, -0.23]	*
	Age at menopause (years)	-0.07 [-0.25, 0.10]		-0.02 [-0.19, 0.14]	
	Spontaneous menopause	-0.06 [-0.24, 0.12]		-0.09 [-0.26, 0.08]	
	History of VMS	-0.01 [-0.17, 0.15]		0.00 [-0.15, 0.15]	
	Postsecondary education	-0.10 [-0.26, 0.06]		-0.07 [-0.22, 0.09]	
	Primary earner status	0.11 [-0.04, 0.27]		0.11 [-0.04, 0.27]	
	MVPA (mins)	-0.25 [-0.45, -0.05]	*	-0.25 [-0.44, -0.06]	*
	StaB (hours)	0.10 [-0.12, 0.32]		0.06 [-0.15, 0.27]	
	Sleep duration (hours)	-0.07 [-0.25, 0.12]		-0.10 [-0.28, 0.08]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	0.03 [-0.14, 0.21]		0.01 [-0.16, 0.17]	
	Delayed MHT Initiation	-0.04 [-0.21, 0.13]		--	--

HDL-C	Age (years)	0.10 [-0.09, 0.28]	0.11 [-0.07, 0.28]	
	Age at menopause (years)	0.05 [-0.13, 0.24]	0.04 [-0.13, 0.21]	
	Spontaneous menopause	0.14 [-0.04, 0.32]	0.10 [-0.07, 0.28]	
	History of VMS	-0.02 [-0.19, 0.14]	-0.05 [-0.21, 0.11]	
	Postsecondary education	0.14 [-0.02, 0.30]	0.12 [-0.04, 0.28]	
	Primary earner status	-0.07 [-0.23, 0.09]	-0.08 [-0.23, 0.08]	
	MVPA (mins)	0.12 [-0.09, 0.32]	0.12 [-0.08, 0.32]	
	StaB (hours)	-0.17 [-0.39, 0.06]	-0.15 [-0.37, 0.07]	
	Sleep duration (hours)	-0.04 [-0.23, 0.15]	-0.02 [-0.21, 0.16]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)			
	Unopposed Estrogen Usage	-0.15 [-0.33, 0.03]	-0.18 [-0.35, -0.01]	*
	Delayed MHT Initiation	-0.08 [-0.25, 0.10]	--	--
LDL-C	Age (years)	-0.17 [-0.36, 0.02]	-0.17 [-0.35, 0.01]	
	Age at menopause (years)	-0.10 [-0.29, 0.09]	-0.14 [-0.31, 0.03]	
	Spontaneous menopause	0.14 [-0.04, 0.33]	0.15 [-0.03, 0.32]	
	History of VMS	-0.02 [-0.19, 0.14]	-0.03 [-0.19, 0.13]	
	Postsecondary education	0.12 [-0.05, 0.29]	0.10 [-0.06, 0.26]	
	Primary earner status	-0.14 [-0.31, 0.02]	-0.13 [-0.29, 0.03]	
	MVPA (mins)	0.08 [-0.14, 0.29]	0.05 [-0.15, 0.25]	
	StaB (hours)	-0.07 [-0.30, 0.16]	-0.07 [-0.29, 0.15]	
	Sleep duration (hours)	-0.01 [-0.21, 0.18]	0.00 [-0.19, 0.19]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)			
	Unopposed Estrogen Usage	0.08 [-0.11, 0.26]	0.08 [-0.09, 0.25]	
	Delayed MHT Initiation	0.02 [-0.16, 0.20]	--	--
logTG	Age (years)	-0.08 [-0.27, 0.11]	-0.07 [-0.25, 0.11]	
	Age at menopause (years)	-0.29 [-0.48, -0.11]	-0.25 [-0.43, -0.08]	*
	Spontaneous menopause	-0.02 [-0.21, 0.16]	-0.02 [-0.20, 0.16]	
	History of VMS	0.06 [-0.11, 0.22]	0.06 [-0.10, 0.22]	
	Postsecondary education	-0.02 [-0.19, 0.14]	-0.02 [-0.18, 0.14]	
	Primary earner status	-0.03 [-0.19, 0.14]	-0.02 [-0.18, 0.14]	
	MVPA (mins)	-0.12 [-0.33, 0.09]	-0.13 [-0.33, 0.07]	
	StaB (hours)	0.01 [-0.22, 0.24]	-0.01 [-0.23, 0.21]	
	Sleep duration (hours)	-0.02 [-0.21, 0.18]	0.01 [-0.18, 0.20]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)			
	Unopposed Estrogen Usage	0.05 [-0.13, 0.23]	0.10 [-0.07, 0.27]	
	Delayed MHT Initiation	0.06 [-0.11, 0.24]	--	--

logGlucose	Age (years)	0.10 [-0.10, 0.30]	0.20 [0.02, 0.38]	*
	Age at menopause (years)	-0.01 [-0.21, 0.19]	0.18 [0.01, 0.36]	*
	Spontaneous menopause	0.04 [-0.16, 0.23]	-0.10 [-0.27, 0.08]	
	History of VMS	-0.02 [-0.20, 0.15]	-0.06 [-0.22, 0.10]	
	Postsecondary education	-0.01 [-0.18, 0.17]	0.01 [-0.15, 0.17]	
	Primary earner status	0.08 [-0.09, 0.25]	0.07 [-0.09, 0.23]	
	MVPA (mins)	-0.19 [-0.41, 0.03]	-0.16 [-0.37, 0.04]	
	StaB (hours)	-0.13 [-0.37, 0.11]	-0.20 [-0.42, 0.03]	
	Sleep duration (hours)	-0.11 [-0.32, 0.09]	-0.03 [-0.22, 0.15]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)			
	Unopposed Estrogen Usage	0.05 [-0.14, 0.24]	0.10 [-0.08, 0.27]	
	Delayed MHT Initiation	0.03 [-0.16, 0.21]	--	--

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 10e. Sensitivity Analysis: Controlling for MHT timing, route exposure, model fit

Outcome	Block	Sensitivity Analysis: Duration				Objective 2B.3			
		Adj. R ²	Sig. F Change	AIC	ΔAIC	Adj. R ²	Sig. F Change	AIC	ΔAIC
aPWV	Block 1	-0.01	0.61	550.3		-0.02	0.82	589.9	
	Block 2	0.07	< 0.01	540.0	-10.3	0.07	< 0.01	575.8	-14.1
	Block 3	0.17	< 0.01	522.2	-17.9	0.16	< 0.01	559.5	-16.2
AIx75	Block 1	-0.01	0.66	1349.6		-0.02	0.85	1432.1	
	Block 2	-0.03	0.99	1355.5	5.9	-0.03	0.93	1436.0	3.8
	Block 3	-0.02	0.29	1357.6	2.0	-0.02	0.19	1437.0	1.0
SBP	Block 1	-0.01	0.62	1433.3		-0.01	0.56	1517.5	
	Block 2	-0.01	0.49	1436.8	3.4	0.00	0.32	1519.1	1.6
	Block 3	0.03	0.02	1432.5	-4.3	0.04	0.01	1513.6	-5.4
DBP	Block 1	0.02	0.18	1315.8		0.00	0.35	1389.9	
	Block 2	0.00	0.99	1321.7	5.9	-0.01	0.96	1393.8	3.9
	Block 3	0.02	0.13	1321.5	-0.2	0.02	0.06	1392.1	-1.8
logFRS	Block 1	0.00	0.40	269.7		-0.01	0.63	290.3	
	Block 2	0.04	0.03	266.3	-3.5	0.03	0.01	285.2	-5.1
	Block 3	0.09	0.01	259.7	-6.5	0.09	< 0.01	276.0	-9.2
WC	Block 1	0.10	< 0.01	1372.1		0.09	< 0.01	1451.0	
	Block 2	0.09	0.73	1376.8	4.6	0.09	0.36	1452.9	
	Block 3	0.22	< 0.01	1352.8	-24.0	0.20	< 0.01	1430.1	
HDL-C	Block 1	0.05	0.03	168.0		0.03	0.06	178.7	
	Block 2	0.05	0.35	170.5	2.5	0.04	0.21	179.3	0.7
	Block 3	0.07	0.08	169.3	-1.2	0.06	0.10	178.6	-0.7
LDL-C	Block 1	0.04	0.05	415.4		0.04	0.04	437.5	
	Block 2	0.03	0.66	419.7	4.3	0.03	0.77	440.9	3.4
	Block 3	0.04	0.15	420.0	0.3	0.04	0.22	442.3	1.3
logTG	Block 1	0.08	< 0.01	169.7		0.05	0.01	182.5	
	Block 2	0.07	0.82	174.8	5.0	0.05	0.81	186.1	3.6
	Block 3	0.07	0.44	177.9	3.1	0.04	0.47	189.4	3.3
logGlucose	Block 1	0.00	0.50	-246.0		0.04	0.04	-199.4	
	Block 2	-0.01	0.62	-241.9	4.1	0.04	0.38	-197.4	2.0
	Block 3	-0.02	0.83	-236.9	5.0	0.04	0.48	-194.0	3.4

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed

Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates entered

Block 2: Transdermal, Vaginal, delayed MHT initiation entered (Oral = reference)

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 10f. Sensitivity Analysis: Controlling for MHT timing, route exposure, coefficients

Outcome	Predictor	Sensitivity Analysis: Duration		Objective 2B.3	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	0.00 [-0.17, 0.16]		0.01 [-0.14, 0.16]	
	Spontaneous menopause	0.18 [0.03, 0.34]	*	0.12 [-0.03, 0.28]	
	History of VMS	-0.06 [-0.21, 0.08]	*	-0.09 [-0.23, 0.04]	
	Postsecondary education	0.05 [-0.09, 0.19]		0.05 [-0.09, 0.19]	
	Primary earner status	-0.02 [-0.16, 0.12]		-0.02 [-0.16, 0.12]	
	MVPA (mins)	-0.27 [-0.44, -0.10]	*	-0.27 [-0.44, -0.11]	*
	StaB (hours)	0.09 [-0.10, 0.28]		0.07 [-0.11, 0.25]	
	Sleep duration (hours)	-0.08 [-0.23, 0.08]		-0.06 [-0.21, 0.10]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	-0.10 [-0.25, 0.05]		-0.08 [-0.23, 0.07]	
	Vaginal Usage	-0.28 [-0.44, -0.11]		-0.28 [-0.42, -0.13]	*
	Delayed MHT Initiation	0.05 [-0.11, 0.21]		--	--
AIx75	Age at menopause (years)	-0.14 [-0.32, 0.04]		-0.09 [-0.26, 0.07]	
	Spontaneous menopause	0.11 [-0.06, 0.28]		0.07 [-0.10, 0.23]	
	History of VMS	0.03 [-0.12, 0.19]		0.01 [-0.14, 0.16]	
	Postsecondary education	0.01 [-0.15, 0.16]		-0.01 [-0.16, 0.14]	
	Primary earner status	0.02 [-0.13, 0.18]		0.05 [-0.10, 0.20]	
	MVPA (mins)	-0.14 [-0.33, 0.05]		-0.15 [-0.34, 0.03]	
	StaB (hours)	0.03 [-0.18, 0.23]		0.02 [-0.18, 0.22]	
	Sleep duration (hours)	0.01 [-0.17, 0.19]		0.01 [-0.16, 0.18]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.01 [-0.15, 0.18]		0.02 [-0.14, 0.18]	
	Vaginal Usage	0.06 [-0.13, 0.24]		0.01 [-0.16, 0.17]	
	Delayed MHT Initiation	-0.04 [-0.22, 0.14]		--	--
SBP	Age (years)	0.01 [-0.16, 0.17]		0.05 [-0.11, 0.21]	
	Age at menopause (years)	0.02 [-0.16, 0.19]		0.02 [-0.14, 0.17]	
	Spontaneous menopause	0.11 [-0.06, 0.28]		0.06 [-0.10, 0.22]	
	History of VMS	0.07 [-0.09, 0.22]		0.03 [-0.12, 0.18]	
	Postsecondary education	0.04 [-0.11, 0.19]		0.04 [-0.11, 0.19]	
	Primary earner status	-0.08 [-0.23, 0.07]		-0.09 [-0.23, 0.06]	
	MVPA (mins)	-0.26 [-0.45, -0.07]	*	-0.30 [-0.48, -0.12]	*
	StaB (hours)	-0.13 [-0.33, 0.07]		-0.17 [-0.36, 0.03]	
	Sleep duration (hours)	-0.16 [-0.33, 0.01]		-0.12 [-0.29, 0.04]	

Oral Usage (MHT reference group)				
DBP	Transdermal Usage	0.04 [-0.13, 0.20]		0.06 [-0.10, 0.22]
	Vaginal Usage	-0.08 [-0.27, 0.10]		-0.05 [-0.22, 0.11]
	Delayed MHT Initiation	0.09 [-0.09, 0.26]		--
	Age (years)	-0.21 [-0.38, -0.04]	*	-0.19 [-0.35, -0.03]
	Age at menopause (years)	-0.04 [-0.21, 0.14]		-0.02 [-0.17, 0.14]
	Spontaneous menopause	0.17 [0.00, 0.34]		0.13 [-0.03, 0.30]
	History of VMS	0.02 [-0.13, 0.18]		0.00 [-0.15, 0.15]
	Postsecondary education	-0.01 [-0.17, 0.14]		-0.02 [-0.17, 0.13]
	Primary earner status	0.02 [-0.13, 0.18]		0.02 [-0.12, 0.17]
	MVPA (mins)	-0.22 [-0.41, -0.03]	*	-0.25 [-0.43, -0.07]
logFRS	StaB (hours)	-0.16 [-0.36, 0.05]		-0.17 [-0.37, 0.03]
	Sleep duration (hours)	-0.10 [-0.27, 0.07]		-0.08 [-0.25, 0.08]
	Oral Usage (MHT reference group)			
	Transdermal Usage	-0.01 [-0.17, 0.16]		0.02 [-0.14, 0.18]
	Vaginal Usage	0.03 [-0.15, 0.22]		0.03 [-0.14, 0.19]
	Delayed MHT Initiation	0.02 [-0.16, 0.20]		--
	Age at menopause (years)	-0.08 [-0.26, 0.09]		-0.09 [-0.24, 0.06]
	Spontaneous menopause	0.15 [-0.01, 0.31]		0.10 [-0.06, 0.25]
	History of VMS	0.03 [-0.12, 0.18]		-0.01 [-0.15, 0.14]
	Postsecondary education	0.03 [-0.12, 0.18]		0.01 [-0.13, 0.16]
WC	Primary earner status	-0.10 [-0.25, 0.05]		-0.11 [-0.26, 0.03]
	MVPA (mins)	-0.25 [-0.43, -0.07]	*	-0.29 [-0.47, -0.12]
	StaB (hours)	-0.03 [-0.22, 0.16]		-0.05 [-0.24, 0.14]
	Sleep duration (hours)	-0.11 [-0.28, 0.05]		-0.07 [-0.23, 0.09]
	Oral Usage (MHT reference group)			
	Transdermal Usage	0.02 [-0.14, 0.18]		0.04 [-0.11, 0.20]
	Vaginal Usage	-0.20 [-0.38, -0.03]	*	-0.16 [-0.31, 0.00]
	Delayed MHT Initiation	0.11 [-0.06, 0.28]		--
	Age (years)	-0.41 [-0.55, -0.26]	*	-0.38 [-0.52, -0.23]
	Age at menopause (years)	-0.09 [-0.24, 0.07]		-0.05 [-0.20, 0.09]
	Spontaneous menopause	-0.02 [-0.17, 0.13]		-0.03 [-0.18, 0.11]
	History of VMS	-0.01 [-0.14, 0.13]		0.01 [-0.13, 0.14]
	Postsecondary education	-0.12 [-0.26, 0.02]		-0.09 [-0.23, 0.04]
	Primary earner status	0.14 [0.00, 0.27]	*	0.14 [0.00, 0.27]
	MVPA (mins)	-0.33 [-0.50, -0.16]	*	-0.33 [-0.49, -0.16]

	StaB (hours)	0.07 [-0.11, 0.25]		0.04 [-0.14, 0.22]	
	Sleep duration (hours)	-0.10 [-0.26, 0.05]		-0.13 [-0.28, 0.02]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.05 [-0.10, 0.20]		0.09 [-0.06, 0.23]	
	Vaginal Usage	-0.02 [-0.19, 0.14]		-0.01 [-0.16, 0.14]	
	Delayed MHT Initiation	0.01 [-0.15, 0.16]		--	--
HDL-C	Age (years)	0.12 [-0.05, 0.28]		0.11 [-0.04, 0.27]	
	Age at menopause (years)	0.04 [-0.13, 0.22]		0.02 [-0.13, 0.18]	
	Spontaneous menopause	0.22 [0.05, 0.38]	*	0.20 [0.04, 0.36]	*
	History of VMS	-0.06 [-0.21, 0.09]		-0.07 [-0.22, 0.08]	
	Postsecondary education	0.13 [-0.02, 0.28]		0.12 [-0.02, 0.27]	
	Primary earner status	-0.05 [-0.20, 0.10]		-0.06 [-0.20, 0.09]	
	MVPA (mins)	0.08 [-0.10, 0.27]		0.08 [-0.10, 0.26]	
	StaB (hours)	-0.16 [-0.36, 0.04]		-0.14 [-0.34, 0.05]	
	Sleep duration (hours)	-0.05 [-0.22, 0.11]		-0.04 [-0.20, 0.12]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.09 [-0.07, 0.25]		0.06 [-0.09, 0.22]	
	Vaginal Usage	-0.06 [-0.25, 0.12]		-0.10 [-0.27, 0.06]	
	Delayed MHT Initiation	-0.04 [-0.21, 0.14]		--	--
LDL-C	Age (years)	-0.13 [-0.30, 0.03]		-0.14 [-0.30, 0.02]	
	Age at menopause (years)	-0.05 [-0.23, 0.12]		-0.13 [-0.28, 0.03]	
	Spontaneous menopause	0.09 [-0.08, 0.26]		0.11 [-0.06, 0.27]	
	History of VMS	-0.06 [-0.21, 0.10]		-0.06 [-0.21, 0.09]	
	Postsecondary education	0.07 [-0.08, 0.22]		0.05 [-0.09, 0.20]	
	Primary earner status	-0.12 [-0.27, 0.03]		-0.12 [-0.27, 0.03]	
	MVPA (mins)	0.13 [-0.05, 0.32]		0.11 [-0.07, 0.29]	
	StaB (hours)	-0.08 [-0.28, 0.12]		-0.07 [-0.27, 0.12]	
	Sleep duration (hours)	-0.01 [-0.18, 0.16]		0.01 [-0.16, 0.18]	
	Oral Usage (MHT reference group)				
	Vaginal Usage	-0.05 [-0.23, 0.14]		0.05 [-0.11, 0.21]	
	Transdermal Usage	0.05 [-0.12, 0.21]		-0.02 [-0.18, 0.15]	
	Delayed MHT Initiation	0.11 [-0.06, 0.29]		--	--
logTG	Age (years)	-0.09 [-0.25, 0.08]		-0.08 [-0.24, 0.08]	
	Age at menopause (years)	-0.25 [-0.43, -0.08]	*	-0.22 [-0.38, -0.06]	*
	Spontaneous menopause	-0.09 [-0.25, 0.08]		-0.09 [-0.26, 0.07]	
	History of VMS	0.01 [-0.14, 0.16]		0.00 [-0.15, 0.15]	

	Postsecondary education	-0.08 [-0.23, 0.08]	-0.07 [-0.22, 0.08]	
	Primary earner status	0.01 [-0.14, 0.16]	0.01 [-0.13, 0.16]	
	MVPA (mins)	-0.12 [-0.30, 0.07]	-0.12 [-0.30, 0.06]	
	StaB (hours)	0.02 [-0.18, 0.21]	0.00 [-0.20, 0.19]	
	Sleep duration (hours)	-0.03 [-0.20, 0.14]	-0.01 [-0.17, 0.16]	
	Oral Usage (MHT reference group)			
	Transdermal Usage	-0.03 [-0.19, 0.13]	-0.01 [-0.17, 0.15]	
	Vaginal Usage	0.03 [-0.15, 0.21]	0.06 [-0.11, 0.22]	
	Delayed MHT Initiation	0.05 [-0.13, 0.22]	--	--
logGlucose	Age (years)	0.12 [-0.05, 0.29]	0.18 [0.02, 0.34]	*
	Age at menopause (years)	0.03 [-0.15, 0.21]	0.16 [0.00, 0.31]	*
	Spontaneous menopause	0.01 [-0.16, 0.19]	-0.08 [-0.25, 0.08]	
	History of VMS	-0.02 [-0.18, 0.14]	-0.05 [-0.20, 0.10]	
	Postsecondary education	0.04 [-0.12, 0.20]	0.04 [-0.11, 0.19]	
	Primary earner status	0.07 [-0.08, 0.23]	0.07 [-0.08, 0.21]	
	MVPA (mins)	-0.08 [-0.28, 0.11]	-0.11 [-0.29, 0.07]	
	StaB (hours)	-0.07 [-0.28, 0.14]	-0.13 [-0.33, 0.06]	
	Sleep duration (hours)	-0.05 [-0.23, 0.13]	-0.01 [-0.17, 0.16]	
	Oral Usage (MHT reference group)			
	Transdermal Usage	-0.01 [-0.18, 0.15]	0.05 [-0.11, 0.21]	
	Vaginal Usage	-0.11 [-0.31, 0.08]	-0.06 [-0.23, 0.10]	
	Delayed MHT Initiation	0.05 [-0.13, 0.23]	--	--

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 11a. Sensitivity Analysis: Controlling for experience of APOs, history exposure, model fit

Outcome	Block	Sensitivity Analysis: APOs				Objective 2B.1			
		Adj. R ²	Sig. F Change	AIC	ΔAIC	Adj. R ²	Sig. F Change	AIC	ΔAIC
aPWV	Block 1	-0.02	0.86	771.0		-0.01	0.89	769.9	
	Block 2	0.08	< 0.01	748.0	-23.0	0.08	< 0.01	747.4	-22.6
	Block 3	0.17	< 0.01	727.5	-20.5	0.17	< 0.01	725.9	-21.5
AIx75	Block 1	-0.02	0.86	1816.61		-0.01	0.77	1814.6	
	Block 2	0.00	0.07	1815.17	-1.4	0.00	0.07	1813.2	-1.4
	Block 3	0.01	0.10	1814.67	-0.5	0.01	0.10	1812.7	-0.4
SBP	Block 1	0.02	0.12	1941.01		0.02	0.08	1939.3	
	Block 2	0.03	0.06	1939.23	-1.8	0.03	0.06	1937.7	-1.7
	Block 3	0.06	0.02	1935.07	-4.2	0.06	0.02	1933.1	-4.5
DBP	Block 1	-0.01	0.74	1800.75		-0.01	0.65	1798.9	
	Block 2	0.00	0.05	1798.81	-1.9	0.00	0.05	1797.0	-1.9
	Block 3	0.01	0.14	1799.12	0.3	0.02	0.13	1797.2	0.1
logFRS	Block 1	-0.01	0.57	380.68		0.00	0.47	378.9	
	Block 2	0.05	< 0.01	367.34	-13.3	0.06	< 0.01	365.5	-13.4
	Block 3	0.11	< 0.01	356.45	-10.9	0.11	< 0.01	355.4	-10.1
WC	Block 1	0.06	0.01	1871.28		0.06	< 0.01	1869.3	
	Block 2	0.07	0.02	1867.65	-3.6	0.08	0.02	1865.7	-3.6
	Block 3	0.18	< 0.01	1842.80	-24.8	0.18	< 0.01	1840.9	-24.8
HDL-C	Block 1	0.03	0.06	286.25		0.03	0.04	284.5	
	Block 2	0.02	0.94	288.24	2.0	0.03	0.96	286.5	2.0
	Block 3	0.04	0.08	287.26	-1.0	0.04	0.09	285.7	-0.8
LDL-C	Block 1	0.03	0.06	568.04		0.02	0.08	568.6	
	Block 2	0.03	0.53	569.62	1.6	0.02	0.48	570.1	1.5
	Block 3	0.03	0.26	571.38	1.8	0.03	0.24	571.7	1.6
logTG	Block 1	0.05	0.01	241.93		0.05	0.01	242.1	
	Block 2	0.05	0.91	243.92	2.0	0.04	0.86	244.1	2.0
	Block 3	0.06	0.06	242.25	-1.7	0.05	0.11	243.8	-0.3
logGlucose	Block 1	0.03	0.048	-280.70		0.03	0.03	-282.5	
	Block 2	0.03	0.20	-280.44	0.3	0.04	0.19	-282.3	0.2
	Block 3	0.03	0.38	-277.64	2.8	0.04	0.41	-279.3	3.0

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed

Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Sensitivity Analysis N=214

Block 1: Covariates + APOs entered

Block 2: Current usage (Former usage = reference)

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 11b. Sensitivity Analysis: Controlling for experience of APOs, history exposure, coefficients

Outcome	Predictor	Sensitivity Analysis: APOs		Objective 2B.1	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	-0.03 [-0.16, 0.09]		-0.03 [-0.16, 0.10]	
	Spontaneous menopause	0.07 [-0.06, 0.20]		0.07 [-0.06, 0.20]	
	History of APOs	-0.04 [-0.16, 0.08]		--	
	History of VMS	-0.05 [-0.17, 0.07]		-0.05 [-0.17, 0.07]	
	Postsecondary education	-0.01 [-0.13, 0.11]		0.00 [-0.12, 0.12]	
	Primary earner status	0.00 [-0.11, 0.12]		0.00 [-0.12, 0.12]	
	MVPA (mins)	-0.25 [-0.40, -0.11]	*	-0.26 [-0.40, -0.12]	*
	StaB (hours)	0.09 [-0.06, 0.25]		0.09 [-0.06, 0.24]	
	Sleep duration (hours)	-0.02 [-0.15, 0.12]		-0.01 [-0.15, 0.12]	
	Former Usage (MHT reference group)				
	Current Usage	-0.28 [-0.40, -0.16]	*	-0.28 [-0.39, -0.16]	*
AIx75	Age at menopause (years)	-0.08 [-0.22, 0.07]		-0.08 [-0.22, 0.06]	
	Spontaneous menopause	0.01 [-0.13, 0.15]		0.01 [-0.13, 0.15]	
	History of APOs	0.02 [-0.11, 0.15]		--	--
	History of VMS	-0.02 [-0.16, 0.11]		-0.02 [-0.15, 0.11]	
	Postsecondary education	-0.03 [-0.16, 0.10]		-0.03 [-0.16, 0.10]	
	Primary earner status	0.04 [-0.09, 0.17]		0.04 [-0.09, 0.17]	
	MVPA (mins)	-0.12 [-0.27, 0.04]		-0.11 [-0.27, 0.04]	
	StaB (hours)	0.08 [-0.09, 0.24]		0.08 [-0.09, 0.24]	
	Sleep duration (hours)	0.06 [-0.09, 0.20]		0.06 [-0.09, 0.20]	
	Former Usage (MHT reference group)				
	Current Usage	-0.10 [-0.23, 0.03]		-0.10 [-0.23, 0.03]	
SBP	Age (years)	0.13 [-0.01, 0.27]		0.13 [-0.01, 0.27]	
	Age at menopause (years)	-0.02 [-0.15, 0.12]		-0.02 [-0.15, 0.12]	
	Spontaneous menopause	-0.02 [-0.16, 0.12]		-0.02 [-0.16, 0.12]	
	History of APOs	-0.02 [-0.14, 0.11]		--	--
	History of VMS	0.05 [-0.08, 0.18]		0.05 [-0.07, 0.18]	
	Postsecondary education	0.01 [-0.12, 0.14]		0.01 [-0.12, 0.14]	
	Primary earner status	-0.07 [-0.19, 0.06]		-0.07 [-0.19, 0.06]	
	MVPA (mins)	-0.24 [-0.39, -0.09]	*	-0.24 [-0.39, -0.09]	*
	StaB (hours)	-0.18 [-0.34, -0.01]	*	-0.18 [-0.35, -0.02]	*
	Sleep duration (hours)	-0.07 [-0.21, 0.07]		-0.07 [-0.21, 0.07]	
	Former Usage (MHT reference group)				

DBP	Current Usage	-0.13 [-0.27, 0.00]	*	-0.13 [-0.27, 0.00]	*
	Age (years)	-0.14 [-0.28, 0.01]		-0.14 [-0.28, 0.01]	
	Age at menopause (years)	-0.07 [-0.21, 0.07]		-0.07 [-0.21, 0.07]	
	Spontaneous menopause	0.06 [-0.08, 0.20]		0.06 [-0.08, 0.20]	
	History of APOs	-0.01 [-0.14, 0.12]		--	--
	History of VMS	0.02 [-0.11, 0.15]		0.02 [-0.11, 0.15]	
	Postsecondary education	-0.02 [-0.15, 0.12]		-0.02 [-0.15, 0.12]	
	Primary earner status	0.01 [-0.12, 0.14]		0.01 [-0.12, 0.14]	
	MVPA (mins)	-0.15 [-0.31, 0.00]		-0.16 [-0.31, 0.00]	
	StaB (hours)	-0.18 [-0.35, -0.01]	*	-0.18 [-0.35, -0.01]	*
	Sleep duration (hours)	-0.04 [-0.19, 0.10]		-0.04 [-0.18, 0.10]	
Former Usage (MHT reference group)					
logFRS	Current Usage	-0.14 [-0.28, 0.00]	*	-0.14 [-0.28, 0.00]	*
	Age at menopause (years)	-0.10 [-0.23, 0.04]		-0.10 [-0.23, 0.03]	
	Spontaneous menopause	0.01 [-0.12, 0.15]		0.02 [-0.12, 0.15]	
	History of APOs	0.06 [-0.06, 0.19]		--	--
	History of VMS	0.02 [-0.11, 0.14]		0.02 [-0.11, 0.14]	
	Postsecondary education	-0.02 [-0.15, 0.10]		-0.03 [-0.15, 0.10]	
	Primary earner status	-0.06 [-0.18, 0.06]		-0.06 [-0.18, 0.06]	
	MVPA (mins)	-0.26 [-0.41, -0.12]	*	-0.25 [-0.40, -0.11]	*
	StaB (hours)	-0.02 [-0.17, 0.14]		-0.01 [-0.17, 0.15]	
	Sleep duration (hours)	-0.01 [-0.14, 0.13]		-0.01 [-0.15, 0.13]	
Former Usage (MHT reference group)					
WC	Current Usage	-0.22 [-0.35, -0.10]	*	-0.23 [-0.35, -0.10]	*
	Age (years)	-0.33 [-0.46, -0.20]	*	-0.33 [-0.46, -0.20]	*
	Age at menopause (years)	-0.03 [-0.16, 0.09]		-0.04 [-0.16, 0.09]	
	Spontaneous menopause	-0.07 [-0.20, 0.06]		-0.07 [-0.20, 0.06]	
	History of APOs	0.01 [-0.10, 0.13]		--	--
	History of VMS	0.04 [-0.08, 0.16]		0.04 [-0.08, 0.16]	
	Postsecondary education	-0.12 [-0.24, 0.00]	*	-0.12 [-0.24, 0.00]	*
	Primary earner status	0.14 [0.02, 0.26]	*	0.14 [0.02, 0.26]	*
	MVPA (mins)	-0.31 [-0.46, -0.17]	*	-0.31 [-0.45, -0.17]	*
	StaB (hours)	0.05 [-0.11, 0.20]		0.05 [-0.11, 0.20]	
	Sleep duration (hours)	-0.09 [-0.22, 0.05]		-0.09 [-0.22, 0.04]	
	Former Usage (MHT reference group)				
	Current Usage	-0.15 [-0.27, -0.02]	*	-0.15 [-0.27, -0.03]	*

HDL-C	Age (years)	0.06 [-0.08, 0.20]		0.06 [-0.08, 0.20]	
	Age at menopause (years)	0.01 [-0.13, 0.15]		0.01 [-0.12, 0.15]	
	Spontaneous menopause	0.19 [0.05, 0.33]	*	0.18 [0.04, 0.32]	*
	History of APOs	-0.04 [-0.17, 0.09]		--	--
	History of VMS	-0.04 [-0.17, 0.09]		-0.04 [-0.17, 0.09]	
	Postsecondary education	0.08 [-0.05, 0.21]		0.09 [-0.04, 0.22]	
	Primary earner status	-0.05 [-0.18, 0.07]		-0.06 [-0.18, 0.07]	
	MVPA (mins)	0.09 [-0.06, 0.25]		0.08 [-0.07, 0.24]	
	StaB (hours)	-0.11 [-0.28, 0.05]		-0.12 [-0.28, 0.05]	
	Sleep duration (hours)	0.01 [-0.13, 0.15]		0.01 [-0.13, 0.15]	
	Former Usage (MHT reference group)				
	Current Usage	-0.01 [-0.15, 0.12]		-0.01 [-0.14, 0.12]	
LDL-C	Age (years)	-0.14 [-0.29, 0.00]	*	-0.15 [-0.29, -0.01]	*
	Age at menopause (years)	-0.08 [-0.22, 0.06]		-0.09 [-0.22, 0.05]	
	Spontaneous menopause	0.06 [-0.08, 0.20]		0.07 [-0.08, 0.21]	
	History of APOs	0.10 [-0.03, 0.23]		--	--
	History of VMS	-0.05 [-0.18, 0.08]		-0.05 [-0.18, 0.08]	
	Postsecondary education	0.04 [-0.09, 0.17]		0.03 [-0.10, 0.16]	
	Primary earner status	-0.07 [-0.19, 0.06]		-0.06 [-0.19, 0.07]	
	MVPA (mins)	0.07 [-0.09, 0.22]		0.08 [-0.07, 0.24]	
	StaB (hours)	-0.07 [-0.24, 0.10]		-0.06 [-0.23, 0.10]	
	Sleep duration (hours)	0.05 [-0.09, 0.19]		0.04 [-0.10, 0.19]	
	Former Usage (MHT reference group)				
	Current Usage	-0.05 [-0.18, 0.09]		-0.05 [-0.19, 0.08]	
logTG	Age (years)	-0.08 [-0.22, 0.06]		-0.08 [-0.22, 0.06]	
	Age at menopause (years)	-0.17 [-0.31, -0.04]	*	-0.18 [-0.32, -0.05]	*
	Spontaneous menopause	-0.09 [-0.23, 0.05]		-0.08 [-0.22, 0.06]	
	History of APOs	0.12 [-0.01, 0.25]		--	
	History of VMS	-0.01 [-0.14, 0.12]		-0.01 [-0.14, 0.12]	
	Postsecondary education	-0.06 [-0.19, 0.07]		-0.07 [-0.20, 0.06]	
	Primary earner status	0.06 [-0.07, 0.18]		0.06 [-0.06, 0.19]	
	MVPA (mins)	-0.18 [-0.33, -0.02]	*	-0.16 [-0.31, -0.01]	*
	StaB (hours)	0.00 [-0.17, 0.16]		0.01 [-0.16, 0.17]	
	Sleep duration (hours)	0.04 [-0.10, 0.18]		0.03 [-0.11, 0.17]	
	Former Usage (MHT reference group)				
	Current Usage	0.00 [-0.14, 0.13]		-0.01 [-0.14, 0.12]	

logGlucose	Age (years)	0.16 [0.01, 0.30]	*	0.16 [0.01, 0.30]	*
	Age at menopause (years)	0.16 [0.02, 0.29]	*	0.15 [0.01, 0.29]	*
	Spontaneous menopause	-0.12 [-0.26, 0.02]		-0.12 [-0.26, 0.02]	
	History of APOs	0.04 [-0.09, 0.17]		--	
	History of VMS	-0.03 [-0.16, 0.10]		-0.03 [-0.16, 0.10]	
	Postsecondary education	0.03 [-0.10, 0.16]		0.03 [-0.10, 0.16]	
	Primary earner status	0.04 [-0.09, 0.17]		0.04 [-0.09, 0.17]	
	MVPA (mins)	-0.13 [-0.28, 0.03]		-0.12 [-0.27, 0.03]	
	StaB (hours)	-0.12 [-0.29, 0.05]		-0.12 [-0.28, 0.05]	
	Sleep duration (hours)	-0.05 [-0.20, 0.09]		-0.06 [-0.20, 0.09]	
Former Usage (MHT reference group)					
	Current Usage	-0.09 [-0.23, 0.04]		-0.09 [-0.23, 0.04]	

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 11c. Sensitivity Analysis: Controlling for experience of APOs, type exposure, model fit

Outcome	Block	Sensitivity Analysis: APOs				Objective 2B.2			
		Adj. R ²	Sig. F Change	AIC	ΔAIC	Adj. R ²	Sig. F Change	AIC	ΔAIC
aPWV	Block 1	0.00	0.47	497.8		-0.02	0.92	500.0	
	Block 2	0.07	< 0.01	486.6	-11.2	0.05	< 0.01	489.5	-10.5
	Block 3	0.21	< 0.01	464.8	-21.7	0.21	< 0.01	464.9	-24.6
AIx75	Block 1	-0.03	0.94	1207.99		-0.02	0.88	1206.0	
	Block 2	-0.02	0.17	1208.05	0.1	-0.02	0.17	1206.1	0.1
	Block 3	-0.01	0.25	1209.59	1.5	-0.01	0.24	1207.6	1.5
SBP	Block 1	0.02	0.21	1260.79		0.00	0.36	1262.0	
	Block 2	0.01	0.55	1262.41	1.6	0.00	0.61	1263.8	1.7
	Block 3	0.05	0.03	1258.84	-3.6	0.05	0.01	1258.3	-5.5
DBP	Block 1	0.01	0.28	1153.98		0.00	0.39	1154.4	
	Block 2	0.01	0.43	1155.33	1.3	0.00	0.49	1155.9	1.5
	Block 3	0.02	0.20	1156.33	1.0	0.02	0.12	1155.6	-0.3
logFRS	Block 1	-0.01	0.55	246.92		-0.01	0.67	246.7	
	Block 2	0.00	0.18	246.98	0.1	-0.01	0.18	246.9	0.1
	Block 3	0.09	< 0.01	235.32	-11.7	0.09	< 0.01	233.6	-13.3
WC	Block 1	0.08	0.01	1213.25		0.08	< 0.01	1211.5	
	Block 2	0.07	0.72	1215.12	1.9	0.08	0.70	1213.4	
	Block 3	0.14	< 0.01	1206.74	-8.4	0.14	< 0.01	1204.7	
HDL-C	Block 1	0.02	0.16	167.32		0.03	0.11	165.6	
	Block 2	0.05	0.03	163.99	-3.3	0.06	0.02	162.2	-3.4
	Block 3	0.08	0.07	162.49	-1.5	0.08	0.07	160.5	-1.6
LDL-C	Block 1	0.06	0.02	357.47		0.07	0.01	355.7	
	Block 2	0.06	0.40	358.71	1.2	0.07	0.42	357.0	1.3
	Block 3	0.05	0.72	363.27	4.6	0.06	0.71	361.5	4.5
logTG	Block 1	0.05	0.05	162.81		0.05	0.03	161.0	
	Block 2	0.05	0.23	163.28	0.5	0.05	0.24	161.5	0.5
	Block 3	0.05	0.47	166.54	3.3	0.05	0.53	165.1	3.6
logGlucose	Block 1	0.03	0.10	-186.86		0.04	0.06	-188.7	
	Block 2	0.03	0.36	-185.77	1.1	0.04	0.37	-187.5	1.1
	Block 3	0.04	0.22	-184.56	1.2	0.04	0.27	-185.7	1.8

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed

Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates + APOs entered

Block 2: Unopposed Estrogen (Combined Estrogen-Progestosterone= reference)

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 11d. Sensitivity Analysis: Controlling for experience of APOs, type exposure, coefficients

Outcome	Predictor	Sensitivity Analysis: APOs		Objective 2B.2	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	-0.02 [-0.18, 0.14]		-0.02 [-0.18, 0.14]	
	Spontaneous menopause	0.03 [-0.13, 0.20]		0.02 [-0.14, 0.18]	
	History of APOs	-0.11 [-0.26, 0.04]		--	--
	History of VMS	-0.12 [-0.26, 0.03]		-0.11 [-0.26, 0.03]	
	Postsecondary education	-0.02 [-0.17, 0.13]		-0.01 [-0.16, 0.14]	
	Primary earner status	-0.01 [-0.16, 0.13]		-0.02 [-0.17, 0.13]	
	MVPA (mins)	-0.34 [-0.52, -0.15]	*	-0.37 [-0.55, -0.19]	*
	StaB (hours)	0.07 [-0.13, 0.28]		0.05 [-0.15, 0.26]	
	Sleep duration (hours)	-0.08 [-0.26, 0.09]		-0.09 [-0.26, 0.08]	
	Combined Estrogen-Progesterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	-0.28 [-0.43, -0.13]	*	-0.28 [-0.43, -0.12]	*
AIx75	Age at menopause (years)	-0.13 [-0.31, 0.05]		-0.13 [-0.31, 0.05]	
	Spontaneous menopause	0.05 [-0.14, 0.23]		0.05 [-0.13, 0.23]	
	History of APOs	0.02 [-0.15, 0.19]		--	--
	History of VMS	-0.03 [-0.19, 0.14]		-0.03 [-0.19, 0.13]	
	Postsecondary education	0.00 [-0.17, 0.16]		0.00 [-0.17, 0.16]	
	Primary earner status	0.00 [-0.16, 0.17]		0.00 [-0.16, 0.17]	
	MVPA (mins)	-0.16 [-0.37, 0.05]		-0.15 [-0.36, 0.05]	
	StaB (hours)	0.02 [-0.21, 0.25]		0.03 [-0.20, 0.25]	
	Sleep duration (hours)	-0.01 [-0.20, 0.18]		-0.01 [-0.20, 0.18]	
	Combined Estrogen-Progesterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	-0.11 [-0.28, 0.06]		-0.11 [-0.28, 0.06]	
SBP	Age (years)	0.06 [-0.12, 0.24]		0.07 [-0.11, 0.25]	
	Age at menopause (years)	0.04 [-0.13, 0.21]		0.04 [-0.13, 0.21]	
	Spontaneous menopause	0.03 [-0.15, 0.21]		0.02 [-0.16, 0.20]	
	History of APOs	-0.10 [-0.26, 0.07]		--	--
	History of VMS	0.01 [-0.15, 0.18]		0.02 [-0.14, 0.18]	
	Postsecondary education	0.04 [-0.12, 0.21]		0.06 [-0.11, 0.22]	
	Primary earner status	-0.11 [-0.27, 0.05]		-0.12 [-0.28, 0.04]	
	MVPA (mins)	-0.32 [-0.52, -0.11]	*	-0.34 [-0.55, -0.14]	*
	StaB (hours)	-0.18 [-0.41, 0.04]		-0.20 [-0.42, 0.02]	
	Sleep duration (hours)	-0.10 [-0.28, 0.09]		-0.10 [-0.29, 0.09]	

	Combined Estrogen-Progestosterone Usage (MHT reference group)			
DBP	Unopposed Estrogen Usage	-0.05 [-0.22, 0.13]	-0.04 [-0.21, 0.13]	
	Age (years)	-0.24 [-0.42, -0.06]	* -0.23 [-0.41, -0.05]	*
	Age at menopause (years)	0.02 [-0.15, 0.20]	0.02 [-0.15, 0.20]	
	Spontaneous menopause	0.14 [-0.04, 0.32]	0.13 [-0.05, 0.31]	
	History of APOs	-0.09 [-0.26, 0.08]	--	--
	History of VMS	-0.03 [-0.20, 0.13]	-0.03 [-0.19, 0.14]	
	Postsecondary education	-0.02 [-0.18, 0.15]	-0.01 [-0.17, 0.16]	
	Primary earner status	0.01 [-0.16, 0.17]	0.00 [-0.16, 0.16]	
	MVPA (mins)	-0.23 [-0.44, -0.02]	* -0.25 [-0.46, -0.05]	*
	StaB (hours)	-0.12 [-0.35, 0.11]	-0.13 [-0.36, 0.09]	
	Sleep duration (hours)	-0.03 [-0.22, 0.16]	-0.04 [-0.23, 0.15]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)			
logFRS	Unopposed Estrogen Usage	-0.06 [-0.24, 0.11]	-0.06 [-0.23, 0.12]	
	Age at menopause (years)	-0.11 [-0.27, 0.06]	-0.11 [-0.27, 0.06]	
	Spontaneous menopause	0.06 [-0.12, 0.23]	0.05 [-0.12, 0.23]	
	History of APOs	-0.04 [-0.20, 0.12]	--	--
	History of VMS	0.00 [-0.16, 0.15]	0.00 [-0.16, 0.15]	
	Postsecondary education	0.01 [-0.15, 0.17]	0.01 [-0.14, 0.17]	
	Primary earner status	-0.15 [-0.30, 0.01]	-0.15 [-0.31, 0.01]	
	MVPA (mins)	-0.36 [-0.56, -0.16]	* -0.37 [-0.56, -0.17]	*
	StaB (hours)	-0.05 [-0.27, 0.17]	-0.06 [-0.27, 0.16]	
	Sleep duration (hours)	-0.08 [-0.26, 0.10]	-0.08 [-0.27, 0.10]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)			
WC	Unopposed Estrogen Usage	-0.09 [-0.26, 0.07]	-0.09 [-0.25, 0.07]	
	Age (years)	-0.40 [-0.57, -0.23]	* -0.40 [-0.57, -0.23]	*
	Age at menopause (years)	-0.02 [-0.19, 0.14]	-0.02 [-0.19, 0.14]	
	Spontaneous menopause	-0.09 [-0.26, 0.08]	-0.09 [-0.26, 0.08]	
	History of APOs	0.00 [-0.16, 0.15]		
	History of VMS	0.00 [-0.16, 0.15]	0.00 [-0.15, 0.15]	
	Postsecondary education	-0.07 [-0.22, 0.09]	-0.07 [-0.22, 0.09]	
	Primary earner status	0.11 [-0.04, 0.27]	0.11 [-0.04, 0.27]	
	MVPA (mins)	-0.25 [-0.45, -0.05]	* -0.25 [-0.44, -0.06]	*
	StaB (hours)	0.06 [-0.15, 0.27]	0.06 [-0.15, 0.27]	
	Sleep duration (hours)	-0.10 [-0.28, 0.08]	-0.10 [-0.28, 0.08]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)	--	--	--

HDL-C	Unopposed Estrogen Usage	0.01 [-0.16, 0.17]		0.01 [-0.16, 0.17]	
	Age (years)	0.11 [-0.07, 0.28]		0.11 [-0.07, 0.28]	
	Age at menopause (years)	0.04 [-0.13, 0.21]		0.04 [-0.13, 0.21]	
	Spontaneous menopause	0.10 [-0.08, 0.28]		0.10 [-0.07, 0.28]	
	History of APOs	0.02 [-0.14, 0.18]			
	History of VMS	-0.05 [-0.21, 0.11]		-0.05 [-0.21, 0.11]	
	Postsecondary education	0.12 [-0.04, 0.28]		0.12 [-0.04, 0.28]	
	Primary earner status	-0.08 [-0.23, 0.08]		-0.08 [-0.23, 0.08]	
	MVPA (mins)	0.11 [-0.09, 0.32]		0.12 [-0.08, 0.32]	
	StaB (hours)	-0.15 [-0.37, 0.07]		-0.15 [-0.37, 0.07]	
	Sleep duration (hours)	-0.02 [-0.21, 0.16]		-0.02 [-0.21, 0.16]	
Combined Estrogen-Progestosterone Usage (MHT reference group)				--	--
LDL-C	Unopposed Estrogen Usage	-0.18 [-0.35, 0.00]	*	-0.18 [-0.35, -0.01]	*
	Age (years)	-0.17 [-0.35, 0.01]		-0.17 [-0.35, 0.01]	
	Age at menopause (years)	-0.14 [-0.31, 0.03]		-0.14 [-0.31, 0.03]	
	Spontaneous menopause	0.14 [-0.04, 0.32]		0.15 [-0.03, 0.32]	
	History of APOs	0.04 [-0.13, 0.20]		--	--
	History of VMS	-0.03 [-0.19, 0.13]		-0.03 [-0.19, 0.13]	
	Postsecondary education	0.10 [-0.06, 0.27]		0.10 [-0.06, 0.26]	
	Primary earner status	-0.14 [-0.30, 0.02]		-0.13 [-0.29, 0.03]	
	MVPA (mins)	0.04 [-0.17, 0.25]		0.05 [-0.15, 0.25]	
	StaB (hours)	-0.07 [-0.30, 0.15]		-0.07 [-0.29, 0.15]	
	Sleep duration (hours)	0.00 [-0.19, 0.19]		0.00 [-0.19, 0.19]	
Combined Estrogen-Progestosterone Usage (MHT reference group)					
logTG	Unopposed Estrogen Usage	0.08 [-0.09, 0.26]		0.08 [-0.09, 0.25]	
	Age (years)	-0.06 [-0.24, 0.12]		-0.07 [-0.25, 0.11]	
	Age at menopause (years)	-0.25 [-0.43, -0.08]	*	-0.25 [-0.43, -0.08]	*
	Spontaneous menopause	-0.03 [-0.21, 0.15]		-0.02 [-0.20, 0.16]	
	History of APOs	0.06 [-0.10, 0.23]		--	--
	History of VMS	0.06 [-0.10, 0.22]		0.06 [-0.10, 0.22]	
	Postsecondary education	-0.02 [-0.18, 0.15]		-0.02 [-0.18, 0.14]	
	Primary earner status	-0.03 [-0.19, 0.13]		-0.02 [-0.18, 0.14]	
	MVPA (mins)	-0.15 [-0.35, 0.06]		-0.13 [-0.33, 0.07]	
	StaB (hours)	-0.02 [-0.24, 0.21]		-0.01 [-0.23, 0.21]	
	Sleep duration (hours)	0.01 [-0.18, 0.20]		0.01 [-0.18, 0.20]	
Combined Estrogen-Progestosterone Usage (MHT reference group)					

logGlucose	Unopposed Estrogen Usage	0.10 [-0.07, 0.28]		0.10 [-0.07, 0.27]	
	Age (years)	0.21 [0.03, 0.39]	*	0.20 [0.02, 0.38]	*
	Age at menopause (years)	0.18 [0.01, 0.36]	*	0.18 [0.01, 0.36]	*
	Spontaneous menopause	-0.10 [-0.28, 0.08]		-0.10 [-0.27, 0.08]	
	History of APOs	0.07 [-0.09, 0.24]		--	--
	History of VMS	-0.05 [-0.22, 0.11]		-0.06 [-0.22, 0.10]	
	Postsecondary education	0.02 [-0.14, 0.18]		0.01 [-0.15, 0.17]	
	Primary earner status	0.07 [-0.10, 0.23]		0.07 [-0.09, 0.23]	
	MVPA (mins)	-0.18 [-0.39, 0.03]		-0.16 [-0.37, 0.04]	
	StaB (hours)	-0.21 [-0.43, 0.02]		-0.20 [-0.42, 0.03]	
	Sleep duration (hours)	-0.04 [-0.23, 0.15]		-0.03 [-0.22, 0.15]	
	Combined Estrogen-Progestosterone Usage (MHT reference group)				
	Unopposed Estrogen Usage	0.10 [-0.07, 0.27]		0.10 [-0.08, 0.27]	
Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose					

Appendix Table 11e. Sensitivity Analysis: Controlling for experience of APOs, route exposure, model fit

Outcome	Block	Sensitivity Analysis: APOs				Objective 2B.3			
		Adj. R ²	Sig. F Change	AIC	ΔAIC	Adj. R ²	Sig. F Change	AIC	ΔAIC
aPWV	Block 1	0.00	0.52	588.8		-0.02	0.82	589.9	
	Block 2	0.08	< 0.01	573.8	-14.9	0.07	< 0.01	575.8	-14.1
	Block 3	0.16	< 0.01	559.9	-13.9	0.16	< 0.01	559.5	-16.2
AIx75	Block 1	-0.02	0.92	1434.1		-0.02	0.85	1432.1	
	Block 2	-0.03	0.93	1437.9	3.8	-0.03	0.93	1436.0	3.8
	Block 3	-0.02	0.19	1438.8	0.9	-0.02	0.19	1437.0	1.0
SBP	Block 1	0.00	0.46	1517.5		-0.01	0.56	1517.5	
	Block 2	0.00	0.28	1518.8	1.3	0.00	0.32	1519.1	1.6
	Block 3	0.04	0.03	1514.9	-3.9	0.04	0.01	1513.6	-5.4
DBP	Block 1	0.01	0.34	1390.6		0.00	0.35	1389.9	
	Block 2	-0.01	0.95	1394.5	3.9	-0.01	0.96	1393.8	3.9
	Block 3	0.01	0.10	1393.7	-0.8	0.02	0.06	1392.1	-1.8
logFRS	Block 1	-0.01	0.62	291.3		-0.01	0.63	290.3	
	Block 2	0.03	0.01	285.8	-5.4	0.03	0.01	285.2	-5.1
	Block 3	0.09	< 0.01	277.9	-7.9	0.09	< 0.01	276.0	-9.2
WC	Block 1	0.09	< 0.01	1451.9		0.09	< 0.01	1451.0	
	Block 2	0.09	0.33	1453.6	1.7	0.09	0.36	1452.9	
	Block 3	0.20	< 0.01	1431.9	-21.7	0.20	< 0.01	1430.1	
HDL-C	Block 1	0.03	0.08	180.1		0.03	0.06	178.7	
	Block 2	0.04	0.22	180.9	0.8	0.04	0.21	179.3	0.7
	Block 3	0.05	0.11	180.4	-0.5	0.06	0.10	178.6	-0.7
LDL-C	Block 1	0.04	0.04	438.2		0.04	0.04	437.5	
	Block 2	0.03	0.79	441.7	3.5	0.03	0.77	440.9	3.4
	Block 3	0.04	0.27	443.5	1.8	0.04	0.22	442.3	1.3
logTG	Block 1	0.05	0.02	184.2		0.05	0.01	182.5	
	Block 2	0.04	0.79	187.7	3.5	0.05	0.81	186.1	3.6
	Block 3	0.04	0.39	190.4	2.7	0.04	0.47	189.4	3.3
logGlucose	Block 1	0.03	0.07	-197.4		0.04	0.04	-199.4	
	Block 2	0.03	0.39	-195.4	2.0	0.04	0.38	-197.4	2.0
	Block 3	0.03	0.45	-192.3	3.2	0.04	0.48	-194.0	3.4

Abbreviations: MHT, menopausal hormone therapy; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed

Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Block 1: Covariates + APOs entered

Block 2: Transdermal, Vaginal (Oral = reference)

Block 3: MVPA, StaB, sleep duration entered

Bold text used to emphasize statistically significant change in model fit in Block 1 and Block 2;

Red bold text used to emphasize statistically significant changes in Block 3

Appendix Table 11f. Sensitivity Analysis: Controlling for experience of APOs, route exposure, coefficients

Outcome	Predictor	Sensitivity Analysis: APOs		Objective 2B.3	
		Standardized β [95% CI]	Sig.	Standardized β [95% CI]	Sig.
aPWV	Age at menopause (years)	0.01 [-0.14, 0.15]		0.01 [-0.14, 0.16]	
	Spontaneous menopause	0.13 [-0.02, 0.29]		0.12 [-0.03, 0.28]	
	History of APOs	-0.09 [-0.23, 0.05]		--	--
	History of VMS	-0.10 [-0.24, 0.04]		-0.09 [-0.23, 0.04]	
	Postsecondary education	0.04 [-0.10, 0.18]		0.05 [-0.09, 0.19]	
	Primary earner status	-0.02 [-0.15, 0.12]		-0.02 [-0.16, 0.12]	
	MVPA (mins)	-0.25 [-0.42, -0.08]	*	-0.27 [-0.44, -0.11]	*
	StaB (hours)	0.08 [-0.10, 0.26]		0.07 [-0.11, 0.25]	
	Sleep duration (hours)	-0.06 [-0.21, 0.10]		-0.06 [-0.21, 0.10]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	-0.08 [-0.22, 0.07]		-0.08 [-0.23, 0.07]	
	Vaginal Usage	-0.28 [-0.43, -0.14]	*	-0.28 [-0.42, -0.13]	*
AIx75	Age at menopause (years)	-0.09 [-0.26, 0.07]		-0.09 [-0.26, 0.07]	
	Spontaneous menopause	0.06 [-0.10, 0.23]		0.07 [-0.10, 0.23]	
	History of APOs	0.03 [-0.13, 0.18]			
	History of VMS	0.01 [-0.14, 0.16]		0.01 [-0.14, 0.16]	
	Postsecondary education	-0.01 [-0.16, 0.15]		-0.01 [-0.16, 0.14]	
	Primary earner status	0.05 [-0.11, 0.20]		0.05 [-0.10, 0.20]	
	MVPA (mins)	-0.16 [-0.35, 0.03]		-0.15 [-0.34, 0.03]	
	StaB (hours)	0.02 [-0.18, 0.22]		0.02 [-0.18, 0.22]	
	Sleep duration (hours)	0.01 [-0.16, 0.18]		0.01 [-0.16, 0.18]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.02 [-0.14, 0.18]		0.02 [-0.14, 0.18]	--
	Vaginal Usage	0.01 [-0.15, 0.17]		0.01 [-0.16, 0.17]	
SBP	Age (years)	0.05 [-0.11, 0.21]		0.05 [-0.11, 0.21]	
	Age at menopause (years)	0.01 [-0.14, 0.17]		0.02 [-0.14, 0.17]	
	Spontaneous menopause	0.07 [-0.10, 0.23]		0.06 [-0.10, 0.22]	
	History of APOs	-0.07 [-0.22, 0.09]		--	--
	History of VMS	0.03 [-0.12, 0.18]		0.03 [-0.12, 0.18]	
	Postsecondary education	0.04 [-0.11, 0.18]		0.04 [-0.11, 0.19]	
	Primary earner status	-0.09 [-0.23, 0.06]		-0.09 [-0.23, 0.06]	
	MVPA (mins)	-0.28 [-0.46, -0.09]	*	-0.30 [-0.48, -0.12]	*
	StaB (hours)	-0.16 [-0.35, 0.04]		-0.17 [-0.36, 0.03]	

	Sleep duration (hours)	-0.12 [-0.29, 0.04]		-0.12 [-0.29, 0.04]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.06 [-0.10, 0.22]		0.06 [-0.10, 0.22]	
	Vaginal Usage	-0.06 [-0.22, 0.11]		-0.05 [-0.22, 0.11]	
DBP	Age (years)	-0.19 [-0.36, -0.03]	*	-0.19 [-0.35, -0.03]	*
	Age at menopause (years)	-0.02 [-0.18, 0.14]		-0.02 [-0.17, 0.14]	
	Spontaneous menopause	0.14 [-0.03, 0.31]		0.13 [-0.03, 0.30]	
	History of APOs	-0.04 [-0.20, 0.11]		--	--
	History of VMS	-0.01 [-0.16, 0.14]		0.00 [-0.15, 0.15]	
	Postsecondary education	-0.02 [-0.18, 0.13]		-0.02 [-0.17, 0.13]	
	Primary earner status	0.02 [-0.12, 0.17]		0.02 [-0.12, 0.17]	
	MVPA (mins)	-0.24 [-0.43, -0.05]	*	-0.25 [-0.43, -0.07]	*
	StaB (hours)	-0.16 [-0.36, 0.04]		-0.17 [-0.37, 0.03]	
	Sleep duration (hours)	-0.08 [-0.25, 0.08]		-0.08 [-0.25, 0.08]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.02 [-0.14, 0.18]		0.02 [-0.14, 0.18]	
	Vaginal Usage	0.02 [-0.15, 0.19]		0.03 [-0.14, 0.19]	
logFRS	Age at menopause (years)	-0.09 [-0.24, 0.06]		-0.09 [-0.24, 0.06]	
	Spontaneous menopause	0.10 [-0.06, 0.26]		0.10 [-0.06, 0.25]	
	History of APOs	-0.03 [-0.17, 0.12]		--	--
	History of VMS	-0.01 [-0.15, 0.14]		-0.01 [-0.15, 0.14]	
	Postsecondary education	0.01 [-0.14, 0.15]		0.01 [-0.13, 0.16]	
	Primary earner status	-0.11 [-0.26, 0.03]		-0.11 [-0.26, 0.03]	
	MVPA (mins)	-0.29 [-0.47, -0.11]	*	-0.29 [-0.47, -0.12]	*
	StaB (hours)	-0.04 [-0.23, 0.15]		-0.05 [-0.24, 0.14]	
	Sleep duration (hours)	-0.07 [-0.23, 0.09]		-0.07 [-0.23, 0.09]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.04 [-0.11, 0.20]		0.04 [-0.11, 0.20]	
	Vaginal Usage	-0.16 [-0.31, -0.01]	*	-0.16 [-0.31, 0.00]	*
WC	Age (years)	-0.38 [-0.53, -0.23]	*	-0.38 [-0.52, -0.23]	*
	Age at menopause (years)	-0.06 [-0.20, 0.09]		-0.05 [-0.20, 0.09]	
	Spontaneous menopause	-0.03 [-0.18, 0.12]		-0.03 [-0.18, 0.11]	
	History of APOs	-0.03 [-0.17, 0.11]		--	--
	History of VMS	0.01 [-0.13, 0.14]		0.01 [-0.13, 0.14]	
	Postsecondary education	-0.10 [-0.23, 0.04]		-0.09 [-0.23, 0.04]	
	Primary earner status	0.14 [0.00, 0.27]	*	0.14 [0.00, 0.27]	*

HDL-C	MVPA (mins)	-0.32 [-0.49, -0.15]	*	-0.33 [-0.49, -0.16]	*
	StaB (hours)	0.05 [-0.13, 0.23]		0.04 [-0.14, 0.22]	
	Sleep duration (hours)	-0.13 [-0.28, 0.02]		-0.13 [-0.28, 0.02]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.09 [-0.06, 0.23]		0.09 [-0.06, 0.23]	
	Vaginal Usage	-0.02 [-0.17, 0.13]		-0.01 [-0.16, 0.14]	
	Age (years)	0.12 [-0.04, 0.28]		0.11 [-0.04, 0.27]	
	Age at menopause (years)	0.02 [-0.13, 0.18]		0.02 [-0.13, 0.18]	
	Spontaneous menopause	0.20 [0.03, 0.36]	*	0.20 [0.04, 0.36]	*
	History of APOs	0.03 [-0.12, 0.18]		--	--
LDL-C	History of VMS	-0.07 [-0.22, 0.08]		-0.07 [-0.22, 0.08]	
	Postsecondary education	0.13 [-0.02, 0.27]		0.12 [-0.02, 0.27]	
	Primary earner status	-0.06 [-0.21, 0.09]		-0.06 [-0.20, 0.09]	
	MVPA (mins)	0.07 [-0.11, 0.26]		0.08 [-0.10, 0.26]	
	StaB (hours)	-0.15 [-0.34, 0.05]		-0.14 [-0.34, 0.05]	
	Sleep duration (hours)	-0.04 [-0.20, 0.13]		-0.04 [-0.20, 0.12]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.06 [-0.09, 0.22]		0.06 [-0.09, 0.22]	
	Vaginal Usage	-0.10 [-0.26, 0.06]		-0.10 [-0.27, 0.06]	
	Age (years)	-0.13 [-0.29, 0.03]		-0.14 [-0.30, 0.02]	
logTG	Age at menopause (years)	-0.12 [-0.28, 0.03]		-0.13 [-0.28, 0.03]	
	Spontaneous menopause	0.10 [-0.06, 0.26]		0.11 [-0.06, 0.27]	
	History of APOs	0.07 [-0.08, 0.22]		--	--
	History of VMS	-0.06 [-0.21, 0.09]		-0.06 [-0.21, 0.09]	
	Postsecondary education	0.06 [-0.09, 0.21]		0.05 [-0.09, 0.20]	
	Primary earner status	-0.12 [-0.27, 0.03]		-0.12 [-0.27, 0.03]	
	MVPA (mins)	0.09 [-0.10, 0.28]		0.11 [-0.07, 0.29]	
	StaB (hours)	-0.08 [-0.28, 0.11]		-0.07 [-0.27, 0.12]	
	Sleep duration (hours)	0.01 [-0.15, 0.18]		0.01 [-0.16, 0.18]	
	Oral Usage (MHT reference group)				
	Vaginal Usage	-0.01 [-0.17, 0.15]		0.05 [-0.11, 0.21]	
	Transdermal Usage	0.05 [-0.11, 0.21]		-0.02 [-0.18, 0.15]	
	Age (years)	-0.07 [-0.23, 0.08]		-0.08 [-0.24, 0.08]	
	Age at menopause (years)	-0.22 [-0.37, -0.06]	*	-0.22 [-0.38, -0.06]	*
	Spontaneous menopause	-0.10 [-0.27, 0.06]		-0.09 [-0.26, 0.07]	
	History of APOs	0.07 [-0.08, 0.22]		--	--

	History of VMS	0.01 [-0.14, 0.16]		0.00 [-0.15, 0.15]	
	Postsecondary education	-0.07 [-0.21, 0.08]		-0.07 [-0.22, 0.08]	
	Primary earner status	0.01 [-0.14, 0.16]		0.01 [-0.13, 0.16]	
	MVPA (mins)	-0.14 [-0.33, 0.04]		-0.12 [-0.30, 0.06]	
	StaB (hours)	-0.01 [-0.21, 0.18]		0.00 [-0.20, 0.19]	
	Sleep duration (hours)	-0.01 [-0.17, 0.16]		-0.01 [-0.17, 0.16]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	-0.01 [-0.17, 0.15]		-0.01 [-0.17, 0.15]	
	Vaginal Usage	0.06 [-0.10, 0.23]		0.06 [-0.11, 0.22]	
logGlucose	Age (years)	0.19 [0.03, 0.35]	*	0.18 [0.02, 0.34]	*
	Age at menopause (years)	0.16 [0.00, 0.32]	*	0.16 [0.00, 0.31]	*
	Spontaneous menopause	-0.09 [-0.25, 0.08]		-0.08 [-0.25, 0.08]	
	History of APOs	0.04 [-0.12, 0.19]		--	--
	History of VMS	-0.05 [-0.20, 0.10]		-0.05 [-0.20, 0.10]	
	Postsecondary education	0.05 [-0.10, 0.19]		0.04 [-0.11, 0.19]	
	Primary earner status	0.07 [-0.08, 0.21]		0.07 [-0.08, 0.21]	
	MVPA (mins)	-0.12 [-0.31, 0.07]		-0.11 [-0.29, 0.07]	
	StaB (hours)	-0.14 [-0.34, 0.06]		-0.13 [-0.33, 0.06]	
	Sleep duration (hours)	-0.01 [-0.17, 0.16]		-0.01 [-0.17, 0.16]	
	Oral Usage (MHT reference group)				
	Transdermal Usage	0.05 [-0.11, 0.21]		0.05 [-0.11, 0.21]	
	Vaginal Usage	-0.06 [-0.22, 0.11]		-0.06 [-0.23, 0.10]	

Abbreviations: MHT, menopausal hormone therapy; VMS, vasomotor symptoms; MVPA, moderate-to-vigorous physical activity; StaB, stationary behaviour; aPWV, aortic pulse wave velocity; AIx75, augmentation index at 75 beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; logFRS, log-transformed Framingham Risk Score; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; logTG, log-transformed triglycerides; logGlucose, log-transformed glucose

Appendix Table 12. Summary of Accessible MHT Guidelines Published Since 2020

Society	Year	Country/ Continents	Initiation	Type of Estrogen	Type of Progestogen	Route	Lifestyle / Movement Behaviours	Other Comments / Conclusions
Society of Obstetricians and Gynaecologists of Canada⁵⁷	2021	Canada	Low risk for CV events when initiated shortly after menopause; Possible increased risk for adverse CV events if initiated 10 or more years after menopause	No specific recommendation	Combined estrogen- progestogen therapy may increase risk of VTE. However, the choice of progestogen is important. MP (or other similar progestogens) may be more favourable for cardiometabolic outcomes	Transdermal routes preferable to oral routes.	No specific recommendation	"Evidence to date suggests that, in appropriately selected, symptomatic women, short- term use of MHT does not appear to confer increased risk of CVD"
British Menopause Society ²³	2020 (update d in 2025)	UK	Initiated within 10 years of menopause or below age 60: reduction in CV risk Initiated more than 10 years after menopause: no difference in CV risk	CEE may confer higher risk of VTE compared to estradiol	MP may be more favourable for metabolic health compared to other progestogens; dydrogesterone appears to have a neutral metabolic effect; MP and dydrogesterone may be preferable for women at increased risk of stroke	Non-oral routes may be preferable because they bypass first- pass metabolism. Transdermal recommended for women over age 60. Oral estradiol may slightly increase risk of stroke, while transdermal estradiol likely has no effect.	Lifestyle advice (e.g., exercise, diet) should be incorporated into routine management of the postmenopausal period.	MHT likely has either a favourable or neutral CV effect, depending on age and timing of initiation. Women should have access to holistic and individualized advice, with emphasis on lifestyle and diet changes.
The Menopause Society (formerly the	2022	International	Reduction or null effect on CHD risk when initiated within	No specific recommendation	MP may be preferable to avoid VTE	Non-oral routes may be preferable, but	Lifestyle interventions should be considered when	Healthy, symptomatic women younger than age 60 or

Society	Year	Country/ Continents	Initiation	Type of Estrogen	Type of Progestogen	Route	Lifestyle / Movement Behaviours	Other Comments / Conclusions
North American Menopause Society) ²²			10 years of menopause or below age 60; Higher absolute risk of CHD, VTE, and stroke otherwise			more research is needed	making treatment decisions. More research is needed on lifestyle modification if chosen in addition to or over MHT in multiple health domains.	within 10 years of menopause can weigh the possible favourable effects of MHT against the possible risks (i.e., VTE). Lifestyle modifications should be considered instead of MHT or in addition.
American College of Cardiology CVD in Women Committee ⁵⁵	2024	USA	Appropriate and safe for women under age 60 or within 10 years of menopause onset	No specific recommendation	No specific recommendation	Non-oral routes may be preferable to oral routes	"The presence of CVD risk factors alone does not preclude the use of HT, but a patient's worsening CV risk profile around the menopausal transition emphasizes the need to optimize primary prevention efforts, including lifestyle and pharmacological management"	"...initiating systemic HT is appropriate for younger, healthy menopausal women with lifestyle limiting bothersome VMS."
International Menopause Society ²⁴	2024	International	Caution in prescribing MHT for	Not enough research to conclude if	MP and other biologically similar progestogens (e.g.,	Transdermal routes may be preferable in	"any medical treatments should be underpinned	Healthcare providers must provide a

Society	Year	Country/ Continents	Initiation	Type of Estrogen	Type of Progestogen	Route	Lifestyle / Movement Behaviours	Other Comments / Conclusions
			women age 60 or older, but it may be needed in some cases	any commonly used estrogen is superior to another	dydrogesterone) may be more favourable than androgenic progestogens	women at risk for VTE, but there is little reason to avoid prescribing oral MHT for women without contraindications	by optimization of lifestyle, diet, exercise, minimizing alcohol, and avoiding or stopping smoking"	supportive, informative environment and offer personalized care.
Korean Society of Menopause ²¹⁵	2025	South Korea	Initiated within 10 years of menopause and/or before age 60 may help prevent CAD Initiated more than 10 years after menopause: no difference in CV risk	CEE may confer higher risk of VTE compared to estradiol	MP or dydrogesterone may be preferable for women at risk of VTE	Non-oral routes may be preferable to oral routes	Mentioned in the context of weight loss to address VMS, but not for general CV health	Long-term impact of MHT is still not understood. Treatment decisions must be tailored to individual risk factors. MHT should be avoided in women with CV conditions (e.g., CAD, stroke, or thromboembolic events).
International Menopause Society ⁵⁶	2025	International	Initiation within 10 years of menopause or before age 60 appears to reduce CHD and mortality	No specific recommendation	MP, dydrogesterone, or levonorgestrel-releasing intrauterine systems are preferable for women at risk of VTE	Non-oral routes may be preferable to oral routes	Regular exercise in midlife and older women is recommended to improve musculoskeletal health, reduce CV and all-cause mortality; At least 150 min of moderate-intensity exercise	MHT should not be used for primary or secondary prevention of CVD but does not appear to increase the risk for CVD events. Any treatment, hormonal or otherwise,

Society	Year	Country/ Continents	Initiation	Type of Estrogen	Type of Progestogen	Route	Lifestyle / Movement Behaviours	Other Comments / Conclusions
							per week is recommended as optimal; with two additional weekly sessions of resistance exercise providing further benefit.	should be underpinned by optimizing lifestyle, diet, exercise, avoiding or stopping smoking and minimizing alcohol consumption. Should not be used for primary or secondary CVD prevention, but may have favourable effects on CV health. Contraindicated in women at high risk of CV events or existing CVD.
European Society of Endocrinology ³³⁷	2025	Europe	Recommended for symptomatic women within 10 years of menopause or before age 60; individualized approaches for women outside of this range	Estradiol generally preferred over CEE in Europe due to it being more "natural"	MP or dydrogesterone may be preferable for women at risk of VTE	Non-oral routes preferable to oral routes for women with risk for VTE or intermediate risk of CVD (e.g., obese, controlled diabetes, older women)	"We recommend that a holistic approach is taken for women during perimenopause and menopause, not having a sole focus on HRT/MHT."	

Abbreviations: CV, cardiovascular; MP, micronized progesterone; VTE, venous thromboembolism; MHT, menopausal hormone therapy; CVD, cardiovascular disease; CEE, conjugated equine estrogens; CHD, coronary heart disease; VMS, vasomotor symptoms; CAD, coronary artery disease; HRT, hormone replacement therapy.

Appendix B: STROBE Checklist.

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	13-52
Objectives	3	State specific objectives, including any prespecified hypotheses	52-59; Table 3
Methods			
Study design	4	Present key elements of study design early in the paper	60
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	60-63
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	63-64
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	64-86; Table 10
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	64-86
Bias	9	Describe any efforts to address potential sources of bias	64-66, 77, 79, 81, 87-89, 91, 100
Study size	10	Explain how the study size was arrived at	60, 63-64
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	64-72, 75-78, 80-84
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Chapter 2.7
		(b) Describe any methods used to examine subgroups and interactions	88-90, 95, 100-101
		(c) Explain how missing data were addressed	87
		(d) If applicable, explain how loss to follow-up was addressed	NA

(e) Describe any sensitivity analyses			Chapter 2.7.4.2 (100-101)
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	103 NA NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	103-106 87, 104-105, Table 12 NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	80-84; Chapters 3.2.1, 3.2.2, 3.2.4, 3.3.2; Appendix Tables 1-4 (unadjusted) NA NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Chapter 3.4 (225-229); Appendix Tables 5-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	Chapter 4.1 (230-234); Table 38
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Chapter 4.3 (242-243)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	235-239; 243-244
Generalisability	21	Discuss the generalisability (external validity) of the study results	235, 242-244

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4
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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.