Characterizing cardiovascular risk in a Manitoba First Nation

by

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ABSTRACT

Background: Prevalence of diabetes and cardiovascular disease among First Nations populations in Canada is higher compared to the non-First Nations population. Consistent monitoring of this epidemic is required. In addition, cardiovascular risk factors derived from research on non-First Nations populations may not be applicable to First Nations populations. Therefore, better understandings of risk factors specific to First Nations populations are required.

Purpose: To characterize cardiovascular risk in a Manitoba First Nation population.

Methods: Data from the 2002/2003 and 2011/2012 Diabetes Screening Studies in Sandy Bay First Nation were used, including fasting blood, anthropometric, and self-report data. The studies were conducted using a community-based participatory framework. All non-pregnant community members aged ≥18 years old were invited to participate in both study periods. First, using a repeated cross-sectional design, the burden of cardiovascular risk in the community in the 2011/2012 sample (n=482) was compared to the 2002/2003 sample (n=596). Second, by linking 2002/2003 and 2011/2012 data, an eight-year follow-up of participants was developed (n=171).

Results: ***Repeated cross-sectional design.*** Sex- and age-standardized prevalence of diabetes in the adult population of the community was estimated at 39.2% (95% CI: 35.3, 43.1) in 2011/2012 and was not significantly different from 2002/2003. Significantly higher crude prevalence of obesity, abdominal obesity, dyslipidemia, and metabolic syndrome among women compared to men persisted from 2002/2003 to 2011/2012. At 80.0%, the crude prevalence of current smoking was significantly higher in 2011/2012 compared to 2002/2003. ***Prospective cohort design.*** There were 35 (95% CI: 26, 45) new cases of diabetes among 128 participants without diabetes at baseline (27% over 8

years or 3.3% per year). Two-thirds of those with diabetes at follow-up lost weight, including 35.1% of men, and 18.9% of women that lost greater than 10kg. Both men and women lost weight in association with decreases in fasting blood insulin, while men also lost weight in association with uncontrolled blood glucose.

Conclusions: This research contributes to the understanding of the diabetes epidemic and how this epidemic has evolved in a high-risk community. Unintentional weight loss related to diabetes is a problem in this population. Further research is needed to better understand how diabetes-related weight loss may contribute to morbidity and mortality.

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As this project was truly community-based and participatory, I would like to acknowledge all the members of the Diabetes Advisory Group for their expertise, comments, and suggestions for my thesis and also their overall support for the study program. I would also like to thank the other employees at the Health Centre for always making me feel very welcome, promoting the study, and being so helpful.

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LIST OF ABBREVIATIONS

ACR	Albumin:creatinine ratio
AIC	Akaike Information Criterion
ApoA	Apolipoprotein A1
ApoB	Apolipoprotein B
BIC	Bayesian Information Criterion
CBPR	Community-based Participatory Research
CDAG	Community Diabetes Advisory Group
CI	Confidence Interval
CIHR	Canadian Institutes of Health Research
CV	Cardiovascular
DPP	Diabetes Prevention Program
eGFR	Estimated Glomerular Filtration Rate
GLM	General Linear Model
HbA1c	Hemoglobin A1c or glycated hemoglobin
Hcy	Homocysteine
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HOMA β	Homeostatic model assessment of β-cell function
HOMA-IR	Homeostatic model assessment of insulin resistance
IDL	Intermediate-density lipoprotein
IFG	Impaired fasting glucose
IQR	Interquartial range
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol

OCAP	Ownership, Control, Access, Possession
OR	Odds ratio
MetS	Metabolic syndrome
MHRC	Manitoba Health Research Council
NEAHR	Network Environment for Aboriginal Health Research
SGBA	Sex and gender-based analysis
TC	Total cholesterol
TG	Triglycerides
VLDL	Very-low density lipoproteins
WC	Waist circumference

1. INTRODUCTION

In Canada, many First Nations people live in environments that promote development of chronic diseases, such as diabetes and heart disease. Many aspects of this environment are rooted in the legacy of colonialism and include limited incomes, low educational attainment, limited access to affordable foods, limited access to safe walking areas and recreational facilities, reduced access to health care, and racism.

In Manitoba, the prevalence of diabetes is over 4 times higher among First Nations people compared to non-First Nations people (Green et al., 2003). Similar gaps in prevalence of diabetes have been noted more recently among First Nations populations compared to non-First Nations people in Saskatchewan (Dyck et al., 2010) and Alberta (Johnson et al., 2009), with higher prevalence noted among First Nations women compared to men (Dyck et al., 2010, Johnson et al., 2009). Dyck and colleagues also reported a significantly higher incidence of diabetes from 1980-2005 among the First Nations population compared to the non-First Nations adult population in Saskatchewan, with relative annual incidence ratios ranging from 2.2-5.9 over the 25 years. The burden is so great among women, that 50% of First Nations women 60 years and older in Saskatchewan have been diagnosed with diabetes (Dyck et al., 2010). Other First Nations community-based studies have also reported high prevalence of diabetes (Horn et al., 2007, Dannenbaum et al., 2008). Importantly, the development of diabetes and its associated risk factors occurs at a younger age among First Nations people compared to non-First Nations people (Wahi et al., 2009, Young et al., 2000). In the study community of Sandy Bay First Nation, Manitoba, the diabetes burden is similarly heavy, in that approximately 30% of adults have diabetes (Bruce & Young, 2008). Furthermore, the

study community is within the Dakota Ojibway Tribal Council, which has the highest adjusted prevalence of diabetes among adults compared to all other Tribal Councils in Manitoba, at approximately 25% (Martens et al., 2002). However, this most recent data regarding diabetes prevalence among First Nations in Manitoba is based on administrative data that is currently over 15 years old. Additionally, there are very few prevalence studies outside of administrative data, which lacks information on undiagnosed diabetes and related cardiometabolic conditions.

Type 2 diabetes is defined by hyperglycemia that results from a combination of insulin resistance and deficits in insulin production. Ultimately, if diabetes goes unmanaged, vascular damage ensues. Microvascular damage can affect the eyes (retinopathy), kidneys (nephropathy), and peripheral vascular system, leading to foot complications. Diabetes is also associated with macrovascular damage, and because of this relationship, the constellation of diabetes and co-occurring risk factors such as obesity, hypertension, and dyslipidemia, is often considered a cardiometabolic condition. Other co-occurring cardiovascular (CV) risk factors associated with diabetes and impaired glucose tolerance are: hypertriglyceridemia, high blood pressure, low high-density lipoprotein (HDL) cholesterol, central obesity, small dense low-density lipoprotein (LDL), albuminuria and high levels of inflammatory markers. A high prevalence of nearly all these risk factors have been identified among Canadian Aboriginal[1] people and have also been identified as co-occurring in cross-sectional studies (Wahi et al., 2009, Anand et al., 2001; Bruce et al., 2011; Chateau-Degat et al.,

[1] In Canada there are three groups of people constitutionally recognized as Aboriginal: First Nations, Metis and Inuit. In this paper the term Aboriginal is used when a cited study does not specify the ethnic group included in the research. However, if the authors identify the particular Aboriginal group then that group or groups are identified.

2011; Chateau-Degat et al., 2008; Chateau-Degat et al., 2009; Connelly et al., 2003; Daniel & Cargo, 2004; Daniel et al., 1999; Daniel et al., 1995; Dannenbaum et al., 2005; Dyck et al., 2010; Foulds et al, 2011; Hanley et al., 2003; Hanley et al., 2005; Harris et al., 2002; Kaler et al., 2006; Liu et al., 2006a; Liu et al., 2006b; McIntyre & Shah, 1986; Oster & Toth, 2009; Oster et al., 2009b; Pollex et al., 2006; Razak et al., 2005; Razak et al., 2007; Retnakaran et al., 2005; Retnakaran et al., 2006a; Retnakaran et al., 2006b; Riediger et al., 2011; Sellers et al., 2009; Sellers et al., 2007; Silha et al., 2007; Smith et al., 2005; Stringer et al., 2009; Thommasen et al., 2004; Thomassen et al., 2006; Young et al., 2002; Zorzi et al., 2009).

Due to the high burden of diabetes and associated cardiometabolic conditions, CV mortality rates have increased among the Canadian First Nation population over the last 30 years (Trovoto, 2001; Tjepkema et al., 2012) and have surpassed the rates of the non-First Nations population (Tjepkema et al., 2012). The gap in CV mortality rates between First Nation women and non-First Nation women is considerably larger compared to the gap between men of these two groups. Among First Nation people from the Six Nations reserve, the age- and sex-standardized prevalence of CV disease, as determined by self-report, was higher compared to Canadians of European origin at 17% versus 7%, in the two groups, respectively (Anand et al., 2001). Furthermore, in the First Nation community of Sandy Lake, Ontario the rate of hospital admission for ischemic heart disease tripled over 15 years (1983-1997) from 35 per 10 000 to 109 per 100 000 (Harris et al., 2002).

The limited research completed to date has revealed significant differences in the relationships among various CV risk factors between First Nations populations and other

non-First Nations populations (Chateau-Degat et al., 2008; Razak et al., 2005; Razak et al., 2007; Silha et al., 2007; Young et al.., 2002; Leslie et al., 2007; Anand et al., 2004). For example, at a given body mass index (BMI) level the risk load according to glycemic status and blood lipid profile is worse among First Nations people compared to individuals of European descent (Razak et al., 2005). The preceding papers highlight the importance of future research to identify ethnic variations in risk factor-disease relationships and determine risk factors for diabetes and CV disease specific to the First Nations population.

Although there is literature related to differences in cardiometabolic disease presentations cross-sectionally in First Nations populations, and there is some literature showing rates of CV outcomes are high, there is a paucity of information about anything in between, specifically disease progression. Studies to describe diabetes and/or CV disease among First Nations populations, beyond merely prevalence, have been mostly limited to 1) cross-sectional studies (Young et al., 2000; Bruce & Young, 2008; Anand et al., 2001; Chateau-Degat et al., 2008; Chateau-Degat et al., 2009; Connelly et al., 2003; Kaler et al., 2006; Liu et al., 2006a; Oster et al., 2009b; Razak et al., 2005; Razak et al., 2007; Retnakaran et al., 2006; Retnakaran et al., 2006b; Smith et al., 2005; Young et al., 2002 Zorzi et al., 2009; Dean et al., 1998; Delisle & Ekoe, 1993), 2) chart review (Sellers et al., 2009; Brassard & Robinson, 1995; Brassard et al., 1993a; Brassard et al., 1993b; Evers et al., 1987; Harris et al., 2011; Maberley et al., 2000; Macaulay et al., 1988; Monsalve et al., 2005; Montour et al., 1985; Montour et al., 1989; Self et al., 2005; Patenaude et al., 2005; Young et al., 1985; Young et al., 1990), and 3) follow-up using administrative data (Harris et al., 2002; Jin et al., 2002a; Jin et al., 2002b). To my

knowledge, there has only been one study that has followed members of a First Nation community (Sandy Lake, Ontario) and collected some of the previously cited cardiometabolic risk factors at both baseline and follow-up; however, the sample size was small, follow-up was only 4-years and completed on high risk individuals only (Hanley et al., 2003; Hanley et al., 2001). Similarly, additional follow-up at 10 years of the original baseline study population only included those without previously diagnosed diabetes and only analysis with diabetes incidence as an outcome has been reported (Ley et al., 2010; Ley at al., 2009; Ley et al., 2011).

There are three areas of interest that are explored in this thesis in terms of progression of diabetes and CV risk in a First Nation population. These areas are: weight loss, changes in apolipoprotein B (apoB), and changes in homocysteine (hcy) over time.

Weight loss. Weight loss was selected because of the strong focus in the literature surrounding weight loss as an intervention for diabetes prevention (Perrealt et al., 2008; Perreault et al., 2009), weight gain as a risk factor for incident diabetes (Kaneto et al., 2013), and the high prevalence of obesity in this population. As mentioned, there is a paucity of longitudinal data in First Nations populations to investigate relationships between changes in weight and changes in other cardiometabolic markers. Additionally, cross-sectional relationships do not necessarily translate to longitudinal relationships. Lastly, but most importantly, anecdotal reports from the study community indicate that there are strong sex-differences in weight loss in response to diabetes that to my knowledge have not been reported in the literature in any population.

Apolipoprotein B. The second area of interest that I will focus on in terms of disease progression is that of changes in apoB. ApoB is the apolipoprotein associated

with low-density lipoproteins (LDL), intermediate-density lipoproteins (IDL), and very-low density lipoproteins (VLDL). ApoB relates to the number of atherogenic lipoprotein particles rather than the cholesterol amount that is carried by LDL (that is, LDL-cholesterol). LDLs are heterogeneous with respect to the amount of cholesterol they contain. Therefore someone may have a preponderance of cholesterol-depleted LDL, resulting in a low LDL-C value but a large number of circulating atherogenic lipoproteins (high apoB), commonly observed among individuals with insulin resistance (**Figure 1.1**). For this reason, First Nations populations have been observed to have low levels of LDL-C, high apoB, and large numbers of small-dense LDL. Importantly, several large epidemiological and clinical trials have demonstrated that apoB is a superior predictor of CV disease compared to either LDL-C or non-HDL-C (McQueen et al., 2008; Hsia et al., 2006; Holme et al., 2008; Simes et al., 2002; Chien et al., 2007; Gotto et al., 2000; Bruno et al., 2006; Van Lennep et al., 2000; Pischon et al., 2005). Because of the larger difference between LDL-C and apoB measures among those with insulin resistance, the population that may benefit the most from using apoB as a target for therapy and/or predictor of CV risk would be those with diabetes or high cardiometabolic risk (hence, the study population).

The shift in the literature toward using apoB as a marker of CV risk as opposed to LDL-C (Doggrell, 2006; Shepherd, 2005; Szapary & Rader, 2004; Sniderman et al., 2001) has slowly been incorporated into clinical practice guidelines (Anderson et al., 2013). The 2012 update of the *Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of dyslipidemia for the Prevention of Cardiovascular disease in the Adult* has now identified apoB as an optional measure among those screened for CV

risk (Anderson et al., 2013). Therefore, it may be important to understand longitudinal changes in apoB and predictors of these changes in a population with high rates of diabetes.

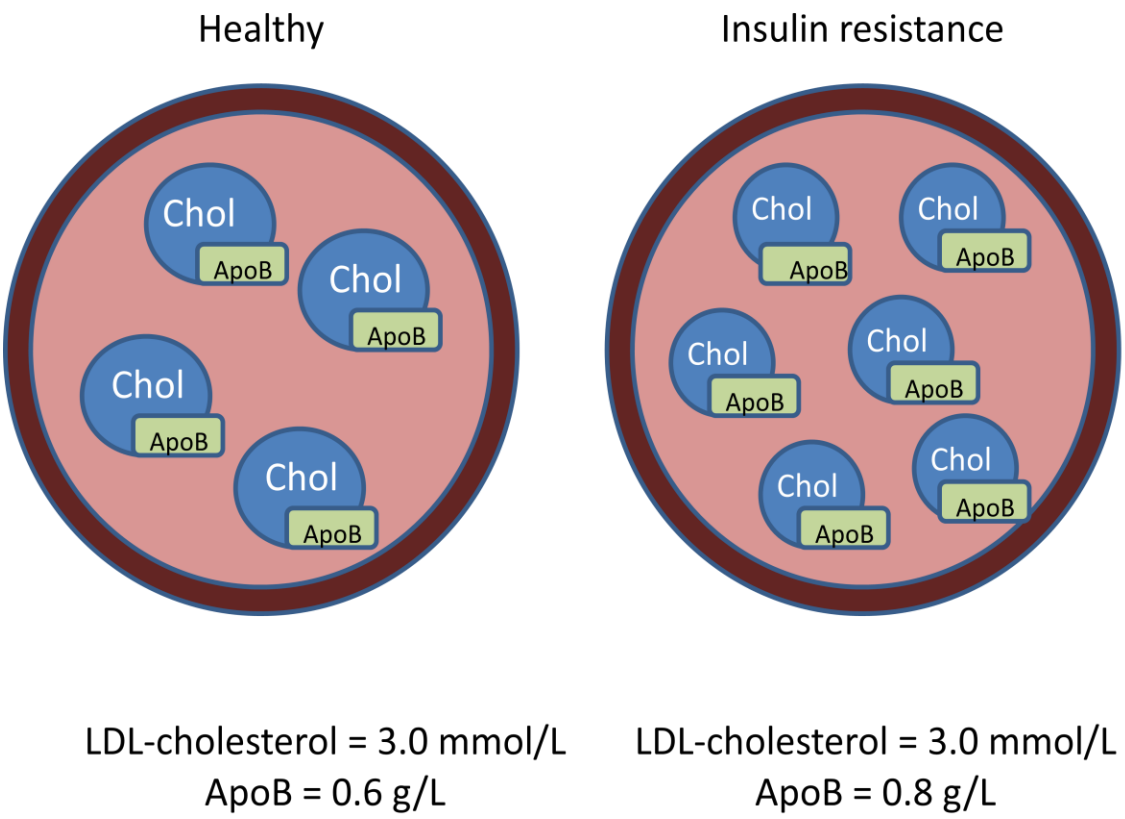


Figure 1.1. Illustration of circulating levels of LDL (cholesterol vs. apoB) in a healthy individual compared to someone with insulin resistance.

LDL, low-density lipoprotein; apoB, apolipoproteinB

Homocysteine. Changes in hcy over time are the third area of interest. Hcy is an amino acid produced in the metabolism of methionine. Vitamins B12, B6, and folate (folic acid) are co-factors in the metabolic pathway from which hcy is produced. For this reason, deficiency or low dietary intake of these vitamins is associated with hyperhomocysteinemia (Cook & Hess, 2005). Hyperhomocysteinemia may also result from a genetic mutation effecting hcy metabolism. Importantly, hcy is positively associated with development of coronary artery disease and mortality, independently of other CV risk factors (Arnesen et al. 1995; Genest et al. 1990; Graham et al. 1997; Matetzky et al., 2003; Anderson et al. 2000; Moustapha et al. 1998; Retterstol et al. 2003; Wald et al. 1998). The magnitude of risk associated with elevated plasma hcy for vascular disease is similar to that of smoking or hyperlipidemia and there is a significant multiplicative interaction between smoking and hcy, and hypertension and hcy (Graham et al., 1997). Additionally, hcy may be a stronger risk factor for CAD among younger participants (Arnesen et al., 1995; Wald et al., 1998) and women (Boushey et al. 1995). For these reasons, hcy may be an important risk factor in a First Nations population that is young, with high prevalence of smoking and hypertension, and with a sub-population of women with a high burden of disease.

In addition, we have reported several important relationships between hcy and outcomes, and hcy and points of intervention in the study population. First, Bruce & Young reported in 2008 that hcy is a significant positive predictor of neuropathy, independent of age, sex, education, HbA1c, and pack-years smoked. Secondly, also in cross-sectional analysis, hcy was positively associated with obesity, independent of age, sex, DBP, diabetes, apoA, apoB, and HOMA-IR (Riediger et al., 2011). Thirdly, we

previously reported that among those with diabetes, high levels of daily stress was significantly and positively associated with hcy; similar relationships were observed with perceived stress, marital problems, negative power relationships in the community, and feelings of control, independent of age, sex, smoking status, and BMI (Riediger, 2010). Therefore, hcy may be an important intermediate marker linking stress to CV disease.

In summary, we have little sense of the recent change in magnitude (ie. prevalence) of the diabetes and cardiometabolic burden over time because of the lack of longitudinal data and study designs incorporating primary data collection with multiple risk factors. For similar reasons, there is limited evidence concerning the progression of cardiometabolic/ CV disease in First Nations populations. Our understanding of CV risk factors has been derived from research on mostly Caucasian populations and these results may not be applicable in a First Nations population. Therefore, it is important to better understand the unique development of diabetes and CV disease among First Nations people using a longitudinal design in order to identify risk factors specific to a First Nation population and develop treatment strategies and prevention interventions that will be effective, sustainable, and appropriate.

1.1 Purpose and Objectives

The purpose of this proposed study is to characterize CV risk in a Manitoba First Nation community. The objectives of the study are to:

1. Test for changes in cardiovascular risk in the study community from 2002/2003 to 2011/2012.

a. Test for differences in prevalence of diabetes, obesity, abdominal obesity, hypertension, dyslipidemia, metabolic syndrome, and current smoking status between the two time periods.
b. Test for differences in glucose, HbA1c, length of time with diabetes, blood pressure, BMI, waist circumference, and lipids between the two time periods.

2. Determine 8-year incidence rates of diabetes, obesity, central obesity, hypertension, dyslipidemia, and metabolic syndrome from 2002/2003 to 2011/2012.
    a. Determine demographic predictors (age and sex) at baseline for incident cardiometabolic conditions at follow-up.
3. Identify CV risk factors at baseline, and changes in those risk factors over time that predicts changes in CV risk factors of interest.
    a. Identify predictors of weight loss.
    b. Identify predictors of changes in apolipoprotein B over time.
    c. Identify predictors of changes in homocysteine over time.

2. LITERATURE REVIEW

The causes of CV disease among First Nations (and non-First Nations) populations form a complex web of socioeconomic factors, psychosocial issues, and genetic risk (including epigenetic) that intersect with lifestyle, which consequently influence biomarkers and disease processes. Independent risk factors for CV disease, as reported in various ethnic populations, and which were investigated in the current study, are listed in **Table 2.1**. These topics as they relate to CV disease among Aboriginal people in Canada will be reviewed, with a focus on First Nations people. PubMed and Scopus search engines were used to locate pertinent articles. Search terms for First Nations populations were: “First Nation” OR “Native” OR “aboriginal” OR “indigenous”.

Table 2.1. Cardiovascular risk factors.

Type of risk factor	Risk factor	Reference
Anthropometric	Body mass index	Jousilahti et al., 1996 Hubert et al., 1983
	Waist circumference	Lakka et al., 2002
	Waist-to-hip ratio	Suk et al., 2003; Lakka et al., 2002
Clinical chemistry	Fasting glucose (Diabetes)[a]	Benjamin et al., 1994; Kannel & McGee, 1979
	Hemoglobin A1c	Bonora & Muggeo, 2001
	Fasting blood insulin (HOMA-insulin resistance)	Haffner, 1999
	Total cholesterol	Harris-Hooker & Sanford, 1994
	LDL-cholesterol	Harris-Hooker & Sanford, 1994
	HDL-cholesterol	Goldbourt & Medalie, 1979
	Fasting triglycerides	Tohidi et al., 2010
	Apolipoprotein A1	Walldius & Jungner, 2006; Walldius et al.,

		2001; Garfagnini et al., 1995; Walldius et al., 2004
	Apolipoprotein B	Walldius & Jungner, 2006; Walldius et al., 2001; Walldius et al., 2004
	Homocysteine	Clarke et al., 1991
Blood pressure	Hypertension Systolic blood pressure Diastolic blood pressure	Stamler et al., 1993; Lawes et al 2006
Behavioural	Smoking status	Kannel et al., 1965; Kannel et al., 1968; Kannel et al., 1984
Framingham score (composite risk load)[b]		Wilson et al., 1998

[a] In the present study, diabetes is defined using fasting glucose

[b] There are many different composite risk scores which have been developed in different populations. The Framingham score was selected because it is the most commonly used and is discussed in the literature review.

2.1 Burden of the problem

Early work by Kue Young (Young et al., 1985), Ann Macaulay and Louis Montour (1985) described the burden of diabetes in the First Nations population during the 1980's. Since this time, the burden of diabetes and chronic disease on the healthcare system in the First Nations population in several provinces has been reported using administrative health data. Increasingly, numerous reports of the diabetes and chronic disease burden in several First Nations communities have also been published. Both these types of reports are reviewed here.

2.1.1 Diabetes

Prevalence. The burden of diabetes and cardiometabolic risk in the proposed study community is substantial. A previous screening study completed in 2002/2003 in the study community, Sandy Bay First Nation, indicated that the crude prevalence of diabetes is nearly 30% in the adult population (Bruce & Young, 2008). Using administrative data, Green and colleagues (2003) reported the prevalence of diabetes in Manitoba between 1989 and 1998. In 1998, the prevalence for First Nations women was 248.7/1000 and 170/1000 for First Nations men compared to 53.5/1000 and 59.6/1000 for non-First Nations women and men, respectively. The prevalence (and incidence) peaked in the 60-69 year old age group among First Nations and among the non-First Nations population both incidence and prevalence increased with each age group, up to 70+. **Table 2.2** summarizes the diabetes prevalence reported for various First Nations and American Indian groups, with corresponding non-indigenous prevalence also reported, if provided. American Indian groups were included due to their similar colonial history, socioeconomic and cultural background with Canadian First Nations populations.

In Canada, the diabetes prevalence among First Nations populations is consistently, at least twice that of the corresponding non-Aboriginal population.

Incidence. No incidence data are available for the study community. In Manitoba, the age-adjusted incidence rate increased slightly for First Nations men between 1989 and 1998 from 15.3/1000 to 21.1/1000 but did not increase for First Nations women (Green et al., 2003). In Alberta, the incidence rate increased between 1995 and 2007 in the First Nations population, although to a lesser extent at the end of that period than earlier in the time period (Oster et al., 2011). In 2007, the age-standardized incidence was 11.9 and 10.3 per 1000 for First Nations women and men, respectively, compared to 5.7 and 7.3 per 1000 for women and men in the general population in Alberta. Similarly, in Saskatchewan, incidence rates for First Nations women have more or less stabilized at 17.95 per 1000 in 2003, whereas the rate for men has over time increased and now approaches that of women at 17.80 per 1000 (Dyck et al., 2010).

Among youth in Alberta (< 20 yrs), the incidence of diabetes in 2007 was 0.59 per 1000 for First Nations and 0.49 per 1000 for the general population; the incidence rate increased from 1995-2007 (Oster et al., 2012). In Manitoba children <18 years old, the incidence rate has also increased from 9.03 per 100 000/yr in 2006-2007 to 20.58 per 100 000/yr in 2010-2011 (Sellers et al., 2012). The incidence rate among First Nations children in Manitoba is unparalleled anywhere else in Canada. As this is a relatively emerging trend, it is unclear how this may influence the diabetes epidemic among First Nations adults.

Currently, the diabetes epidemic among First Nations in Canada continues to grow. It appears that incidence rates among adults are starting to peak and are now

shifting to higher incidence rates among youth. This further supports the need for research to understand the progression of disease.

Table 2.2. Prevalence of type 2 diabetes among indigenous populations in Canada and United States stratified by sex and non-Indigenous comparison groups (when available).

Population (n)	Measure of diabetes	Type of prevalence	Prevalence of diabetes in men (%)	Prevalence of diabetes in women (%)	Reference
Sandy Bay First Nation ≥ 18 yrs in 2002/2003 (482)	Self-report + fasting glucose (convenience sample)	Crude	27	31	Bruce & Young, 2008
Sandy Lake First Nation ≥10 yrs (728)	Medical chart review and OGTT	Crude			Harris et al., 1997
10-19			0[a]	3	
20-29			5	10	
30-39			27	29	
40-49			29	36	

50-59 **≥60** **All ages**			43 50 16.0	54 45 18.1	
River Desert and Lac Simon Algonquin communities ≥15 years (621)	OGTT	Crude	12	17	Delisle & Ekoé, 1993
Saskatchewan adult population in 1990 **First Nations** **Non-First Nations**	Self-report, chronic disease registry, and family files	Age-adjusted	7.2 5.6	12.1 6.6	Pioro et al., 1996
Manitoba adults ≥20 yrs **First Nations** **1989** **1998** **Non-First Nations**	Administrative data[b]	Age-adjusted	104.2/1000[c] 170/1000	181.6/1000 248.7/1000	Green et al., 2003

1989 **1998**			41.9/1000 59.6/1000	37.1/1000 53.5/1000	
Albertan First Nation Youth **Albertan non-First Nation Youth**	Administrative data[b]	Crude	0.25 0.31	0.31 0.30	Oster et al., 2012
Albertan Status adults (≥20 yrs) (n=72 725) **General Albertan population (n=2 433 695)**	Administrative data[b]	Age-adjusted	11.5 6.2	15.4 5.8	Oster et al., 2011
Adult population in Saskatchewan ***2005*** **Non-First Nations** **First Nations**	Administrative data[b]	Age-adjusted	6.2 16.0	5.5 20.3	Dyck et al., 2010
1980 **Non-First Nations** **First Nations**		Age-adjusted	2.0 4.9	2.0 9.5	
Cree population in Quebec	Self-report	Crude	20.0[d]		Château-Degat

	and fasting glucose				et al., 2009
Navajo adults ≥20 yrs old	Oral Glucose Tolerance Test	Age-standardized	16.9	23.5	Will et al., 1997
American Indian adults from Phoenix, Arizona (n=32 052)	Electronic medical record	Crude	9.7	11.8	O'Connell et al., 2012
California Health Interview Survey (n=43 020) **Native American (n=554)** **Caucasians (n=28 979)**	Self-report	Crude	 16.8 6.8	 13.4 5.2	Harjo et al., 2011
EARTH Study of northern plains and southwest American Indians (n=4457)	Self-report	Crude	15.4	23.2	Sinclair et al., 2011
Behavioral Risk Factor Surveillance System – American Indian and Alaska Natives **1995-1996 (n=2548)**	Self-report	Age-adjusted	 6.0	 7.5	Jernigan et al., 2010

2005-2006 (n=11104)			8.4	8.7	
Behavioral Risk Factor Surveillance System (BRFSS) 2005 **American Indians in North Dakota (n=404)**	Self-report	Age-adjusted	 15.0	 13.0	Holm et al., 2010
BRFSS young adults 18-34 yrs ***1994*** **American Indian/Alaska Native** **Non-Hispanic white** ***2000*** **American Indian/Alaska Native** **Non-Hispanic white** ***2006*** **American Indian/Alaska Native** **Non-Hispanic white**	Self-report	Crude	 1.4[d] 0.8 1.1 0.9 4.4 1.2		Roberts et al., 2009
Cree adults of Eeyou Istchee, Quebec	Physician	Crude			Dannenbaum et

(≥20 years)	diagnosis				al., 2008
20-29			1.9	5.5	
30-39			9.6	15.0	
40-49			15.0	25.3	
50-59			31.6	44.0	
60-69			38.8	50.0	
≥70			25.1	42.5	
Overall crude prevalence			17.3[d]		
Age-adjusted to Quebec pop'n			22.4		
Quebec adults ≥20 yrs old			6.4		

Percent reported unless otherwise noted; OGGT, oral glucose tolerance test

[a] Estimated from figure

[b] Administrative data (includes type 1 and type 2 diabetes)

[c] Prevalence per 1000 cases

[d] Includes both men and women; no significant sex differences were detected or not reported

2.1.2 Obesity

The high incidence and prevalence of diabetes among First Nations populations are partially attributed to the higher prevalence of obesity and abdominal obesity. Prevalence of both obesity and abdominal obesity in several Aboriginal and American Indian groups are summarized in **Table 2.3**. Again, prevalence of obesity is consistently higher among indigenous populations compared to non-indigenous comparison populations. Importantly, prevalence of abdominal obesity (based on waist circumference (WC)) tends to be higher compared to prevalence of obesity (based on BMI), indicating a tendency toward a central body fat distribution. A third pattern observed in Table 2.3 is the higher prevalence of obesity and abdominal obesity among women compared to men. In 2002/2003, 81% of the women in the study population had abdominal obesity compared to 53% of the men (Bruce & Young, 2008).

Table 2.3. Recent reports of prevalence of obesity among indigenous populations in Canada and United States stratified by gender and non-Indigenous comparison groups (when available).

Population (n)	Measure of obesity	Type of prevalence	Prevalence of obesity in men (%)[a]	Prevalence of obesity in women (%)	Reference
Western Canada and province of Ontario (ages 19-50) **Off reserve Indigenous (n=76)** **Non-Indigenous Canadians (n=3468)**	BMI (overweight and obese; BMI ≥ 25)	Estimate of Canadian off-reserve indigenous and non-indigenous populations	33 21	41 18	Garriguet, 2008
Canadian (ages ≥ 18) **Oji-Cree Indians, northern Ontario and**	BMI or WHR >.9 for men or	Crude	35.4	72.2	Liu et al., 2006a

Manitoba (n=1180) **Non-indigenous, Manitoba (n=2058)**	>.85 for women		22.8	29.2	
American (Montana) (ages ≥ 18) **Indians, living on/near to reservations** **(n=1000)** **Non-Indians (n=905)**	BMI	Crude	 30 15	 35 14	Harwell et al., 2001
American (North Dakota) (ages ≥ 18) **American Indian (n=404)** **North Dakota (n=3045)** **United States (n=303,822)**	BMI	Age-adjusted	 53.6 24.6 23.2	 46.7	Holm et al., 2010
American Indian and Alaska Natives (ages>=18) **1995-1996 (n=2548)** **2005-2006 (n=11104)**	BMI	Age-adjusted	 24.4 30.6	 25.5 31.8	Jernigan et al., 2010
Behavioral Risk Factor Surveillance	BMI	Age-			Holm et al.,

System (BRFSS) 2005 **American Indians in North Dakota (n=404)** **North Dakota general population (n=3045)** **US general population (n=303822)**		adjusted	53.6 24.6[a] 23.2	46.7	2010
Quebec Cree adults around James Bay (n=394)	WC[b]	Crude	67.7	94.8	Château-Degat et al., 2011
Adult subjects without diabetes attending screening clinics in Alberta **First Nations (n=1790)** **Non-Aboriginal (n=491)**	 BMI WC[c] BMI WC[c]	Crude	 55.0[a] 76.8 43.5 57.3		Oster & Toth, 2009a
British Columbia adults >=18 from	BMI >27	Crude			Self et al.,

Bella Coola Valley					2005
Aboriginal			65		
Non-aboriginal			47		

BMI, body mass index; Obesity based on BMI defined as BMI ≥ 30 kg/m^2 unless otherwise noted; WC, waist circumference; WHR, waist-to-hip ratio

[a] Refers to the prevalence of obesity for men and women together if separate prevalence are not reported

[b] Obesity defined as waist circumference >94 cm in men and >80 in women

[c] Obesity defined as waist circumference ≥102 cm in men and ≥ 88 cm in women

2.1.3 Cardiometabolic burden

Cardiometabolic measures, including blood pressure, fasting triglycerides (TG), HDL-cholesterol, body mass index (BMI), and waist circumference (WC), are also disproportionately worse among First Nations compared to non-First Nations populations (**Table 2.4**). These measures are generally attributed to high prevalence of abdominal obesity and are consistently shown to be associated with diabetes.

In 2002/2003, 41% of women and 44% of men in the study population were found to have hypertension (Bruce & Young, 2008). Prevalence of hypertension is considerably higher among those with diabetes (Montour & Macaulay, 1988). In addition, high blood pressure increases the risk of complications among those with diabetes (Zacharias et al., 2012).

Dyslipidemia, including high TG, low HDL-cholesterol, is especially common in First Nations populations (**Table 2.4**). Similarly, metabolic syndrome (metS), a composite measure of cardiometabolic health, is highly prevalent. In the study population, the crude prevalence of metS, using the National Cholesterol Education Program's Adult Treatment Panel III criteria, was 53% in 2002/2003 (Riediger et al., 2011) compared to approximately 20% in the Canadian population as reported using the Canadian Health Measures Survey (Riediger & Clara, 2011).

Table 2.4. Mean values of common cardiovascular risk factors among indigenous populations in Canada and U.S. compared to non-indigenous populations when available.

Population (n)	BMI	WC (cm)	SBP (mm Hg)	DBP (mm Hg)	Fasting TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	Reference
NHANES Non-Hispanic white ≥ 20 years old (2003/2004) (n=1519)	N/A	N/A	N/A	N/A	1.5	1.4	3.1	Ghandehari et al., 2008
Adults ≥18 years old Oji-Cree Indians (mean age 36.6) (n=1180)	27.9 ± 5.4	96.6 ± 13.1	125.2 ± 17.2	74.7 ± 12.7	1.3 (0.94-1.84)[a]	1.25 ± 0.32	N/A	Liu et al., 2006b

Non-Aboriginal Manitobans (mean age 49.7) (n=2058)	26.5 ± 4.84	88.6 ± 13.9	129.5 ± 18.9	78.2 ± 9.47	1.33 (0.94-1.94)	1.25 ± 0.33		
Cree, Mistissini, Quebec								Chateau-Degat et al., 2008
Men (n=382)	28.6 ± 5.2	98.3 ± 14.5	123 ± 14	77 ± 9	1.4 ± 0.9	1.2 ± 0.3	3.1 ± 0.8	
Women (n=435)	31.6 ± 6.1	99.1 ± 14.9	120 ± 18	74 ± 10	1.3 ± 0.6	1.3 ± 0.3	2.8 ± 0.6	
Non-indigenous Quebecers (older population compared to Cree)								
Men (n=699)	25.5 ± 3.7	89.8 ± 10.8	125 ± 14	78 ± 9	1.8 ± 1.1	1.2 ± 0.3	3.3 ± 0.9	
Women	24.3 ± 4.8	76.8 ± 11.3	118 ± 17	73 ± 9	1.4 ± 0.8	1.4 ± 0.3	3.2 ± 0.9	

(n=718)								
Quebec Cree **Men (n=69)**[b] **Women (n=103)**[b]	30.4 (26.6-34.9) 34.1 (30.1-38.2)	105 (99-118) 109 (101-118)	121(111-130) 120 (110-131)	74 (70-81) 72 (67-80)	1.55 (1.21-2.28) 1.50 (1.13-1.98)	1.20 (1.1-1.35) 1.27 (1.1-1.48)	N/A	Chateau-Degat et al., 2009
Quebec Cree adults **Men (164)** **Women (230)**	31.7 ± 6.4* 34.7 ± 7.2	109.8 ± 15.8 111.7 ± 16.0	126 ± 15* 120 ± 15	77 ± 10 72 ± 11	1.5 (1.4, 1.6)[c] 1.5 (1.4, 1.6)	1.23 ± 0.3* 1.3 ± 0.3	2.8 ± 0.8* 2.44 ± 0.6	Chateau-Degat et al., 2011
Six Nations Band members Age 35-75 years (Canada; n=301)	N/A	N/A	N/A	N/A	1.94 ± 1.37	1.09 ± 0.40	3.16 ± 0.87	Anand et al., 2001

Cree-Ojibwa Indians (873) **Non-aboriginal (2,670)**	27.7 (27.3, 28.1)[d] 26.4 (26.2, 26.6)	97.0 (96.0, 97.9)[d] 88.5 (87.9, 89.0)	130.6 (129.3, 131.8)[d] 128.6 (127.9, 129.3)	79.8 (79.1, 80.6)[d] 77.8 (77.4, 78.1)	1.66 (1.52, 1.79)[d] 1.59 (1.55, 1.64)	1.28 (1.25, 1.30)[d] 1.24 (1.24, 1.25)	N/A	Young et al., 2002
Pima Indians ≥ 5 years old; no diabetes (787) **Men** **Women**	 31.4 ± 7.3 32.1 ± 6.8	 N/A	 125.3 ± 16.0 112.0 ± 14.6	 76.0 ± 11.6 68.4 ± 11.4	 1.26[b] 1.16	 1.14[b] 1.18	 2.93[b] 2.72	Fagot-Campagna et al., 1997
Strong Heart Study **Diabetes** **Men (211)** **Women (460)**	 32 ± 6 34 ± 6	 N/A	 N/A	 N/A	 1.42 (0.70-3.01)[e] 1.49 (0.86-2.87)	 1.04 (0.78-1.40)[e] 1.12 (0.85-1.50)	 2.89 (1.94-4.01)[e] 2.89 (1.94-3.85)	Fagot-Campagna et al., 1998
Albertan First								Kaler et al.,

Nation community (diabetics excluded)								2006
Adults (176)	31.9 ± 7.0	108.2 ± 17.2	119.4 ± 15.2	77.7 ± 9.8	1.77 ± 0.76	1.04 ± 0.28	2.89 ± 0.86	
Sandy Lake First Nation adults								Pollex et al., 2006
MetS (73)	31.3 ± 0.5[f]	104 ± 1	N/A	N/A	2.36 ± 0.11	1.09 ± 0.03	N/A	
MetS absent (93)	27.4 ± 0.5	92.9 ± 1.2			1.24 ± 0.05	1.27 ± 0.02		
Sandy Lake Oji-Cree adults (≥ 18 years old) Men								Pollex et al., 2006
HTGW (62)	29.9 ± 3.0	106 ± 6.9	124 ± 13	73.6 ± 11.6	2.75 ± 0.71	0.97 ± 0.16	3.29 ± 0.71	

No HTGW (161)	25.6 ± 4.6	93.6 ± 12.1	121 ± 15	68.9 ± 12.2	1.20 ± 0.38	1.27 ± 0.29	2.77 ± 0.82	
Women								
HTGW (45)	31.3 ± 3.6	100 ± 7.2	119 ± 13	69.0 ± 9.1	2.66 ± 0.64	1.18 ± 0.22	2.99 ± 0.74	
No HTGW (254)	28.6 ± 5.7	94.0 ± 12.2	118 ± 16	66.2 ± 10.3	1.30 ± 0.48	1.30 ± 0.28	2.56 ± 0.61	

Results are presented as mean ± standard deviation unless otherwise noted; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; metS, metabolic syndrome; HTGW, hypertriglycermidemic waist

[a] Reported as median (IQR)

[b] Geometric mean (IQR)

[c] Geometric mean (95% CI)

[d] Mean (95% CI)

[e] Geometric mean (10^{th}, 90^{th} percentiles)

[f] Mean ± standard error

2.1.4 Cardiometabolic burden among women

The risk load carried by First Nations women is especially clear. Women are consistently found to have higher prevalence of diabetes (**Table 2.2**) and obesity (**Table 2.3**), whereas the opposite sex difference is true for most other non-indigenous populations with regard to diabetes (**Table 2.2**). This sex difference has also been observed in youth, such that in Alberta, among the under-20 status First Nations population, girls and young women have had a higher diabetes prevalence compared to boys from 1995-2007 (Oster et al., 2009a). In Sandy Lake First Nation, where diabetes prevalence was also higher for women, age-standardized prevalence of impaired glucose tolerance was also significantly higher among women compared to men, at 19.8% vs 7.1% (Harris et al., 1997). The reason for this ethnic-sex difference is unknown but is speculated to relate to pregnancy and the development of gestational diabetes among women.

In Sandy Bay, obesity was significantly more common among women; approximately 80% of women had abdominal obesity (waist circumference >88 cm) and of those 50 years or older, 95% had abdominal obesity. Even among the youngest age group (19-29 years old), 75% of women had abdominal obesity (Bruce et al., 2011). Additionally, women aged 18-29 and aged 50 or older had significantly more chronic conditions (diabetes, hypertension, obesity, dyslipidemia) compared to men in the same age group.

2.1.5 Cardiometabolic burden among youth

The other main feature of the diabetes and chronic disease epidemic among the First Nations population is the young age at which disease occurs and its rapid

progression (Dyck et al., 2010; Dannenbaum et al., 2008). Importantly and as previously mentioned, the incidence and prevalence of diabetes among First Nations youth continues to increase (Oster et al., 2012).

In 2007, there were just over 800,000 registered First Nations people in Canada and they are one of the fastest growing populations, with half of their population being under 25 years old. There are 606 First Nations communities in Canada with the majority (90%) of them having a population less than 1000 persons (Health Canada, 2009). With such a young and growing population (Health Canada, 2009), the diabetes and chronic disease epidemic is only expected to worsen, as many First Nations children have risk factors for diabetes if they have not already been diagnosed (Zorzi et al., 2009; Wahi et al., 2009; Nsiah-Kumi et al., 2013; Kaler et al., 2006; Retnakaran et al., 2005; Retnakaran et al., 2006a; Retnakaran et al., 2006b; Stringer et al., 2009)

2.2 Environment of Risk

2.2.1 Organization & Finance of the Healthcare System for First Nations

Any discussion regarding the health and health care of Canadian First Nations people must be conducted with an understanding of the organization and financing of health care compared to non-First Nations Canadians. Since the introduction of the British North America (BNA) Act and the establishment of Canada as a country, First Nations and Inuit affairs have been under the jurisdiction of the federal government, specifically those with 'Indian status' living on reserve. The BNA Act also assigns health care as being under provincial jurisdiction (Waldram et al., 2006). The term 'status Indian' has been around since the introduction of the first Indian Act. The purpose of this registration as 'status' is to determine eligibility for services promised under treaties,

namely, living on reserve, federally funded health services, and other social and educational benefits (Lavoie et al., 2010a).

The First Nations and Inuit Health Branch (FNIHB) of the Federal government is responsible for funding and in the past, administering the health services on reserve. The federal government, through FNIHB, provides funding for First Nations communities specifically for public health activities, health promotion, and environmental health hazards. Primary care services are only provided on reserve when the community is isolated and no provincial services are reasonably available (Health Canada, 2009). The types of health care provided (community health centre, nursing station, primary care, etc.) is dependent on the degree of isolation.

However, today the majority of communities (>80%) are involved in their own governance of health care or are moving in that direction, with Health Canada still being the primary funder (Romanow, 2002, p213). Despite the high burden of disease, First Nations people received roughly half the funding per capita compared to the general Canadian population (Waldram et al., 2006). Therefore, the organization of healthcare for First Nations people can also contribute to the environment of risk for CV disease with regard to access to quality care.

2.2.2. Colonialism

Colonialism and the low socioeconomic status of Aboriginal people is the proposed broad underlying reason for increased obesity, diabetes and CV disease in this population (Young, 1994). Even though the income gap between Aboriginal people and other Canadians is decreasing, the gap remains unacceptably large (Wilson & Macdonald, 2010). In 2006, Aboriginal people had a median income 30% lower

compared to the general Canadian population, $18,962 compared to $27,097, respectively. Additionally, 8% of Aboriginal people have a bachelor's degree compared to 22% of the general Canadian population (Wilson & Macdonald, 2010).

Studies have consistently shown that low socioeconomic status is associated with poor health, regardless of ethnicity. Among participants of Aboriginal, European, Chinese, and south Asian origin living in Canada, high scores of social disadvantage were associated with older age, female sex, smoking, increasing body weight, high waist-to-hip ratio, blood glucose, and markers of inflammation (Anand et al., 2006). Furthermore, prevalence of CV disease increased with increasing levels of social disadvantage in all ethnic groups; however at every income level, Aboriginal people still had higher rates of CV disease (Anand et al., 2006). Thus differences in socioeconomic status may not fully account for differences in chronic disease rates between Aboriginal and non-Aboriginal people.

Colonisation may have also influenced cultural changes among First Nations populations and for some, the subsequent abandonment of their traditional lifestyles. Although genetic vulnerability plays a role in the excessive burden of chronic disease among Canadian First Nations populations (Ley et al., 2011; Hegele, 1999; Lahiry et al., 2010), it must be mentioned that genetic risk does not equate to inevitability of disease occurrence. In this regard, it was found that genetic risk among Canadian Inuit was equivalent to that of Oji-Cree of Northern Ontario, yet the Inuit experienced much lower rates of diabetes and CV disease (Hegele, 1999). This is attributed to greater participation in traditional activities among the Inuit. Additionally, First Nations people living on reserves in Canada who maintain traditional activities are more likely to rate themselves

as healthy compared to Aboriginal people who do not participate in these activities (Wilson & Rosenberg, 2002). Therefore, the rapid rate of cultural change associated with colonisation may partially explain the increased prevalence of obesity and chronic diseases observed among Aboriginal populations compared to their non-Aboriginal counterparts.

The impact of colonialism remains to this day at the individual, the institutional, and government level (Cook, 2003) (personal communication Marcia Anderson, Colloquium October 1, 2010). In this way, colonisation has not only impacted socioeconomic status and losses in cultural identity but also self-determination at all these levels, which further impacts health (Czyzewski, 2011). Specifically, self-determination and governance in First Nations communities, by way of degree of independence through health transfer, is associated with better health outcomes (Lavoie et al., 2010b). Furthermore, the longer a community has retained control over community health services, the lower its rate of hospitalization for Ambulatory Care Sensitive Conditions (Lavoie et al., 2010b).

2.3 Ethnic-specific risk factors

Treatment and prevention of diabetes and CV outcomes is based on the identification of risk factors such as elevated blood pressure and blood lipids (elevated triglycerides, total cholesterol, and low-density lipoprotein cholesterol, and low high-density lipoprotein cholesterol) and treating those with levels known to increase risk. For this reason understanding the relationship between these risk factors among First Nations populations is essential for optimal treatment and identifying suitable target goals.

Our understanding of First Nation-specific risk factors or First Nation-specific cut-points for established risk factors are limited. This research may play a significant role in population or community level interventions and the importance of this research on individual patient care could be critical. By better understanding risk factors in First Nations populations, health professionals can better treat them. In this section, literature relating to other indigenous groups has also been reviewed due to limited literature regarding First Nations populations and to demonstrate ethnic differences found in other indigenous groups.

2.3.1 Cardiovascular risk scores

Wang and Hoy (2005) provide an excellent example of the differences in the predictive power of varying risk factors in different ethnic groups through the application of the Framingham score to an Australian Aboriginal cohort. The Framingham score is based on traditional CV risk factors derived from a mostly Caucasian population, which includes age, sex, systolic blood pressure, cholesterol levels, high-density lipoprotein (HDL) cholesterol, diabetes status, and smoking status. Their results indicated that CV outcomes among the Australian Aboriginal sample were substantially under-estimated using the Framingham score. The predicted rate of coronary events was 2.5 times lower than the observed rate. The difference between observed and predicted rates was greatest among Aboriginal women; the observed rate of coronary events was 30 times greater than the predicted rate for women under 35 years. This vast difference in predicted and observed rates of coronary heart disease suggests that non-traditional risk factors or differences in the strength of established risk factors for CV disease play a significant role among indigenous people. Importantly, this research demonstrates that research

derived from non-indigenous populations may not necessarily apply to indigenous populations.

Similar results have been reported among other ethnic groups, such that risk equations derived from a mostly Caucasian population (Framingham Offspring study), were not as accurate in prediction of diabetes in a multi-ethnic population compared to equations derived from populations with either African Americans and Caucasian (ARIC study) or Caucasians and Mexican Americans (San Antonio Heart Study) (Mann et al., 2010). Equations from both the ARIC and San Antonio Heart Studies included either African American or Mexican American ethnicity as a variable to be included in the prediction equation, whereas the equation derived from the Framingham Offspring study did not. Furthermore, predictions based on Framingham scores overestimated 5 year risk of coronary heart disease events among Japanese Americans, Hispanic men and American Indian women. D'Agostino and colleagues noted that the difference in CV risk for Native Americans was attributed to differences in risk for HDL cholesterol levels and diabetes (D'Agostino Sr et al., 2001).

2.3.2 Obesity

The issue of defining obesity and the level at increased risk for co-morbidity like CVD is complicated in many ethnic groups, including First Nations populations. Most of the research regarding ethnic specific risk factors has been in the area of BMI or waist circumference. Many have argued that ethnic specific cut-off values for indigenous populations are needed (Carroll et al., 2008; Lear et al., 2007; Misra et al., 2005; Sumner, 2008).

Waist circumference ≥80 cm in women and ≥94 cm in men is considered high risk for individuals of European, Sub-Saharan Africa, Eastern Mediterranean, or Middle East origin according to the International Diabetes Federation (IDF) (International Diabetes Federation, 2012; Alberti et al., 2009); whereas the ATP III WC cut-offs are ≥88 cm for women and ≥102 cm for men, regardless of ethnicity. Some other ethnic groups have their own cut-off values for WC, according to the IDF. For example, South Asians, Chinese, and ethnic south and central Americans have a cut-off of ≥80 cm and ≥90 cm and Japanese have a cut-off of ≥85 cm and ≥90 cm for women and men, respectively. It must be noted that these ethnic specific values have been based on limited evidence. Nevertheless, values for indigenous populations are not provided. Genest and colleagues, representing the Canadian Cardiovascular Society, suggest that South Asian recommendations according to the IDF be used for First Nations people (men ≥ 90cm; women ≥ 80 cm) (Genest et al., 2009).

The use of different cut-offs for various ethnic groups may be related to differences in length of legs or torso. Differences in these proportions may significantly increase or decrease BMI values, such that those with shorter limbs were more likely to be wrongly categorized as obese (Bagust & Walley, 2000; Norgan, 1994). Charbonneau-Roberts and colleagues argue for changes to measuring obesity using sitting height, which would more accurately assess torso length. Previous literature reviewed by Charbonneau-Roberts and colleagues indicates that people of Far East Asian descent and Inuit descent have the highest sitting height to standing ratio at 0.55 and 0.54, respectively (Demirjian, 1980; Pheasant, 1986). On the other hand, Europeans have a mean ratio of 0.52 (Norgan, 1995). This difference in sitting height ratio may explain the

difference in the relationship of BMI and other CV risk factors among Inuit compared to the general Canadian population (Young, 1996a; Young, 1996b).

An alternative explanation is that of differing body composition between ethnic groups. With respect to First Nations, Leslie and colleagues reported that although total body mass was similar among a sample of First Nations and Caucasian women, trunk adipose tissue, trunk lean tissue weight, and total body fat tissue mass were greater among First Nations women (Leslie et al., 2007).

Cardiometabolic burden has been observed to be worse at lower BMI categories among First Nations populations. Razak and colleagues have reported poorer levels of measures related to glucose and lipid metabolism at each respective BMI group among a First Nations sample compared to a sample of individuals of European origin; these results may indicate that lower levels of BMI be recommended among First Nations populations (Razak et al., 2007). Additionally, metabolic risk, assessed using HbA1c, varied between ethnic groups even when age, sex and BMI were matched, potentially indicating the need for ethnic specific cut-off values for BMI (Razak et al., 2005). This research is important to provide rationale for screening those individuals of specific ethnic origin in the traditional 'normal weight' category (18.5-24.9 kg/m^2).

With regard to waist circumference, Chateau-Degat and colleagues reported that non-Aboriginal study participants had lower waist circumference compared to either Cree or Inuit participants, among those that had the same number of metS abnormalities (Chateau-Degat et al., 2008). This is despite the fact that Inuit in general had lower overall CV risk according to metS compared to the non-Aboriginal sample (Chateau-Degat et al., 2008). This finding also supports the notion that Aboriginal populations may

have a different representation of metS compared to a mostly European population. However, this finding is contrary to the previously discussed report by Razak and colleagues (2007) in that Chateau-Degat and colleagues suggest waist circumference cut-points are thought to be higher among First Nations people compared to a non-Aboriginal Quebec population and Razak and colleagues suggested a lower BMI cut-point. This may indicate differences between BMI and waist circumference as a measure of adiposity or differences between First Nations groups.

2.3.3 Other cardiometabolic conditions

Cardiometabolic conditions, aside from BMI and WC, have also shown to vary in their relationships with each other for different ethnic groups. Previous research investigating ethnic differences in CV risk in the Multiethnic Cohort Study, found that there were significant differences in prevalence of risk factors (diabetes, hypertension, smoking) between African Americans, Native Hawaiians, Japanese, and whites (Henderson et al., 2007). The differences in the prevalence of these risk factors significantly explained differences in rates of acute myocardial infarction and other CV outcomes. However, among Native Hawaiians another 69% excess in acute myocardial infarction and other CV outcomes compared to the white sample could not be explained by differences in prevalence of risk factors (Henderson et al., 2007). Therefore, this large study supports the notion that CV risk factors have different degrees of predictability of CV disease and/or different risk factors altogether in different ethnic groups, specifically the indigenous Hawaiian population.

With respect to First Nations populations, elevated C-reactive protein levels among a First Nation sample compared to a sample of European descent is not fully

accounted for by differences in other cardiometabolic risk factors (Anand et al., 2004). Others have also found that relationships between insulin resistance and inflammatory markers differed between First Nations women compared to Caucasian women (Silha et al., 2007).

Some general statements can be made about the research completed to date on cardiometabolic markers. In comparison to general non-Aboriginal populations, First Nations and other Aboriginal populations have on average a large waist circumference and high BMI. With respect to lipids, TG levels are high while HDL-cholesterol is low as is LDL-cholesterol given the risk load. Compared to the general Canadian population, prevalence of diabetes is higher, glucose control is worse, and significant differences between sexes are found at the population level. Although much of the research regarding ethnic differences in relationships between risk factors (as compared to prevalence of risk factors) summarized here is derived from other indigenous groups or other ethnic groups completely, this only further supports the need for Canadian First Nations populations to be included in research comparing ethnic groups, as well as longitudinal research to dig deeper into how the disease progresses.

2.4 Summary of the literature review

The burden of diabetes and CVD among the First Nations population is disproportionately high compared to the overall Canadian population. Importantly, the prevalence has only increased in recent years. Therefore, the implementation of policies and intervention programs are necessary to stem this growing health issue. However, in order to evaluate any future policy changes and intervention programs, we must

understand the direction of the epidemic and the unique development of diabetes and CV risk in this understudied population.

Much of what is known regarding CV risk factors has been derived from research on non-aboriginal populations. Other research indicates that there are substantial ethnic differences in the presentation of these risk factors and their inter-relationships. Despite, a relatively small population, Aboriginal people are one of the fastest growing populations in Canada. Historically, CV research was limited to Caucasian populations and clinical practice guidelines based on those results may not be applicable to a First Nations population. Others have noted that the Canadian Diabetes Clinical Practice Guidelines requires improvement with regards to First Nations guidelines, including messages about related diabetes risk factors (Shubair & Tobin, 2010).

3. METHODS

3.1 Framework

This study was approached using a community-based participatory research (CBPR) framework. CBPR may also be known as “involved”, “collaborative”, “action”, or “centered research” (Isreal et al., 2005). Although the exact scope of each of these methods may differ slightly, the general premise is the same, in that there is a sharing of power. Isreal and colleagues describe 6 core aspects of CBPR: 1) the participatory component is to take into account local context; 2) there should be cooperation and equal contribution between community members and researcher(s); 3) co-learning of both the researcher(s) and community; 4) capacity building in the local community and expanding the “strength and resources in community”; 5) empowerment to reduce social inequities; 6) a balance between research and action or policy change, which may or may not include a direct ‘action’ component, so that all partners can benefit (Isreal et al., 2005).

A Community Diabetes Advisory Group (CDAG) was formed to govern all research in the study community. The CDAG is chaired by Joanne Roulette, Director of the community Health Centre, and Dr. Sharon Bruce (my advisor). Members of the group include the director of home and community care, the Aboriginal Diabetes Initiative (ADI) worker, the community nurse, and others. In keeping with the CBPR framework (Isreal et al., 2005; Minkler & Wallerstein, 2008), the Community Diabetes Advisory Group (CDAG) was an active partner throughout the planning, data collection, and sharing and interpretation of the results. Capacity building was also attained through the employment of community research assistants. Knowledge translation with the community is further described in the ‘Discussion’ chapter.

CBPR should be a long term commitment as it takes time to establish a relationship and the commitment should be beyond a single project and beyond available funding (Minkler & Wallerstein, 2008). In the current study, Dr. Sharon Bruce has an established relationship with Sandy Bay. She has built a foundation of trust, which is why as her student, I was able to conduct my thesis work with the community.

3.2 Study Community

The study community is Sandy Bay Ojibway First Nation, located in southwest Manitoba, approximately 200 km northwest of Winnipeg. This community is accessible year round by road. The total on-reserve population in 2011 was approximately 4100 people with 50% under 19 years old. Sandy Bay was one of the first reserves in Manitoba to apply for and obtain health transfer from the federal government.

3.3 Design

Repeated cross-sectional and prospective cohort designs were adopted. Both designs incorporate baseline data, collected in 2002/2003, and data collected in 2011/2012. Data from the 2002/2003 Diabetes Screening Study were included as baseline data for the prospective cohort component as well as for the repeated cross-sectional design. The repeated cross-sectional design is appropriate for achieving objective 1 of testing differences in diabetes and cardiometabolic risk between 2002/2003 and 2011/2012. The prospective cohort design is appropriate for achieving objective 2 and 3 of determining incidence of diabetes and cardiometabolic conditions as well as predictors of change in risk over time. An 8-year follow-up allows for sufficient time to observe

changes in disease risk over time while minimizing the potential loss to follow-up attributed to long follow-up periods.

Detail regarding the 2002/2003 screening study can be found elsewhere (Bruce & Young, 2008). Briefly, Sandy Bay First Nation invited researchers to conduct a Diabetes Screening Study. Fasting blood, anthropometric, and self-report data were collected between October 2002 and December 2003. The study was previously approved by the University of Manitoba Health Research Ethics Board (H2001:178).

The second cross-sectional study (2011/2012) also included fasting blood, anthropometric, and self-report data. Data collection began July 14, 2011 and was completed on June 5, 2012. The study was previously approved by the University of Manitoba Health Research Ethics Board (H2011:171)

3.4 Sampling

All adults, 18 years and over and non-pregnant, were invited to participate in both study periods. Convenience samples were used because random sampling was not acceptable to the study community; random sampling was not considered fair or equitable to the CDAG. Inclusion criteria were: participants had to be a registered member of Sandy Bay First Nation or a registered member of another First Nation but living in Sandy Bay. Recruitment was conducted through advertisement at the community health centre and radio station, word of mouth, and home visits from community research assistants. Transportation was offered to all participants and provided, if required.

For both the 2002/2003 and 2011/2012 studies we received de-identified population lists from the community, which were aggregated by age and sex, including estimates of number of pregnancies during the study period. In this way, we had proportions of eligible men and women in each age group. Community research assistants were hired from different demographic groups in the community to facilitate recruitment of all demographic groups from the community. In this way, we were able to ascertain throughout the study period whether participants recruited were representative of the community population according to age and sex.

A total of 482 community members participated in 2002/2003, representing 44% of the eligible population. The sample was representative of the community according to age, sex, and employment status (Bruce & Young, 2008). The 2011/2012 sample recruited 596 participants or 28% of the eligible population (eligible population = 2164). The percent of the eligible population was equal between men and women (27.8% for men and 27.3% for women). The age and sex structure of the population and 2011/2012 sample is outlined in **Table 3.1**. The sample is representative of the population according to age and sex. While the samples may not be representative of the population according to other characteristics (outside of age and sex), the convenience sampling strategy was considered the best compromise between representing the community population and values of equity and fairness.

Table 3.1. Age and sex structure of the population and 2011/2012 sample

	Eligible population		Sample	
Age group (years)	Men	Women	Men	Women
18-19	100 (8.9)	71 (6.8)	27 (8.7)	17 (6.0)
20-24	192 (17.1)	157 (15.1)	63 (20.2)	49 (17.3)
25-29	175 (15.6)	132 (12.7)	47 (15.1)	34 (12.0)
30-39	229 (20.4)	256 (24.6)	60 (19.2)	67 (23.6)
40-49	217 (19.3)	233 (22.4)	67 (21.5)	67 (23.6)
50+	210 (18.9)	207 (19.9)	49 (15.7)	49 (17.3)
Total	1123	1041	312	284

Data presented as n (percent)

3.5 Longitudinal data linkage

It is important to note that many participants in the 2011/2012 sample were not included in the 2002/2003 screening study; for example those under 18 years old in 2002/2003 as well as those who chose not to participate. Targeted recruitment was employed to optimize the longitudinal sample size. Specifically, we identified those from the 2002/2003 study that were known to be alive and residing in the community; community research assistants then personally invited those participants to return for the 2011/2012 study. In this way, participants from both the 2002/2003 and 2011/2012 sample were linked to create an 8-year follow-up cohort.

During data collection for the 2011/2012 sample, participants were given new study numbers regardless of their participation in the 2002/2003 study. Subsequently,

returning participants needed to be identified and linked to their previous results. Linking was determined using first name, middle name, last name, birth date, and treaty number. Correct linkage was also further verified using height (cm) collected during both time periods.

3.6 Variables

In the present study, measures included in both the 2002/2003 and 2011/2012 sample were used, with the exception of urinary albumin (mg/dl) and creatinine (g/dl) (2002/2003) and serum creatinine (μmol/L) (2011/2012). The following are CV risk factors that were measured or were necessary for amalgamation to a risk factor: plasma total cholesterol (mmol/L; TC), high-density lipoprotein cholesterol (mmol/L; HDL-C), low-density lipoprotein cholesterol (mmol/L; LDL-C), triglycerides (mmol/L; TG), glucose (mmol/L), insulin (pmol/L), apolipoprotein A1 (g/L), apolipoprotein B (g/L), homocysteine (μmol/L), systolic and diastolic blood pressure (mm Hg; SBP and DBP), height (m), weight (kg), hip circumference (cm), and waist circumference (cm). The measurements previously listed were also used to create several derived variables summarized in **Table 3.2**. With the exception of estimated glomerular filtration rate, HDL-cholesterol, and apoA, all variables are positively associated with CV risk, that is higher values indicate greater CV risk. Information such as self-declared diabetes, self-declared previous diagnosis of hypertension, and medication use in addition to other data, were collected from the questionnaire. These variables are listed and described in **Table 3.3**.

Table 3.2. Description of derived variables for men and women.

Derived variable	Men	Women	Reference
Body Mass Index (BMI)	Weight (kg)/Height $(m)^2$		Standard definition
Obesity	BMI ≥ 30 kg/m^2		World Health Organization, 2012
Abdominal obesity	Waist circumference ≥ 102 cm	Waist circumference ≥ 88 cm	Alberti et al., 2009 Lean et al., 1995
Diabetes	Currently on an oral hypoglycemic, self-declared, or fasting glucose ≥ 7.0 mmol/L		IDF, 2012; American Diabetes Association, 2013; Canadian Diabetes Association, 2013
Impaired fasting glucose	Fasting glucose between 6.1-6.9 mmol/L		World Health Organization, 2006;

			Canadian Diabetes Association, 2013
Hypertension	Previous diagnosis of hypertension; or systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg; or for those with diabetes (previous diagnosis and undiagnosed), SBP ≥130 mm Hg or DBP ≥80 mm Hg		American Diabetes Association, 2011; IDF, 2012; American Diabetes Association, 2013
Dyslipidemia	Fasting plasma TG ≥ 1.7 mmol/L and fasting plasma HDL < 1.03 mmol/L	Fasting plasma TG ≥ 1.7 mmol and plasma HDL < 1.3 mmol/L	Alberti et al., 2009
Metabolic syndrome	Meeting 3 or more of the following criteria: Waist circumference ≥ 102 cm; fasting glucose ≥ 5.6 mmol/L (or previous diabetes diagnosis); fasting TG ≥ 1.7 mmol/L; HDL-	Meeting 3 or more of the following criteria: Waist circumference ≥ 88 cm; fasting glucose ≥ 5.6 mmol/L (or previous diabetes diagnosis); fasting TG ≥ 1.7 mmol/L;	Alberti et al., 2009

	cholesterol < 1.03 mmol/L; or blood pressure ≥ 130/85 mm Hg (or previous diagnosis of hypertension)	HDL-cholesterol < 1.30 mmol/L; or blood pressure ≥ 130/85 mm Hg (or previous diagnosis of hypertension)	
HOMA-IR (Insulin resistance)	(insulin (pmol) x glucose (mmol/L)/22.5) And adjusted to population norms		Matthews et al., 1985
HOMA-β-cell function	20 x insulin/(glucose-3.5) And adjusted to population norms		Matthews et al., 1985
Albumin:creatinine ratio (ACR) (2002/2003 only)	Albumin/ creatinine		N/A
Microalbuminuria (2002/2003 only)	No positive dipstick reading for protein and at least one test with ACR >2.0 mg/mmol	No positive dipstick reading for protein and at least one test with ACR >2.8 mg/mmol	Zacharias et al., 2012
Proteinuria (2002/2003 only)	Dipstick positive proteinuria (>1g/L) or ACR ≥30 mg/mmol on at least one sample		Zacharias et al., 2012

Estimated Glomerular Filtration Rate (eGFR) (2011/2012 only)	$175 \times (\text{creatinine}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \times 1$	$175 \times (\text{creatinine}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \times 0.742$	Levey et al., 2006

Table 3.3. Description of other variables derived from the questionnaire.

Variable	Coding	Question derived from
Age	Continuous (1-80)	Birthdate
Sex	0 – Male 1 - Female	Sex
Current smoker	0 – No 1 – Yes	Do you smoke now?
Ever smoker	0 – No 1 – Yes	Have you ever smoked cigarettes?
Pack years	Continuous ((Years smoke x number of cigarettes/day)/20)	How long have you or did you smoke? (years) How many cigarettes do you or did you smoke in a day?
Employment	0 – Unemployed 1 – Currently employed	Are you currently working for pay (wages, salary, self-employment)?

Education	0 <= Grade 9 1 – Completed higher than grade 9 education	What is the highest level of education you have completed (i.e., graduated)?
Previous history of diabetes	0 – No 1 – Yes	Do you have diabetes?
Previous history of hypertension	0 – No 1 - Yes	Do you have high blood pressure?

3.7 Protocols

Due to the number of participants, each participant had a scheduled day of data collection. During 'data collection day', each participant presented for approximately 1.5 hours to provide anthropometric measurements, blood samples, blood pressure measures and complete questionnaire information. This data collection process was followed in both study periods and was based on the recommendation of the CDAG. The University of Manitoba research team members travelled to the community 5 days per week in 2002/2003 and 2-3 days per week in 2011/2012 until completion of the study. Each participant was instructed to arrive for data collection after a minimum 12 hour fast. No honorarium was provided in 2002/2003 at the request of the CDAG. A $20 honorarium was provided in 2011/2012.

Venous blood samples were drawn by a registered nurse after a minimum 12-hour fast, and processed on site at the health centre, and stored at -20°C. Every week, samples were packed in ice and delivered to the Clinical Chemistry Laboratory at the Health Sciences Centre, Winnipeg for measurement. The Clinical Chemistry Laboratory at the Health Sciences Centre uses internationally recognized standard protocols for measurement of clinical indicators that are standardized against the Centres for Disease Control (CDC). This standardization ensures that the values are comparable to other laboratories. All measures obtained from blood samples were processed at the Clinical Chemistry Laboratory. LDL-C was calculated using the Friedewald equation among those with TG <4.5 mmol/L (Friedewald et al., 1972).

Blood pressure and heart rate were assessed by trained research assistants using an automated cuff. Participants were instructed to sit quietly for a minimum of 5 minutes

to ensure a resting rate. Measurements were taken while the participant sat upright with both feet flat on the floor. Participants were also instructed not to talk while the measurement was taken. At least two blood pressure readings were taken and averaged. When two readings were not reasonably similar, additional readings were taken to determine the most accurate measure.

All anthropometric measures were taken by trained research assistants and participants were instructed to remove footwear and heavy outerwear (jackets, hoodies, and sweaters). Weight in kilograms was recorded to the nearest 0.1 kg using a beam scale. Height was assessed using a metric wall tape. Participants were instructed to stand erect with their back and feet against the wall and their arms hanging by their sides. A set level was placed on the head and the distance from the floor was recorded to the nearest 0.5 cm.

Waist and hip circumference were collected by an inelastic tape with participants standing erect with their arms loosely at their sides. The measurement was taken at the level of natural waist narrowing or at the estimated lateral level of the twelfth or lower floating rib. Among obese participants, the waist was more difficult to identify and could often be more accurately identified by asking the participant to "put their hands on their waist" or identify the bottom of their rib cage. A second research assistant assisted some measurements to ensure the tape remained on a horizontal plane. The research assistant held the tape long enough to ensure the measurement was taken at the end of normal expiration. For hip circumference, the research assistant squatted next to the participant to identify the maximum extension of the buttocks. Again, the tape was placed on a horizontal plane for measurement. For both waist and hip measures, sufficient tension

was applied to maintain its position but not enough to cause indentation of the skin surface. The measurement was recorded to the nearest 0.5 cm.

Random urine samples were collected in the 2002/2003 sample and tested by a Multistix Reagent strips for the presence of protein and blood. For those samples that tested negative, the Bayer® DCA 2000^{TM} Point-of-Care Analyzer was used to determine ACR, which has shown to be accurate and reproducible (Collins et al., 2001; Parsons et al., 1999). Those that tested positive for either protein or blood were requested to return on another day. A maximum of three samples were taken.

3.8 Statistical Analysis

All statistical analysis was conducted using the current version of SPSS (version 22) using a nominal level of significance of α=0.05. The data were cleaned and all relevant variables were explored for their distribution and potential outliers.

A sex and gender-based analysis (SGBA) was used. Briefly, SGBA is a process whereby considerations regarding both sex-based biological and gender-based social influences are taken into consideration. In this regard, sex was not just included as a control variable, rather analysis was also stratified by sex and/or sex*variable interactions were explored to fully understand sex-specific relationships between CV risk factors.

Sociodemographic characteristics are reported for each of the samples. Differences in mean age were tested using an independent sample t-test. Differences in proportion of other characteristics were tested using a χ^2 test of independence.

3.8.1 Objective 1 (repeated cross-sectional)

Firstly, the means (standard deviation), median (IQR), minimum, maximum and distributions (skewness and kurtosis) were determined for all relevant continuous variables. Secondly, frequencies were determined for categorical variables. Crude prevalence of relevant cardiometabolic conditions during each time period for each sex and age group are presented including 95% confidence intervals (95% CI). Sex- and age-standardized prevalence, using the direct method (Young, 2005), were also determined for each cardiometabolic condition, according to the Canadian population, 18 years and older, in 2010 (Milan, 2010). Ninety-five percent CIs were calculated for each sex- and age-standardized prevalence as follows: proportion(p) ± 1.96 * (√(p(1-p)/n)). The 'n' refers to the sample from which the proportion was calculated.

To determine differences in cardiometabolic conditions between the two study periods a non-linear mixed model with random intercept was used. For binary variables, this model can determine if, for example, the odds of diabetes had increased over time while also noting the variance for the random intercept because within-subject errors are correlated. 'Time' was included as both a fixed and random variable. Both age group and sex were used as fixed covariates and time*sex, time*age, and time*sex*age interactions were explored for each outcome variable. The subject-specific heterogeneity of the odds of the respective condition at baseline is important to note as a part of total error variance in the model. This model is also appropriate because data are not available for each participant in both time periods and in this case, the 'missing data' are missing-at-random. There is no reason to assume the data are not missing at random although differences among those with missing data may be reflected in non-measured variables. In situations when the mixed model did not converge, differences in the sex- and age-

adjusted prevalence rates between time periods were tested using χ^2 test of independence. If additional analyses were required to test for differences in specific sex- or age groups, or to adjust for underlying conditions, a binary logistic regression was used with time period as a predictor.

To determine differences in continuous variables between time periods, for example, glucose, a generalized linear mixed model was used. Again, both a random intercept and time as a random variable were used. When mixed models did not converge, a generalized linear model was used with either a linear response (GLM) (for normally distributed variables) or gamma distribution with log link for skewed variables; in other words, the random intercept was dropped from the model. Similarly, age and sex were adjusted for in all models and time*sex, time*age group, and time*sex*age group interactions were explored. Depending on the outcome variable, additional control (confounder) variables were added. For example, to determine differences in fasting glucose between the two time periods, diabetes was added as a control variable.

3.8.2 Objective 2 (prospective cohort)

This analysis was based on data for individuals who had measurements taken during both studies. Firstly, the number of new cases of each of the relevant conditions was determined together with a 95% CI. The 95% CI was calculated as number of new cases ± (1.96 x √(npq)), where n is the number at risk, p is the probability of disease, and q is 1-p. Only those without the respective condition at baseline were included in the denominator.

Age group and sex were explored as potential predictors of incident disease (diabetes, hypertension, obesity, abdominal obesity, and metabolic syndrome) using a

generalized linear model with either Poisson or negative binomial distribution. When the variance approximated the mean, a Poisson distribution was used. In situations of overdispersion (variance was greater than the mean), a negative binomial distribution was used and the BIC and AIC produced were compared to the BIC and AIC from a Poisson distribution. A lower BIC and AIC indicated a better fitting model. The relative risk according to age group and sex is reported, not adjusting for the other in each respective analysis.

3.8.3 Objective 3 (prospective cohort)

This analysis was also based on data for individuals who had measurements for each time period. Changes in the continuous variables in 2011/2012 from 2002/2003 were calculated. Change in each respective variable over time is calculated as follow-up value minus baseline value. As such, positive values are interpreted as an increase in the respective variable over time and negative values are interpreted as a decrease in the respective variable over time. Weight loss was defined as (BMI at follow-up minus BMI at baseline) <0 and weight gain/stable weight was defined as (BMI at follow-up minus BMI at baseline) ≥ 0.

Data analysis for predictors of weight loss, change in apoB, and change in hcy is outlined in **Figure 3.1.** Although statistical analysis clearly informs the final multivariate regression model (step 4), theory is the dominant consideration at each step regarding inclusion of predictor/control variables, and inclusion of additional explanatory analysis. Further description of the statistical considerations at each step is summarized in **Table 3.4.** Both partially adjusted and fully adjusted regression models were fit to the data to determine how the relationship of predictors with the outcome changed with the inclusion

of additional variables in the fully adjusted model. This assisted with understanding issues of strength of association, multi-colinearity, confounding, and independence. Investigation of a dose-response relationship was also necessary given the biological nature of the data and issues with assuming a linear relationship.

The following variables were included in the Spearman and Pearson correlation matrix to determine the relationships with the three outcomes of interest: change in SBP, change in DBP, change in BMI, change in waist, change in waist-to-hip ratio, change in glucose, change in HbA1c, change in total cholesterol, change in HDL-cholesterol, change in LDL-cholesterol, change in TG, change in apoA, change in apoB, change in insulin, change in hcy, change in HOMA-IR, and change in HOMA-β cell function as well as the baseline variables for each of these measures. Furthermore, pack-years and current smoking exposure at baseline were explored as correlates of change in Hcy because current smoking exposure was reported as a significant positive predictor of Hcy cross-sectionally, independent of sex, total cholesterol:HDL ratio, serum Vitamin B12 and serum folate among First Nation youth from Sandy Lake, Ontario, (Retnakaran et al., 2005). Current smoking exposure is defined as number of cigarettes smoked per day, for those that are current smokers. Lastly, ACR at baseline and eGFR at follow-up were also included in the correlation matrix.

Individual continuous variables were used rather than dichotomized derived variables (ex. Diabetes, hypertension, metS, etc) for this objective because the aim was to determine how variables change together. Deriving and dichotomizing variables results in lost information; this is more acceptable for determining population burden (such as in objective 1) as opposed to measures of intra-individual change.

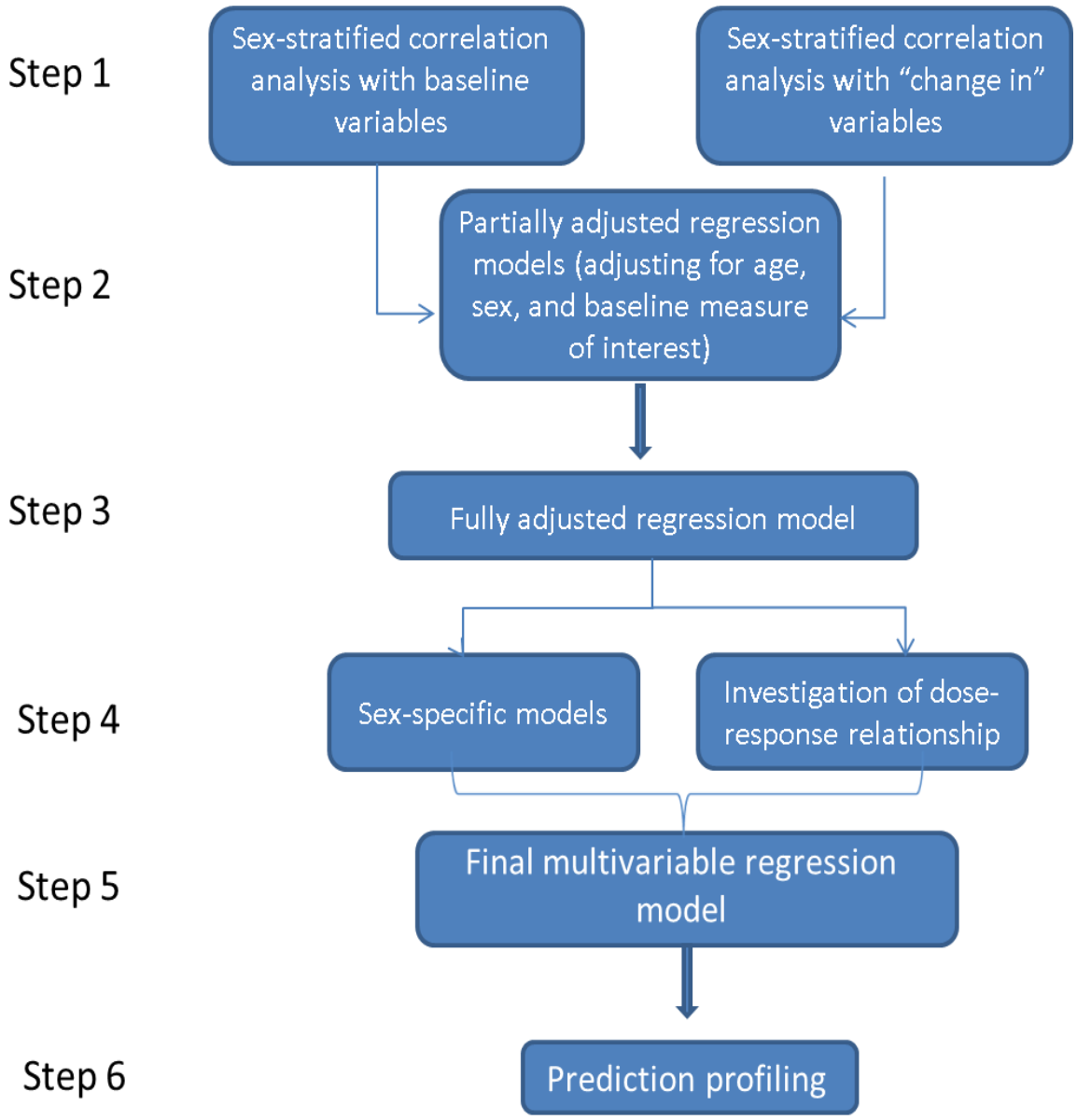


Figure 3.1. Flowchart of steps in statistical analysis for determining predictors of change in cardiometabolic measures.

Table 3.4. Statistical descriptions and considerations at each step in the analysis.

Step	Sub-step(s)	Description
1 - Correlations	Correlation with baseline variables	- Pearson correlation coefficients were used for normally distributed data - Spearman correlation coefficients were used for non-normally distributed data
	Correlation with change in[a] variables	- Pearson correlation coefficients were used for normally distributed data - Spearman correlation coefficients were used for non-normally distributed data
2 – Partially adjusted analysis[b]		- General linear models will be used if all assumptions are met or logistic regression for weight loss - Those variables that were significant in the correlation analysis (for either sex) were investigated in partially adusated analysis adjusted for age, sex, and the baseline variable of interest - For those variables with differing relationships with the outcome between sexes in correlation analysis, a sex-interaction was also included
3 – Fully adjusted analysis[b]		- Those variables (including their interaction term) that were statistically significant in the partially adjusted analysis or required as control variables were included in a multivariable model - After inclusion in the multivariable model some variables were removed from the multivariable model if they were no longer significant ($p<0.05$) or

		were strongly correlated with another predictor
4- Refining the model	Investigation of dose-response relationship	- Tertiles were substituted for continuous variables to investigate the extent of a dose-response relationship
	Sex-specific models	- Sex-specific models were conducted to verify that relationships were similar between the sexes that did not include a sex interaction
5 – Development of a final multivariable model		- The final model will take into account the findings from step 3 and step 4 to produce a final multivariate model that best describes the outcome of interest (based on both theory and statistics) Note: Since theory is a major factor in building the model, neither BIC nor AIC values will be reported in developing the models
6 – Prediction profiling		- Estimating the outcome was conducted using Microsoft Excel - The outcome (either continuous outcome or odds of outcome) was predicted using different values of predictors. - This analysis was conducted to illustrate the relationships between predictor and outcome, particularly any interaction effects, in the final model.

[a] Change in refers to follow-up value minus baseline value, therefore a positive value denotes an increase over time and a negative value denotes a decrease over time

3.9 Ethical considerations

My advisor, Dr Sharon Bruce, has forged a strong relationship with the community of Sandy Bay First Nation. As such, we have the support of the community to undertake this study in partnership with them using a CBPR framework, previously described. Specifically, the studies were approved by the Health Centre and by Band Council Resolution. We have and will continue to follow the principles of OCAP (Ownership, Control, Access and Possession) (Assembly of First Nations, 2007) and adhere to the Tri-council Policy Statement: Ethical Conduct for Research Involving Humans Chapter 9: Research involving First Nations, Inuit and Métis peoples of Canada (Tri-council policy statement, 2010, chapter 9).

Lastly, the larger project was approved from the University of Manitoba Health Research Ethics Board. As such, every participant provided informed consent prior to their completion of the questionnaires and all data has remained confidential. Additionally, I obtained ethical approval for secondary data analysis (H2012:036) for the work presented in this thesis.

4. RESULTS

There were a total of 482 participants in the 2002/2003 sample, 596 participants in the 2011/2012 sample, and 171 participants that completed study protocol during both time periods. A description of the participation is illustrated in **Figure 4.1.**

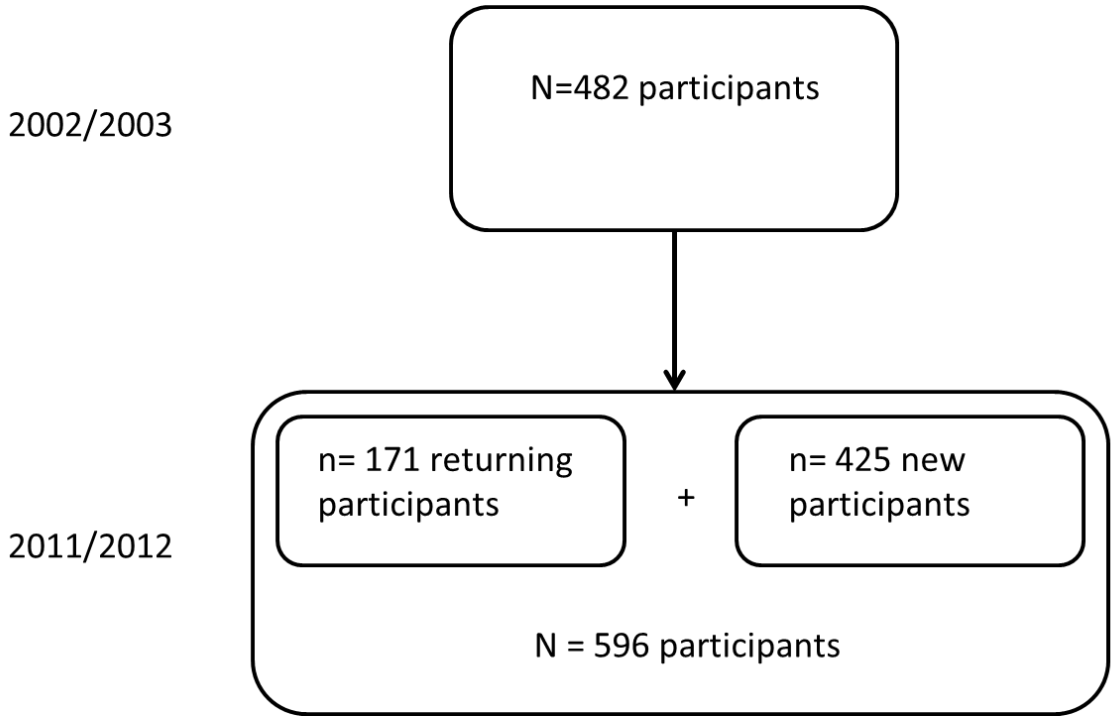


Figure 4.1. Illustration of datasets.

4.1 Repeated cross-sectional study results (Objective 1)

A description of the study samples for both time periods is found in **Table 4.1**. As previously mentioned, both samples, although convenience samples, were representative of the community population at the time according to age and sex. The sample in 2011/2012 is significantly younger (p=0.007) but has a similar proportion of men and women (p=0.131). In addition, the sample in 2011/2012 has a significantly higher level of education but a significantly lower employment rate compared to 2002/2003. The

higher level of education may be a result of the cohort effect of those that attended residential school; specifically, those that attended residential school generally had a lower level of education. Please note that many of the results for objective 1 have also been published elsewhere (Riediger et al., 2014).

Table 4.1. Description of cross-sectional study samples ((mean ±std dev) or n (%)).

Variable	2002/2003 (n=482)	2011/2012 (n=596)	p-value
Age (years)	37.8 ± 12.3	35.7 ± 12.9	0.007[b]
Age groups			0.001[c]
18-29 years	142 (29.5)	237 (39.8)	
30-39 years	144 (29.9)	127 (21.3)	
40-49 years	108 (22.4)	134 (22.5)	
≥50 years	88 (18.3)	98 (16.4)	
Sex			0.117[c]
Men	230 (47.7)	313 (52.5)	
Women	252 (52.3)	283 (47.5)	
Marital status			0.070[c]
Never married	184 (39.3)	189 (36.1)	
Married/common-law	255 (54.5)	281 (53.7)	
Separated/divorced/widow/widower	29 (6.2)	53 (10.1)	
Highest level of education			<0.001[c]
< grade 9[a]	248 (53.0)	159 (27.2)	
≥ grade 9	220 (47.0)	426 (72.8)	
Employed			0.002[c]
Yes	137 (28.8)	123 (20.6)	
No	338 (71.2)	473 (79.4)	

[a] Based on median split in 2003 sample

[b] Independent sample t-test

[c] chi-square

4.1.1 Diabetes

The crude prevalence of diabetes in 2002/2003 was 29.0% (95% CI: 25.0, 33.1) and 25.9% (95% CI: 22.4, 29.4) in 2011/2012. An additional 6.2% (95% CI: 4.1, 8.4) had IFG in 2002/2003 and 6.1% (95% CI: 4.2, 8.0) in 2011/2012. During both study periods the diabetes prevalence was not significantly higher among women compared to men at 31.0% (95% CI: 25.2, 36.7) vs 27.0% (95% CI: 21.2, 32.7) in 2002/2003 (p=0.334) and 27.1% (95% CI: 21.9, 32.2) vs 24.8% (95% CI: 20.0, 29.6) in 2011/2012 (p=0.513). The sex- and age-stratified crude prevalence of diabetes and IFG are illustrated in **Figures 4.2 and 4.3**, respectively. The sex- and age-standardized diabetes prevalence was 39.4% (95% CI: 35.1, 43.8) and 39.2% (95% CI: 35.3, 43.1) in 2002/2003 and 2011/2012 (Appendix 8.1), respectively.

In determining changes in odds of diabetes between time periods, non-linear mixed models did not converge. This is likely due to the limited number of participants with data for both time periods. Consequently, differences in sex- and age-adjusted prevalence rates between time periods were tested using χ^2 test. Using a χ^2-test, the sex- and age-standardized prevalence of diabetes was not statistically significant between the time periods (p=0.992). Similarly, mixed models did not converge for any other outcomes and results for χ^2 test are reported throughout.

In 2002/2003, 75.0% of all those with diabetes had previously diagnosed diabetes and 25.0% had undiagnosed diabetes corresponding to 7.3% (95% CI: 5.0, 9.6) of the total sample (35/478); in 2011/2012, 76.6% (118/154) of all those with diabetes had previously diagnosed diabetes and 23.4% (36/154) had undiagnosed diabetes corresponding to 6.1% (95% CI: 4.2, 8.0) of the total sample (36/595). Of those with

diabetes, 25.4% (35/138; 95% CI: 18.1, 32.7) met the HbA1c target of <7.0% (IDF, 2005) in 2002/2003 and 26.0% (40/154; 95% CI: 19.1, 32.9) met the target in 2011/2012.

Among those with diabetes, there was not a significant difference in length of time with diabetes (years) between time periods (p=0.151), independent of age group and sex (generalized linear model with gamma distribution, data not shown). In 2002/2003, the mean age of diabetes diagnosis was 38.6 years for men and 38.0 years for women and in 2011/2012 the mean ages were 37.9 and 37.0 for men and women, respectively.

Similar to the non-linear mixed models, generalized linear mixed models did not converge. For this reason, the random intercept was dropped (ie. non-mixed models were used) for all remaining analysis to test for differences in continuous variables between time periods. Descriptions of the distributions of continuous variables related to glucose metabolism are in **Table 4.2**. Fasting glucose and HbA1c were not normally distributed and generalized linear models with gamma distribution and log link function were most appropriate in each case to determine differences between time periods; also, compared to a general linear model, the generalized linear model with gamma distribution and log link produced a lower BIC and AIC.

There was a significant interaction (p=0.033) of sex and diabetes status with time period on fasting glucose independent of age group. Therefore the difference in fasting glucose between time periods was dependent on sex and diabetes status. The models were then stratified by sex and diabetes status to better understand this interaction. Fasting glucose was significantly higher in 2011/2012 compared to 2002/2003 among men and women without diabetes (p<0.001), independent of age group (**Table 4.3**). Mean fasting glucose was 5.39 mmol/L (SD: 0.49) among those without diabetes in 2011/2012

compared to 5.21 mmol/L (SD: 0.58) in 2002/2003. Men and women differed in their relationship between time period and glucose among those with diabetes. However, in stratified analysis among those with diabetes, neither men nor women had a significantly different mean glucose between time periods. Although an interaction with age group was not statistically significant, the higher glucose between time periods is probably more apparent in the younger age groups because the majority of those without diabetes are under 50 years old. HbA1c was also significantly higher ($p<0.001$) among those without diabetes in 2011/2012 compared to 2002/2003, independent of age group and sex (model 2; **Table 4.4**). Among those without diabetes, mean HbA1c was 5.78% (SD: 0.34) in 2011/2012 compared to 5.60% (SD: 0.42) in 2002/2003.

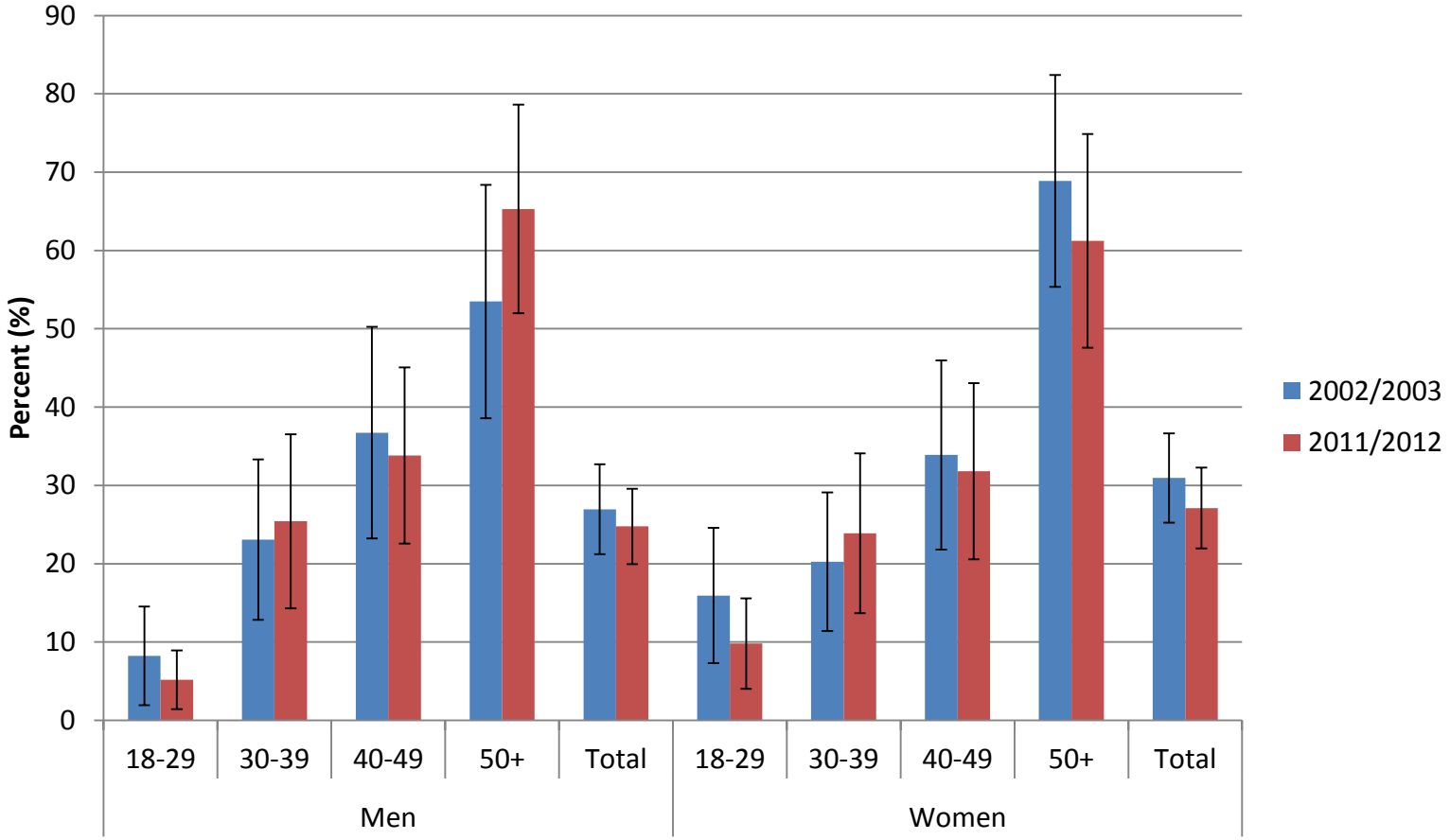


Figure 4.2. Sex- and age-specific crude prevalence of diabetes in each time period.

Note that bars represent 95% CIs.

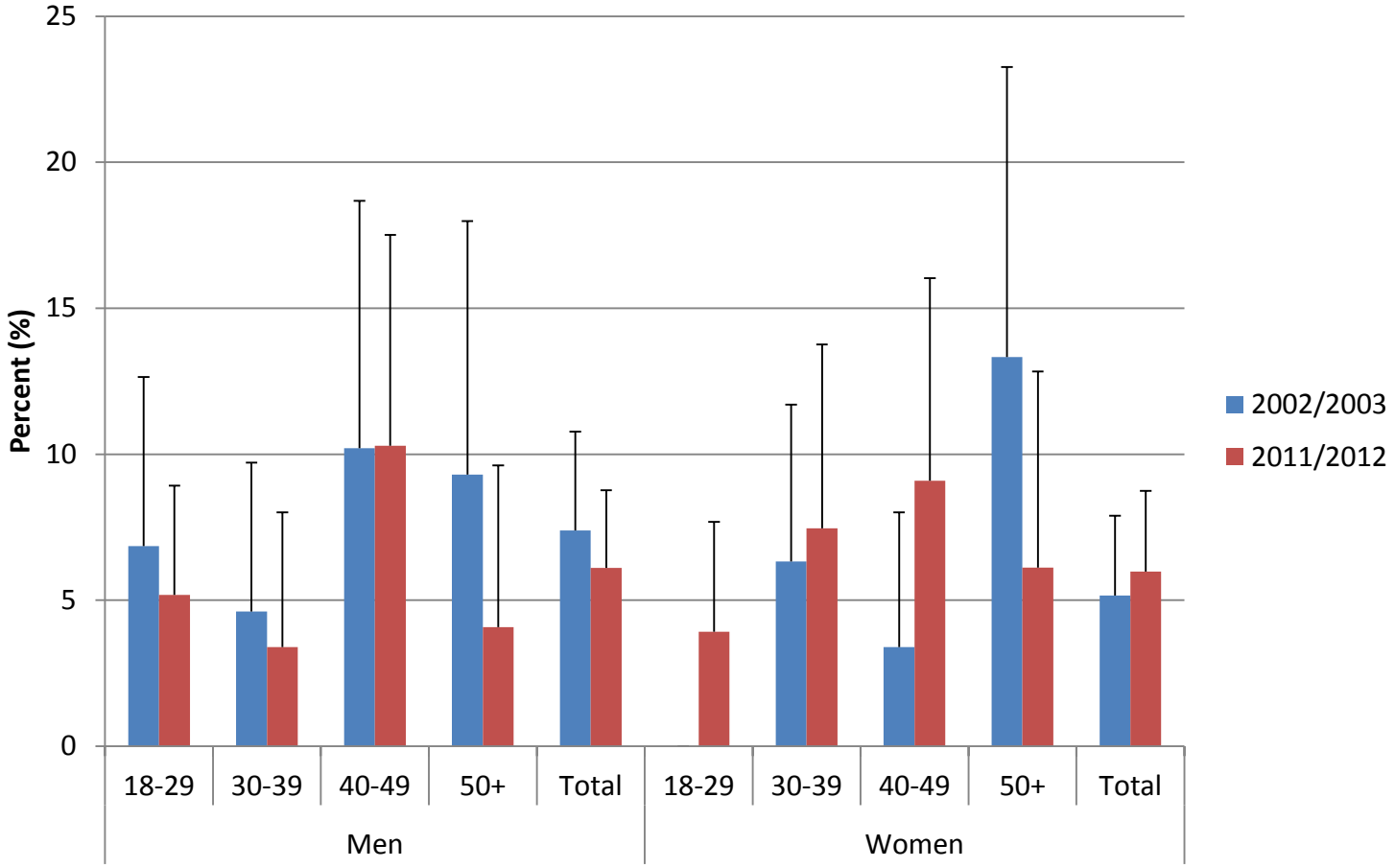


Figure 4.3. Sex- and age-specific crude prevalence of impaired fasting glucose in each time period.

Note that bars represent 95% CIs.

Table 4.2. Description of continuous variables related to glucose metabolism

Variables	Mean ± standard deviation	Median (25^{th}, 75^{th} percentiles)	Skewness	Kurtosis
Fasting glucose	6.898 ±3.3585	5.5 (5.1, 6.7)	2.173	4.168
HbA1c	6.578 ±1.9078	5.8 (5.5, 6.5)	2.153	4.234

Table 4.3. Time period as predictor of fasting glucose stratified by diabetes status and sex.

Sex	No Diabetes		Diabetes	
	β (standard error)	p-value	β (standard error)	p-value
Men	0.038 (0.0093)	<0.001	0.044 (0.0594)	0.458
Women	0.042 (0.0101)	<0.001	-0.077 (0.0560)	0.168

Coefficients presented are those for 2011/2012 compared to 2002/2003 as reference period and adjusted by age group.

Table 4.4. Time period as a predictor of Hba1c.

Sex	No Diabetes		Diabetes	
	β (standard error)	p-value	β (standard error)	p-value
Model 1	0.031 (0.0047)	<0.001	0.014 (0.0302)	0.651
Model 2[a]	0.036 (0.0044)	<0.001	0.007 (0.0295)	0.806

Coefficients presented are those for 2011/2012 compared to 2002/2003 as reference period

[a] Adjusted for sex and age group

4.1.2 Hypertension

The crude prevalence of hypertension in 2002/2003 was 40.8% (95% CI: 36.3, 45.2) and 39.4% (95% CI: 35.4, 43.3) in 2011/2012. Sex- and age-stratified crude prevalence in each time period are illustrated in **Figure 4.4**. Crude prevalence for men was 37.3% (95% CI: 31.0, 43.6) and 44.0% (95% CI: 38.5, 49.5) and 44.0% (95% CI: 37.8, 50.3) and 34.3% (95% CI: 28.7, 39.8) for women, in 2002/2003 and 2011/2012, respectively. The prevalence was not significantly different between men and women in 2002/2003 (p=0.136). However, the crude prevalence of hypertension was significantly higher for men compared to women in 2011/2012 (p=0.029). The sex- and age-standardized prevalence of hypertension was 52.4% (95% CI: 47.9, 56.9) and 53.1% (95% CI: 49.1, 57.2) in 2002/2003 and 2011/2012 (Appendix 8.2), respectively, and not significantly different (p=0.970). Undiagnosed hypertension was found in 13.6% (95% CI: 10.5, 16.7) of the sample in 2002/2003, comprising 34.1% of those with hypertension, and 18.6% (95% CI: 15.5, 21.7) in 2011/2012, comprising 47.2% of those with hypertension. Among those with diabetes (including those newly diagnosed) in 2002/2003, 82.2% (95% CI: 75.6, 88.8) had hypertension and among these, 31.0% (95% CI: 23.0, 39.0) of cases were undiagnosed. In 2011/2012, 78.0% (95% CI: 71.5, 84.5) of those with diabetes had hypertension and 34.4% (95% CI: 26.9, 41.9) of these cases were undiagnosed (**Figure 4.5).**

Both SBP and DBP closely approximated a normal distribution (**Table 4.5**), therefore a general linear model was used to determine differences between time periods. A significant interaction between sex and time period on SBP was found; this relationship was further explored in sex-stratified analysis. SBP was not significantly

different between time periods for men, independent of age group and hypertension status. For women, there was a significant interaction between time period and hypertension status and in a separate model, a significant interaction between time period and age group. Upon further stratification, among women with hypertension, SBP was not significantly (p=0.504) different between time periods, independent of age group (**Table 4.6**). However, among women without hypertension, SBP was 7.919 mmHg (SE: 1.1847) lower in 2011/2012 compared to 2002/2003 (p<0.001), independent of age group (**Table 4.6**); no significant interactions of time period with age group on SBP were found among those with hypertension or those without.

DBP was 3.421 mm Hg higher in 2011/2012 for men compared to 2002/2003 (p<0.001), independent of age group and hypertension status (model 2; **Table 4.7**). For women, a significant interaction of time with hypertension status was found (model 3) and further investigated in a hypertension-stratified analysis. While women without hypertension did not have significantly different DBP between time periods (p=0.318), women with hypertension had a mean DBP 6.6 mm Hg (SE: 1.654) higher in 2011/2012 compared to 2002/2003 (p<0.001), independent of age group.

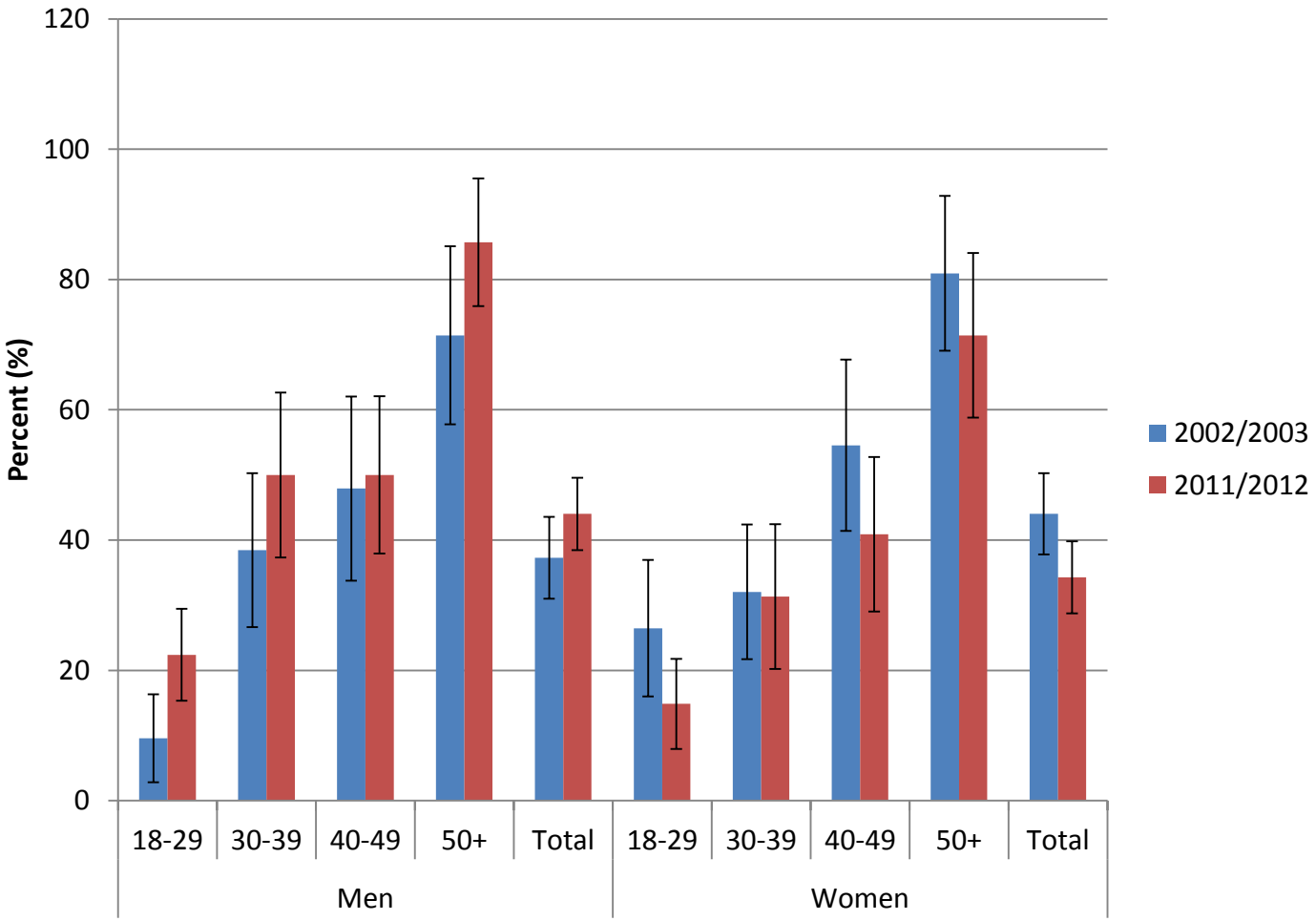


Figure 4.4. Sex- and age-specific **c**rude prevalence of hypertension in each time period.

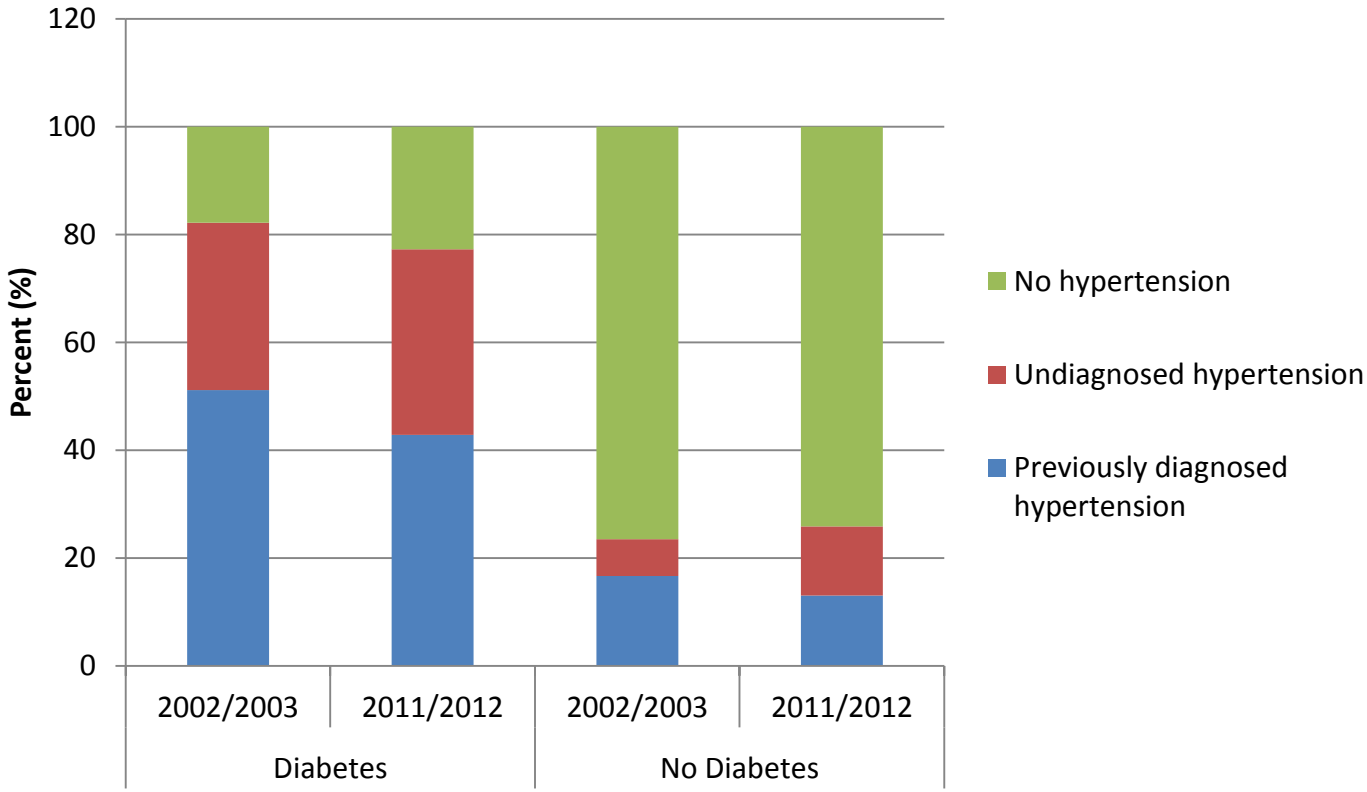


Figure 4.5. Hypertension status according to diabetes status in 2002/2002 and 2011/2012.

Table 4.5. Description of continuous variables related to blood pressure.

Variables	Mean ± standard deviation	Median (25^{th}, 75^{th} percentiles)	Skewness	Kurtosis
SBP	125.8 ± 17.9	124.0 (113, 136)	0.756	1.637
DBP	78.4 ± 11.3	77.5 (70.0, 85.0)	0.607	0.867

SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 4.6. Time period as a predictor of systolic blood pressure among women.

Model	Hypertension		No hypertension	
	β (standard error)	p-value	β (standard error)	p-value
Model 1	-1.768 (2.6451)	0.504	-7.919 (1.1847)	<0.001

Coefficients for time period, adjusted by age group, are presented with 2002/2003 as reference period.

Table 4.7. Time period as a predictor of diastolic blood pressure.

Sex	Model	β (standard error)	p-value
Men	Model 1	3.887 (0.947)	<0.001
	Model 2[a]	3.421 (0.801)	<0.001
Women	Model 1	1.792 (0.993)	0.071
	Model 2[a]	3.039 (0.833)	<0.001
	Model 3[a]		
	Time	0.761 (1.059)	0.472
	Hypertension[b]	9.836 (1.255)	<0.001
	Time*Hypertension[b]	5.767 (1.683)	0.001

Coefficients for time period are presented with 2002/2003 as reference period.

[a] Adjusted by age group and hypertension

[b] No hypertension is the reference group

4.1.3 Obesity

The crude prevalence of obesity in 2002/2003 was 56.6% (95% CI: 52.1, 43.4) and 47.4% (95% CI: 43.4, 51.4) in 2011/2012. Sex- and age-stratified crude prevalence of obesity are illustrated in **Figure 4.6**. Sex-specific crude prevalence for men and women were 47.6% (95% CI: 41.1, 54.1) and 65.1% (95% CI: 59.1, 71.2) in 2002/2003 and 35.6% (95% CI: 30.3, 40.9) and 60.2% (95% CI: 54.5, 65.9) in 2011/2012. During both time periods, the sex-specific prevalence was significantly higher in women compared to men (2002/2003, $p<0.001$; 2011/2012, $p<0.001$). The sex- and age-standardized prevalence was 60.8% (95% CI: 56.4, 65.2) and 48.6% (95% CI: 44.6, 52.7) in 2002/2003 and 2011/2012, respectively (Appendix 8.3). The sex- and age-standardized prevalence of obesity was significantly lower in 2011/2012 ($p<0.001$). However, this is mostly accounted for by a lower prevalence of obesity among men aged 40-49 and 50 years and older (Figure 6.5). For example, among men aged 40-49 years, crude prevalence of obesity was 62.5% (95% CI: 48.8, 76.2) in 2002/2003, and 27.3% (95% CI: 16.5, 38.0) in 2011/2012. Logistic regression models confirmed a significantly lower odds of obesity in 2011/2012 compared to 2002/2003 among men aged 40-49 and ≥50 years (**Table 4.8**). The models for men were further adjusted by diabetes status, because diabetes can result in weight loss. However, these adjustments did not change the significant difference in odds of obesity between time periods among men in either age group (model 2; Table 4.11).

BMI has a normal distribution (**Table 4.9**), therefore, a general linear model was used to test for differences in BMI between time periods. In pooled analysis of men and women, a three-way interaction with age group, sex, and time period was found; again, a

sex-stratified analysis was completed. Similar to obesity, BMI was not significantly different between time periods among women, independent of age group. Among men, the analysis was further stratified by age group (**Table 4.10**). In 2011/2012, BMI was 4.4 kg/m^2 lower among men 40-49 years old and 1.9 kg/m^2 lower among men 50+ compared to 2002/2003 (models 1, Table 4.13). Again, the significant difference of BMI between time periods remained after adjustment for diabetes status (models 2, Table 4.13).

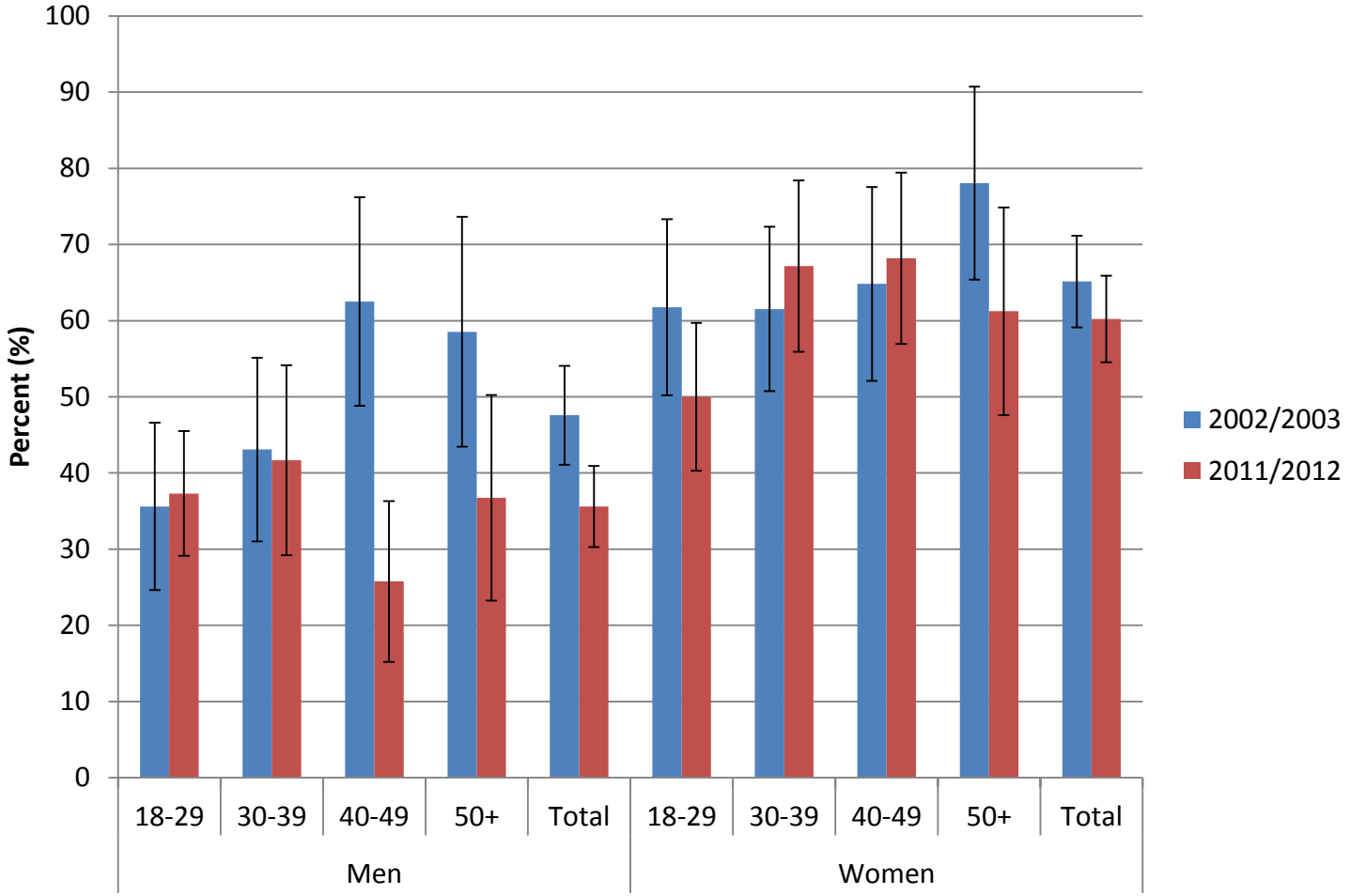


Figure 4.6. Sex- and age-specific crude prevalence of obesity in each time period.

Note that bars represent 95% CIs.

Table 4.8. Odds of obesity for time period among men only and stratified by age group.

Age group	Odds of obesity (95% CI)	p-value
18-29 years		
Model 1	1.051 (0.581, 1.901)	0.869
30-39 years		
Model 1	0.944 (0.464, 1.920)	0.873
40-49 years		
Model 1	0.213 (0.095, 0.475)	<0.001
Model 2[a]	0.212 (0.095, 0.475)	<0.001
≥50 years		
Model 1	0.411 (0.176, 0.963)	0.041
Model 2[a]	0.336 (0.135, 0.832)	0.018

Binary logistic regression with coefficients for time period presented with 2002/2003 is the reference period.

[a] Adjusting for diabetes status

Table 4.9. Description of continuous variables related to adiposity.

Variables	Mean ± standard deviation	Median (25^{th}, 75^{th} percentiles)	Skewness	Kurtosis
BMI	30.828 ±7.110	30.2 (25.935, 34.700)	0.699	0.836
Waist circumference	103.992 ±16.680	103.00 (92.250, 115.000)	0.377	0.735

Table 4.10. Time period as a predictor of BMI among men and stratified by age group.

Age group	Model	β (standard error)	p-value
18-29 years	Model 1	-0.425 (0.9968)	0.670
30-39 years	Model 1	1.040 (1.0202)	0.308
40-49 years	Model 1	-4.436 (0.9749)	<0.001
	Model 2[a]	-4.429 (0.9747)	<0.001
≥50 years	Model 1	-1.915 (0.9158)	0.037
	Model 2[a]	-2.169 (0.9059)	0.017

Coefficients for time period presented with 2002/2003 as the reference period.

[a] Adjusted by diabetes status

4.1.4 Abdominal obesity

The crude prevalence of abdominal obesity in 2002/2003 was 67.4% (95% CI: 63.1, 71.7) and 64.6% (95% CI: 60.7, 68.4) in 2011/2012. The sex- and age-stratified crude prevalence of abdominal obesity are illustrated in **Figure 4.7**. Sex-specific crude prevalence were 53.1% (95% CI: 46.6, 59.6) and 81.0% (95% CI: 76.0, 86.0) in 2002/2003 and 47.6% (95% CI: 42.0, 53.1) and 83.0% (95% CI: 78.7, 87.4) in 2011/2012, for men and women, respectively. Again, the prevalence was significantly higher for women compared to men in each time period (2002/2003, $p<0.001$; 2011/2012, $p<0.001$). Sex- and age-standardized prevalence was 73.8% (95% CI: 69.8, 77.8) and 69.1% (95% CI: 65.3, 72.8) in 2002/2003 and 2011/2012, respectively (Appendix 8.4), which was not significantly different ($p=0.258$).

WC was normally distributed (**Table 4.9**), therefore a general linear model was used to determine differences in WC between time periods. Because of the difference in WC between men and women, a stratified analysis was conducted *a priori*. A significant time*age group interaction was found for both men and women in the 40-49 year old age group. Therefore, analysis for each sex was further stratified by age group (**Table 4.11**). For women aged 40-49 years, WC was 9.06 cm greater in 2011/2012 compared to 2002/2003 ($p=0.002$). Among men age 30-39 years, WC was 5.35 cm greater in 2011/2012 ($p=0.039$) and among men 40-49 years, WC was 9.07 cm less in 2011/2012 ($p=0.002$) compared to 2002/2003.

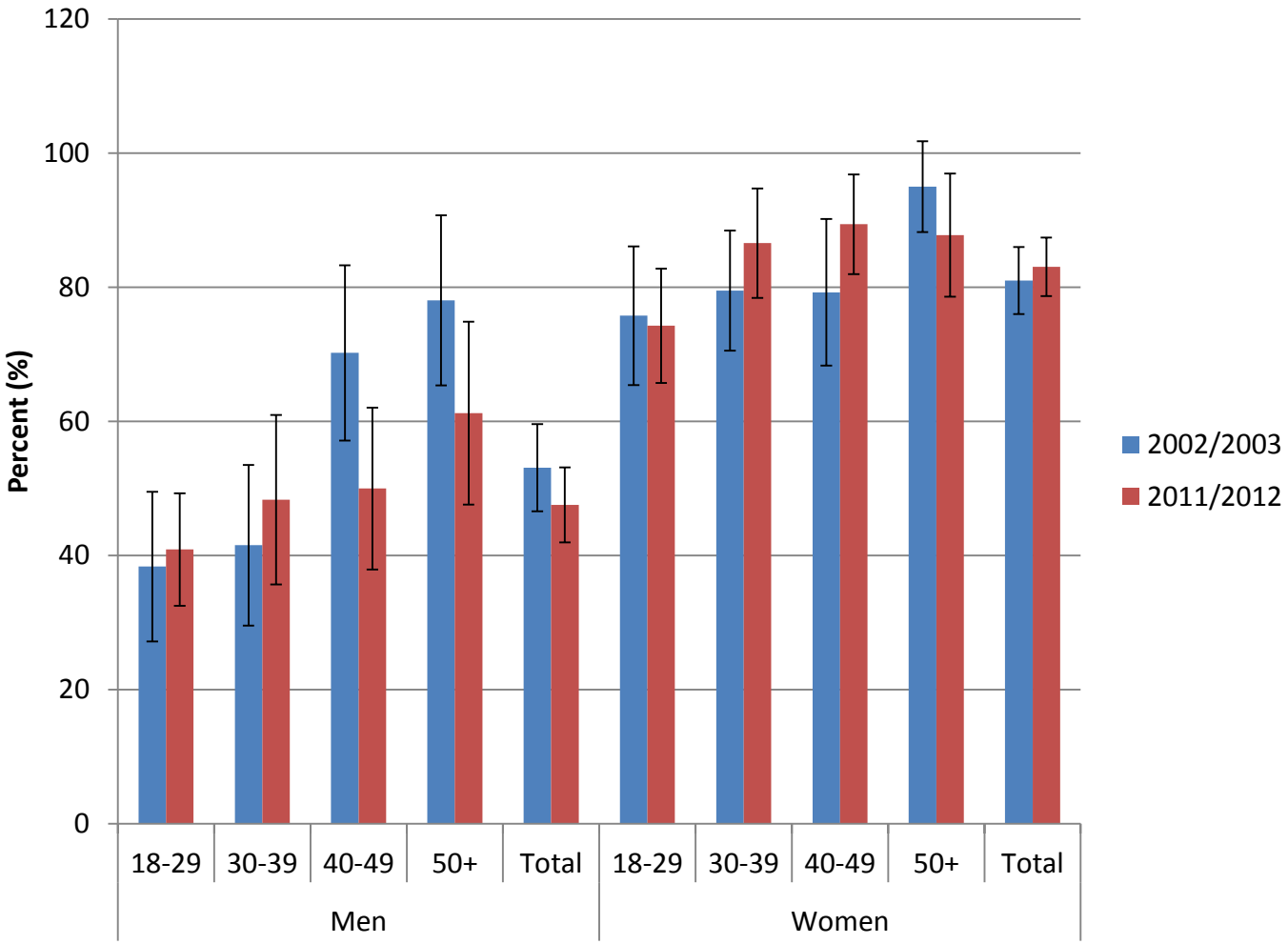


Figure 4.7. Sex- and age-specific crude prevalence of abdominal obesity in each time period.

Note that bars represent 95% CIs.

Table 4.11. Time period as a predictor of waist circumference according to sex and age group.

	Men		Women	
Age group	β (standard error)	p-value	β (standard error)	p-value
18-29 years	1.395 (2.502)	0.577	-1.566 (2.967)	0.598
30-39 years	5.347 (2.585)	0.039	2.234 (0.431)	0.431
40-49 years	-9.072 (2.988)	0.002	9.058 (2.933)	0.002
≥50 years	-2.191 (2.453)	0.372	-2.357 (3.083)	0.445

Coefficients for time period are presented with 2002/2003 as the reference period.

4.1.5 Dyslipidemia

The crude prevalence of dyslipidemia in 2002/2003 was 31.1% (95% CI: 27.0, 35.3) and 25.4% (95% CI: 21.9, 28.9) in 2011/2012. The sex- and age-stratified crude prevalence of dyslipidemia in each time period is illustrated in **Figure 4.8**. Sex-specific crude prevalence were 25.2% (95% CI: 19.6, 30.8) and 36.5% (95% CI: 30.6, 42.5) in 2002/2003 and 20.3% (95% CI: 15.8, 24.7) and 31.0% (95% CI: 25.6, 36.4) in 2011/2012, for men and women, respectively. The sex-specific prevalence was significantly higher in women compared to men in each time period (2002/2003, p=0.007; 2011/2012, p=0.003). The sex- and age-standardized prevalence was 32.6% (95% CI: 28.5, 36.8) and 30.4% (95% CI: 26.8, 34.1) in 2002/2003 and 2011/2012, respectively (Appendix 8.5), and not significantly different (p=0.731).

The distribution of the individual lipids is summarized in **Table 4.12**. Both TC and LDL-C were not included because their interpretation between time periods would be complex to interpret. TC includes cholesterol from both LDL and HDL hence it would be of more value to measure the individual lipoprotein cholesterol levels. LDL-C likely has an inverse U-shaped relationship with cardiometabolic disease progression. This, together with the heterogeneity of disease progression at the population level, would complicate comparisons between time periods. TG and HDL-C have a skewed distribution, therefore models to test differences between time periods used a gamma distribution as a GLM assumes a normal distribution.

For men, a significant interaction between time period and age group on HDL-C was found; Sex- and age group-stratified models were completed for HDL-C (**Table 4.13**). For men aged 40-49 years old, HDL-C was 0.169 mmol/L higher (p=0.022) in

2011/2012 compared to 2002/2003. HDL-C was not significantly different between time periods for women in any age group.

There was a significant age group, sex, time period interaction for TG (p=0.040). Analyses were stratified by age group and sex (**Table 4.14**). TG was 1.327 mmol/L lower in 2011/2012 compared to 2002/2003 among men aged 40-49 years old. Among women, TG was not significantly different between time periods for women in any age group.

ApoA was significantly higher in 2011/2012 by 0.22 g/L compared to 2002/2003 (p<0.001), independent of age group and sex (model 2, **Table 4.15**). In full models (ie. non-stratified), a significant interaction between time and age group for apoB was found, therefore age group-stratified analysis was completed (**Table 4.16**). ApoB was significantly lower in every age group in 2011/2012 compared to 2002/2003, independent of sex, but at varying degrees. ApoB was 0.06, 0.06, 0.16, and 0.08 g/L lower among 18-29 year olds, 30-39 year olds, 40-49 year olds, and those 50 years and older, respectively, in 2011/2012 compared to 2002/2003.

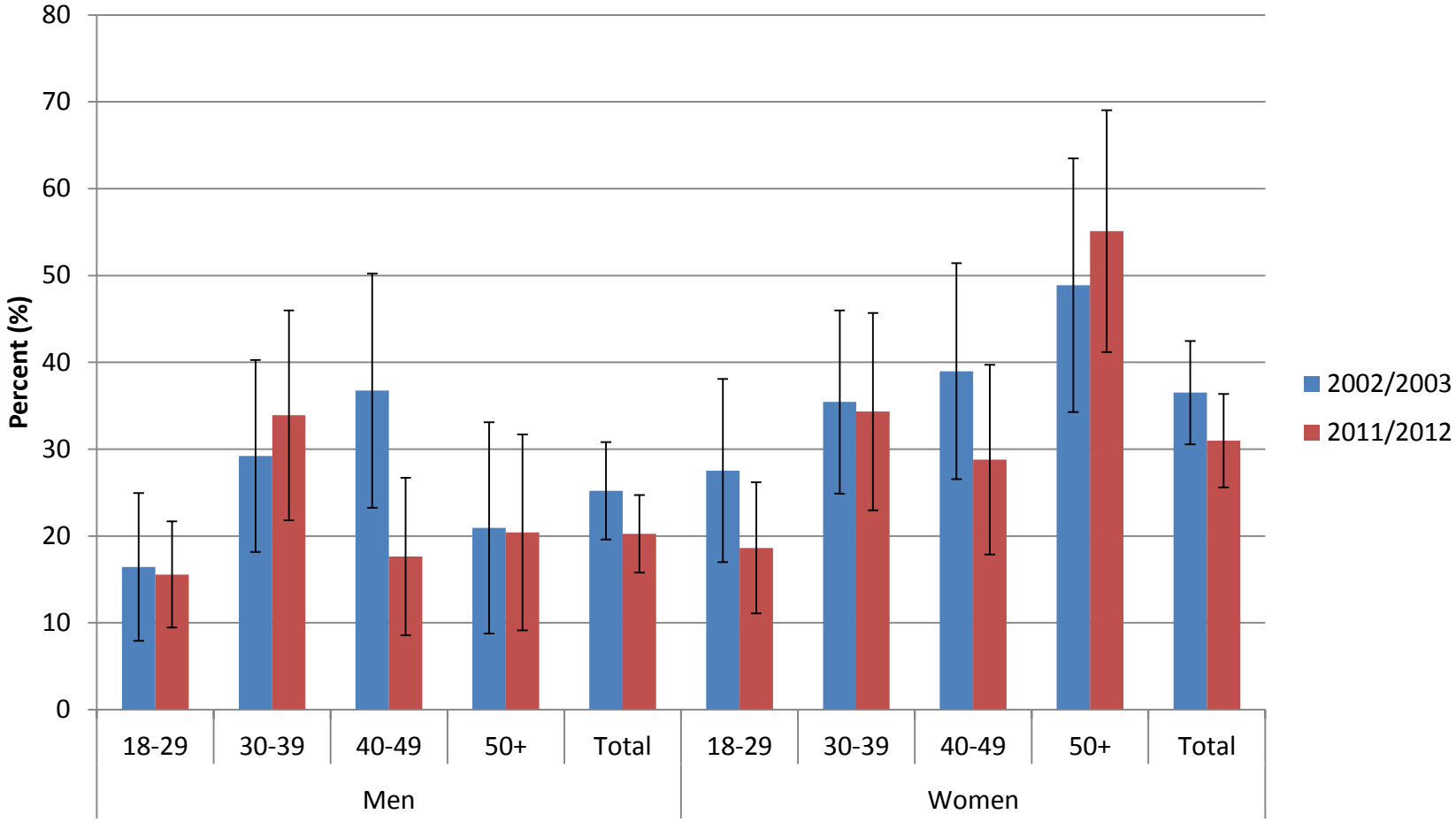


Figure 4.8. Sex- and age-specific crude prevalence of dyslipidemia in each time period.

Note that bars represent 95% CIs.

Table 4.12. Description of continuous variables related to lipid metabolism.

Variables	Mean ± standard deviation	Median (25^{th}, 75^{th} percentiles)	Skewness	Kurtosis
HDL-cholesterol	1.203 0.326	1.16 (1.00, 1.40)	0.998	2.312
TG	1.991 1.983	1.50 (1.00, 2.30)	6.379	65.825
Apolipoprotein A	1.282 0.235	1.25 (1.13, 1.41)	0.899	1.829
Apolipoprotein B	0.866 0.257	0.830 (0.690, 1.00)	0.579	0.233

Table 4.13. Time period as a predictor of HDL-cholesterol stratified by age group and sex.

	Men		Women	
Age group	β (standard error)	p-value	β (standard error)	p-value
18-29 years	0.010 (0.0326)	0.768	-0.013 (0.0429)	0.771
30-39 years	-0.070 (0.0489)	0.150	-0.079 (0.0409)	0.055
40-49 years	0.152 (0.0526)	0.004	-0.038 (0.0480)	0.423
≥50 years	-0.020 (0.0528)	0.711	-0.024 (0.0578)	0.681

Coefficients for time period are presented with 2002/2003 as the reference period.

Table 4.14. Time period as a predictor of triglycerides stratified by age group and sex.

	Men		Women	
Age group	β (standard error)	p-value	β (standard error)	p-value
18-29 years	-0.207 (0.1385)	0.135	-0.136 (0.2607)	0.603
30-39 years	-0.179 (0.3932)	0.649	-0.586 (0.4188)	0.161
40-49 years	-1.327 (0.5327)	0.013	-0.119 (0.2823)	0.674
≥50 years	-0.226 (0.3988)	0.571	0.184 (0.3338)	0.582

Coefficients for time period are presented with 2002/2003 as the reference period.

Table 4.15. Time period as a predictor of apolipoproteinA.

Model	**β (standard error)**	**p-value**
Model 1	0.211 (0.0129)	<0.001
Model 2[a]	0.217 (0.0128)	<0.001

Coefficients for time period are presented with 2002/2003 as the reference period.

[a] Adjusted by age group and sex

Table 4.16. Time period as a predictor of apolipoproteinB stratified by age group.

Age group	β (standard error)	p-value
18-29 years	-0.056 (0.0241)	0.020
30-39 years	-0.060 (0.0277)	0.031
40-49 years	-0.155 (0.0310)	<0.001
≥50 years	-0.080 (0.0392)	0.042

Coefficients for time period are presented, adjusted by sex, with 2002/2003 as the reference period.

4.1.6 Metabolic syndrome

The overall crude prevalence of metS in 2002/2003 was 54.3% (95% CI: 49.8, 58.9) and 49.5% (95% CI: 45.4, 53.5) in 2011/2012. The sex- and age-stratified crude prevalence of metS in each time period are illustrated in **Figure 4.9**. Sex-specific crude prevalence were 47.3% (95% CI: 40.8, 53.9) and 61.0% (95% CI: 54.8, 67.2) in 2002/2003 and 43.5% (95% CI: 37.9, 49.0) and 56.0% (95% CI: 50.2, 61.8) in 2011/2012, for men and women, respectively. The sex-specific prevalence was higher for women compared to men in each time period (2002/2003, p=0.003; 2011/2012, p=0.002). The age-standardized prevalence of metS were 62.5% (95% CI: 58.1, 66.9) and 59.92% (95% CI: 56.0, 63.9) in 2002/2003 and 2011/2012, respectively (Appendix 8.6), and not significantly different (p=0.671).

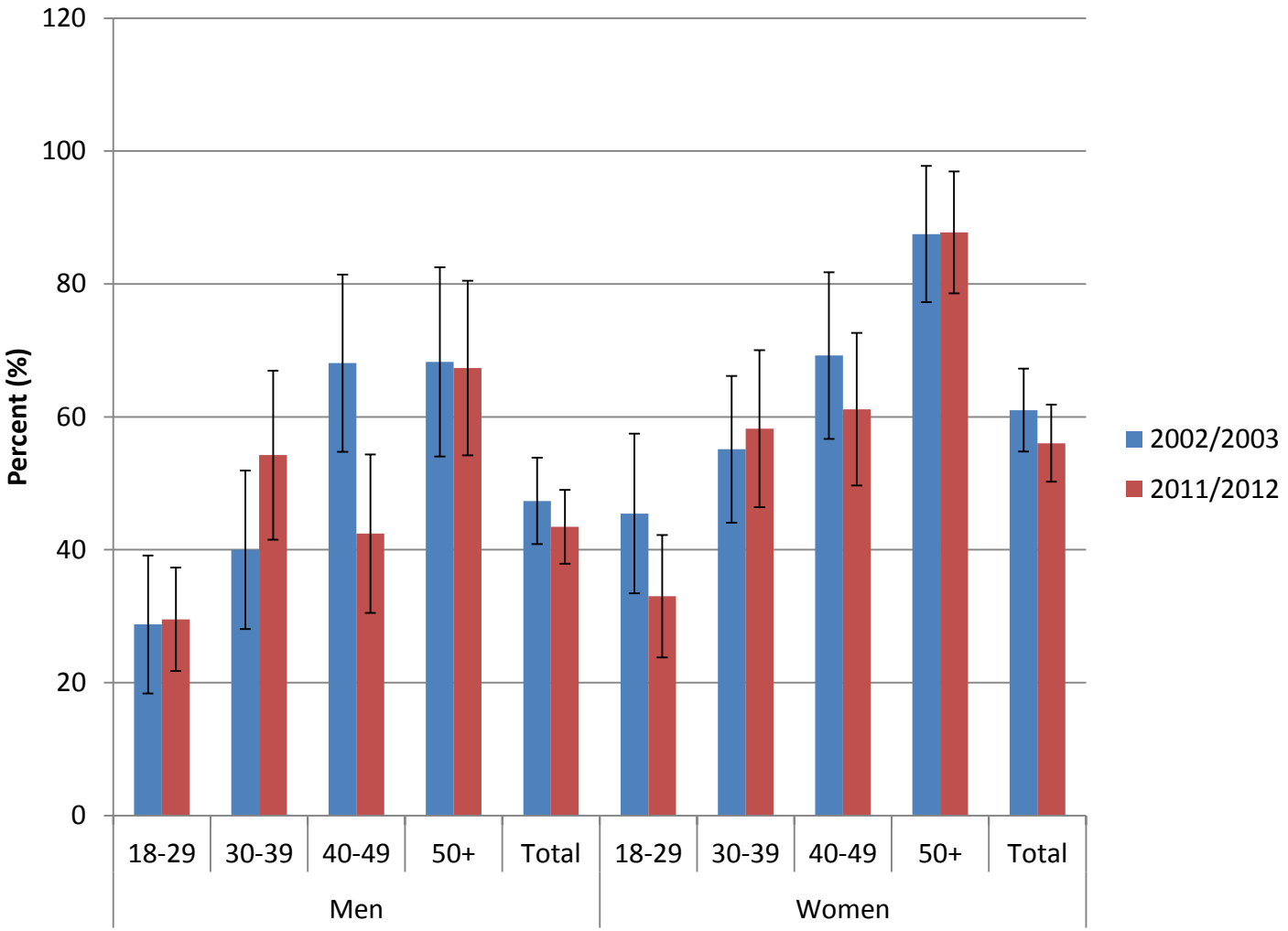


Figure 4.9. Sex- and age-specific prevalence of metabolic syndrome in each time period.

Note that bars represent 95% CIs.

4.1.7 Smoking status

The percent of current smokers in 2002/2003 was 74.0% (95% CI: 70.1, 78.0) and 80.0% (95% CI: 76.8, 83.2) in 2011/2012. The crude prevalence of current smoking was significantly higher in 2011/2012 compared to 2002/2003 according to χ^2-test (p=0.020). The sex- and age-stratified crude prevalence of current smoking in both time periods are illustrated in **Figure 4.10**. The crude prevalence of ever smokers was 83.0% (95% CI: 79.6, 86.4) in 2002/2003 and 91.4% (95% CI: 89.2, 93.7) in 2011.2012 (p<0.001). The discrepancy in prevalence of current and ever smoking status between time periods indicates that there were likely a greater proportion of ex-smokers in 2011/2012, illustrated in **Figure 4.11**. The proportion of ever smokers that had at the time successfully quit smoking in 2011/2012 was 11.8% of men and 13.3% of women, whereas the proportions in 2002/2003 were 8.8% and 12.4%, respectively. Importantly, among women 50 years and older, the proportion of ex-smokers (among ever smokers) in 2002/2003 was 35.5% and 15.4% in 2011/2012, while among men 50 years and older, the prevalence was 18.8% and 15.6%, respectively.

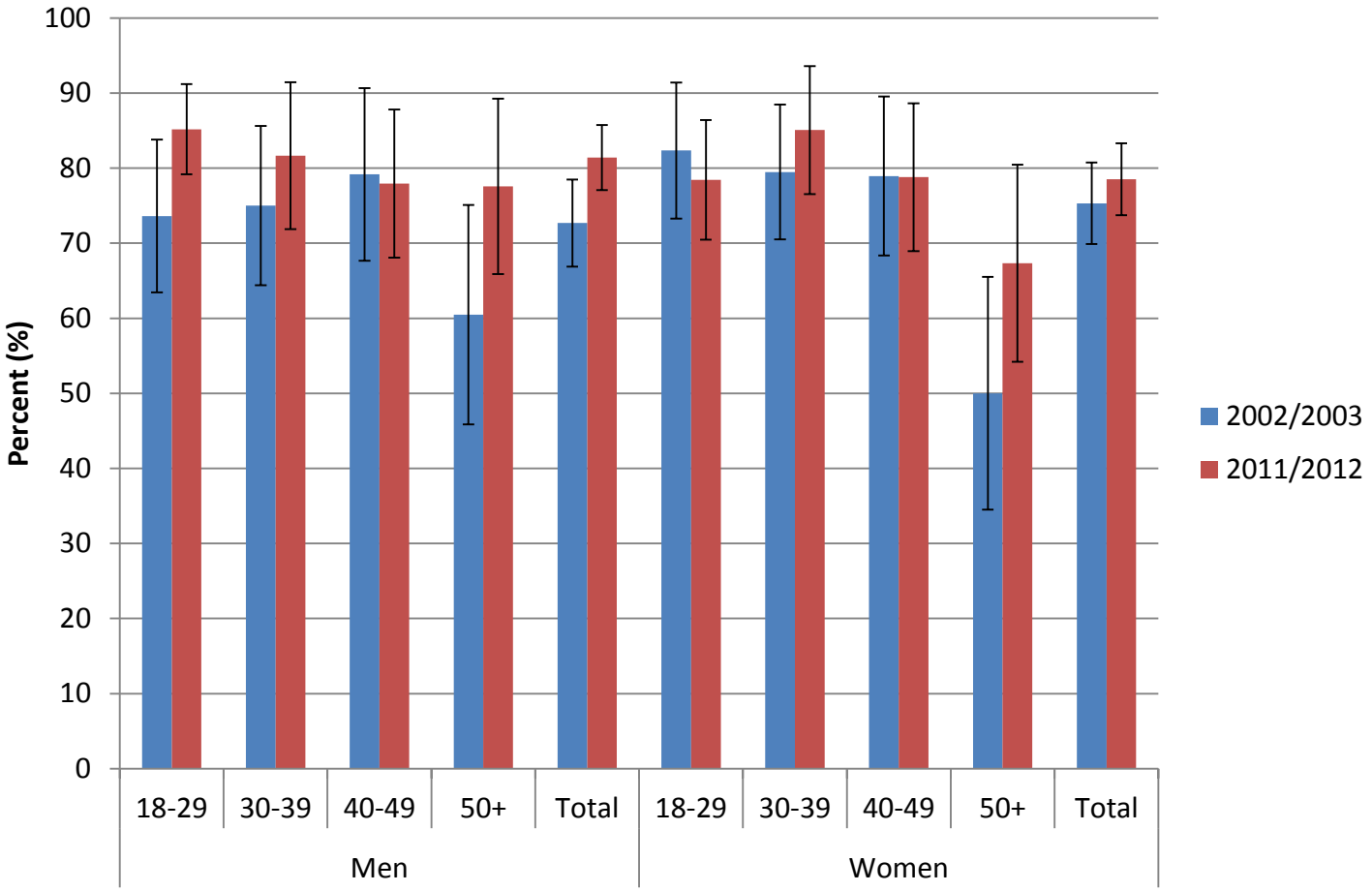


Figure 4.10. Sex- and age-specific crude prevalence of current smoking status in each time period.

Note that bars represent 95% CIs.

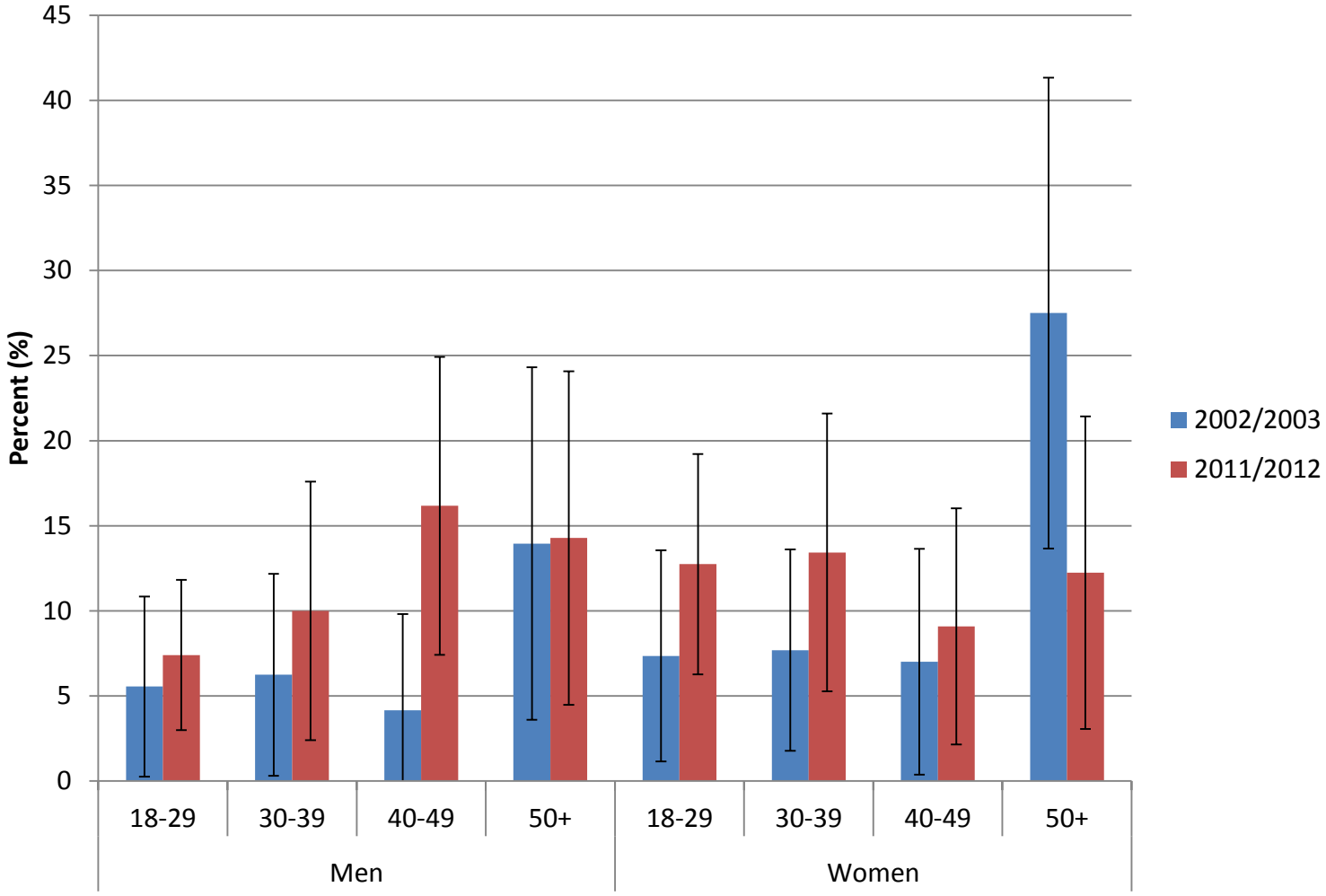


Figure 4.11. Sex- and age-specific crude prevalence of ex-smoking status in each time period.

Note that bars represent 95% CIs.

4.1.8 Summary of repeated cross-sectional results (Objective 1)

● While the age-standardized prevalence of diabetes was high during both time periods, at 39%, the prevalence rates were not significantly different between time periods.

●Fasting glucose and HbA1c was significantly higher among those without diabetes in 2011/2012 compared to 2002/2003.

●The sex- and age-adjusted prevalence of obesity was significantly lower in 2011/2012 compared to 2002/2003.

●The sex- and age-standardized prevalence of abdominal obesity, dyslipidemia, and metS were also not significantly different between time periods.

● Men aged 40-49 years old had lower crude prevalence of obesity, abdominal obesity, dyslipidemia, and metS in 2011/2012 compared to 2002/2003 as well as better mean measures of lipids.

● Significantly higher crude prevalence of obesity, abdominal obesity, dyslipidemia, and metS among women compared to men persisted during both time periods.

●The proportion of current smokers in 2002/2003 was 74.0% and significantly higher, at 80.0%, in 2011/2012.

4.2 Prospective cohort results (Objectives 2-3)

One-hundred seventy one participants were included in both study periods. Although attempts were made to recruit the 2002/2003 participants in 2011/2012, a larger number than anticipated moved, passed away, refused to participate, or were unable to locate. A description of the study sample at baseline is provided in **Table 4.17**. In addition, a comparison to the overall sample in 2002/2003 was included to verify the representativeness of the cohort. The prospective cohort was two years younger compared to the baseline sample, which was mostly accounted for by fewer participants aged over 50 years old at baseline. However, the two samples were not significantly different according to sex, education, employment, marital status, diabetes, obesity, or hypertension.

Participants were followed for a mean (std dev) 8.22 ± 0.67 years (min: 7; max: 10). Follow-up varied slightly between participants because data collection took place over approximately 1 year during both time periods and also varied depending on when their birth date fell in relation to how early they attended the study data collection during each time period. Nevertheless, because there were only two data collection periods and overall variation in follow-up was minimal, length of follow-up was not adjusted for.

Table 4.17. Description of longitudinal study sample at baseline compared to the 2002/2003 sample.

Variables	Longitudinal sample (*n*=171)	2002/2003 sample (*n*=478)	p-value
Age	35.7 ± 9.6	37.8 ± 12.3	0.041[a]
Age groups			0.009[b]
18-29 years	48 (28.1)	142 (29.5)	
30-39 years	65 (38.0)	144 (29.9)	
40-49 years	44 (25.7)	108 (22.4)	
≥50 years	14 (8.2)	88 (18.3)	
Sex			0.834[b]
Men	80 (46.8)	230 (47.7)	
Women	91 (53.2)	252 (52.3)	
Marital status			0.099[b]
Never married	61 (36.5)	184 (39.3)	
Married/common-law	102 (61.1)	255 (54.5)	
Separated/divorced/widow/widower	4 (2.4)	29 (6.2)	
Highest level of education			0.465[b]
< grade 9	83 (49.7)	248 (53.0)	
≥ grade 9	84 (50.3)	220 (47.0)	
Employed			0.237[b]
Yes	41 (24.1)	137 (28.8)	

No	129 (75.9)	338 (71.2)	
Diabetes			0.329[b]
Yes	43 (25.1)	140 (29.0)	
No	128 (74.9)	342 (71.0)	
Hypertension			0.510[b]
Yes	64 (37.9)	192 (40.8)	
No	105 (62.1)	279 (59.2)	
Obese			0.940[b]
Yes	94 (56.3)	265 (56.6)	
No	73 (43.7)	203 (43.4)	

Data presented as either *n* (%) or mean ± standard deviation

[a] Independent-sample t-test

[b] Chi-square test

4.2.1 Objective 2

Diabetes. There were 35 (95% CI: 26, 45) new cases of diabetes among 128 participants without diabetes at baseline (27% or 3.3% per year). Assuming the 35 cases were diagnosed at the mid-point of follow-up, the incidence density is 38.6 cases/1000 person-years. Assuming a diagnosis at mid-point is based on another assumption that incidence was constant throughout the study period. We acknowledge that incidence density, in this case, has several limitations; it is reported to facilitate comparison to the literature. Among the 13 cases of IFG at baseline, 9 cases progressed to diabetes (69% or 8.4% per year). Among those with normal glucose tolerance at baseline (*n*=115), 10 (95% CI: 5, 16) progressed to IFG and 26 (95% CI: 18, 35) to diabetes.

Given that the variance of incident diabetes approximated the mean, a generalized linear model with a Poisson distribution was used to test for age group and sex as predictors (**Table 4.18**). Additionally, the Poisson distribution resulted in a lower BIC compared to a negative binomial distribution (170.482 vs 181.728). Compared to those 18-29 years old at baseline, those 50 years and older had four times the risk of developing diabetes (p=0.012). Those 40-49 years old had just over two times the risk of developing diabetes compared to the youngest age group, however this trend did not reach significance (p=0.078). Men and women did not differ in their risk of incident diabetes (p=0.771).

Table 4.18. Risk of incident diabetes according age group and sex.

	Incident cases	Number at risk	Relative risk (95% CI)	p-value
Age				
18-29 years	9	44	Reference	
30-39 years	9	51	0.863 (0.342, 2.173)	0.754
40-49 years	12	27	2.173 (0.916, 5.157)	0.078
≥50 years	5	6	4.074 (1.365, 12.156)	0.012
Sex				
Men	15	58	Reference	
Women	20	70	1.105 (0.566, 2.158)	0.771

Generalized linear model with Poisson distribution.

Hypertension. There were 36 (95% CI: 31, 42) new cases of hypertension among 104 participants without hypertension at baseline (34.6%). Again, a generalized linear model with a Poisson distribution was the best fitting model to test for differences in risk according to age group and sex (**Table 4.19**). There was a strong trend toward a three times higher risk of incident hypertension among the highest age group compared to the lowest age group (p=0.073). Also, women had half the risk of developing hypertension compared to men (p=0.039).

Table 4.19. Risk of incident hypertension according to age group and sex.

	Incident cases	Number at risk	Relative risk (95% CI)	p-value
Age				
18-29 years	13	41	Reference	
30-39 years	12	42	0.901 (0.411, 1.975)	0.795
40-49 years	8	18	1.402 (0.581, 3.382)	0.452
≥50 years	3	3	3.154 (0.899, 11.067)	0.073
Sex				
Men	24	51	Reference	
Women	12	53	0.481 (0.241, 0.962)	0.039

Generalized linear model with Poisson distribution.

Obesity. Due to high prevalence of obesity at baseline and relatively little movement of participants between weight categories during the two time periods, it was decided to model weight gain. Weight gain is defined as a positive change in BMI from 2002/2003 to 2011/2012 or (follow-up BMI minus baseline BMI) > 0. Both models were adjusted for BMI at baseline. The highest risk of weight gain occurred in the youngest age group; all other age groups had approximately half the risk of weight gain compared to those 18-29 years olds (**Table 4.20**). Men and women had a similar risk of weight gain over the 8 years of follow-up. Among women aged 18-29 at baseline (n=23), the mean weight gain was 8.6 kg (std dev: 14.3; median: 7.5 kg) or 1.05 kg/year. Among men aged 18-29 at baseline (n=25), the mean weight gain was 8.6 kg (std dev: 10.9, median: 10.2 kg) or 1.05 kg/year.

Table 4.20. Risk of weight gain according to age group and sex.

	Incident cases	Number at risk	Relative risk (95% CI)	p-value
Age				
18-29 years	36	48	Reference	
30-39 years	27	63	0.595 (0.361, 0.983)	0.043
40-49 years	16	41	0.534 (0.296, 0.964)	0.037
≥50 years	4	13	0.430 (0.153, 1.211)	0.110
Sex				
Men	39	78	Reference	
Women	43	87	1.198 (0.759, 1.890)	0.438

Generalized linear model with Poisson distribution.

***Abdominal obesity*.** There were 21 (95% CI: 15, 28) new cases of abdominal obesity at follow-up among 50 without abdominal obesity at baseline (42%). Age group was not associated with risk of abdominal obesity (**Table 4.21**). However, there was a significantly higher risk of incident abdominal obesity among women ($p<0.050$); women were over two times more likely to develop abdominal obesity compared to men.

Table 4.21. Risk of abdominal obesity according to age group and sex.

	Incident cases	Number at risk	Relative risk (95% CI)	p-value
Age				
18-29 years	8	18	Reference	
30-39 years	8	23	0.783 (0.294, 2.085)	0.624
40-49 years	5	9	1.250 (0.409, 3.821)	0.695
≥50 years	0	0	N/A	
Sex				
Men	12	38	Reference	
Women	9	12	2.375 (1.001, 5.636)	0.050

Generalized linear model with Poisson distribution. For the age group analysis the 50+ age group was excluded because there were no participants at risk.

***Dyslipidemia*.** There were 28 (95% CI: 20, 37) new cases of dyslipidemia at follow-up among 112 without dyslipidemia at baseline (25%). Risk of dyslipidemia did not significantly differ between the age groups (**Table 4.22**). There was not a significant difference in risk of dyslipidemia between men and women.

Table 4.22. Risk of dyslipidemia according to age group and sex.

	Incident cases	Number at risk	Relative risk (95% CI)	p-value
Age				
18-29 years	13	38	Reference	
30-39 years	5	41	0.356 (0.127, 1.000)	0.050
40-49 years	7	25	0.818 (0.327, 2.051)	0.669
≥50 years	3	8	1.096 (0.312, 3.847)	0.886
Sex				
Men	12	59	Reference	
Women	16	53	1.484 (0.702, 3.137)	0.301

Generalized linear model with poisson distribution.

***Metabolic syndrome*.** There were 33 (95% CI: 25, 42) new cases of metS at follow-up among 71 participants without MetS at baseline (46%). Most participants experienced an increase in the number of components of metS over time; thirty-two (95% CI: 23, 42) participants, or 19.5%, had fewer components at follow-up; 58 (95% CI: 46, 71), or 35.4%, stayed with the same number of components, and 74 (95% CI: 62, 87), or 45.1% developed more components at follow-up.

In order to include a greater sample (n=145), rather than model incident metS (which would eliminate those with metS at baseline), it was decided to model gain in metS components compared to those that remained with the same number of components or reduced number at follow-up (**Table 4.23**). Only those with 4 or less components of metS at baseline were included as those with 5 components would not be able to gain components. Analyses were adjusted for the number of metS components at baseline.

There was no difference in risk of worsening metabolic profile between men and women or among the age groups.

Table 4.23. Risk of worsening metabolic issues according to age group and sex.

	Incident cases	Number at risk	Relative risk (95% CI)	p-value
Age				
18-29 years	29	47	Reference	
30-39 years	27	57	0.802 (0.473, 1.359)	0.412
40-49 years	15	33	0.934 (0.485, 1.799)	0.839
≥50 years	3	8	0.795 (0.231, 2.733)	0.716
Sex				
Men	39	72	Reference	
Women	35	73	1.091 (0.679, 1.752)	0.720

Generalized linear model with Poisson distribution adjusting for the number of metabolic syndrome components at baseline.

Objective 2: Summary of results.

●Incidence of diabetes was significantly higher among adults 50 years and older compared to adults 18-29 years old.

●There was a significantly higher risk of hypertension among men compared to women.

●There was a significantly higher risk of abdominal obesity among women compared to men.

●Risk of weight gain and metS was highest in the youngest age group.

4.2.3 Objective 3

In order to investigate predictors of change in cardiometabolic risk, distributions of change in all continuous risk factors were determined (**Table 4.24**). Most variables had a skewed distribution, therefore in investigating correlations between change in BMI and changes in other cardiometabolic measures, Spearman correlation coefficients were used. Also, tertiles for changes in each variable were created to assist in determining whether relationships were dose-response.

Table 4.24. Distributions of changes[a] in cardiometabolic variables over time.

Variable	Mean (std dev)	Tertiles	Skewness	Kurtosis
Change in[a] glucose	1.21 ± 3.14	<0.2760 0.2760-1.0520 >1.0520	0.619	5.119
Change in HbA1c	0.86 ± 1.60	<0.40 0.40-0.80 >0.80	0.043	6.918
Change in insulin	-3.61 ± 109.79	<-20.140 -20.140-18.000 >18.000	0.220	11.122
Change in HOMA-IR	0.69 ± 5.08	<-0.2887 -0.2887-1.4310 >1.4311	1.190	12.792
Change in HOMA β-cell function	-29.54 ± 84.81	>-2.8119 -27.0220- -2.8119 <-27.0220	-2.872	12.954
Change in HDL-cholesterol	-0.038 ± -0.040	<-0.1400 -0.1400-0.0352 >0.0352	0.381	4.943
Change in TG	0.099 ± 2.428	<-0.3800 -0.3800-0.3052 >0.3052	-1.495	23.836
Change in ApoA	0.239 ± 0.2139	<0.1443 0.1443-0.3300 >0.3300	0.174	1.096

Change in ApoB	-0.014 ± 0.233	<-0.0957 -0.0957-0.0800 >0.0800	-0.511	1.519
Change in BMI	0.237 ± 4.774	<-1.9032 -1.9032-1.4710 >1.4710	2.181	15.424
Change in Hcy	0.693 ± 5.88	<-0.1240 -0.1240-1.400 >1.400	-5.100	56.754
Change in SBP	2.86 ± 18.64	<-5.8 -5.8-8.5 >8.5	0.412	0.621
Change in DBP	5.29 ± 13.65	<-0.5 -0.5-11.4 >11.4	0.130	-0.100
ACR at baseline	2.15±3.76	<0.7648 0.7648-1.3796 >1.3796	3.746	13.901
eGFR at follow-up	98.19±22.34	<91.27 91.27-105.20 >105.20	-0.496	2.394

[a] "Change in" refers to the difference between each respective variable at time 2 minus time 1.

Objective 3a. Predictors of weight loss. All variables with a significant correlation coefficient with change in BMI (Appendix 8.7) were explored in logistic regression analysis with weight loss as the outcome (weight gain/stable weight as the reference group), adjusted for age at baseline, sex, and baseline BMI (**Table 4.25**). Sex-interactions were explored for those variables that demonstrated differing relationships between sexes in correlation analysis. All variables that were significant in these analyses were included in a multivariable model (including their main effects): baseline HbA1c, sex*baseline apoB, sex*baseline HOMA-IR, sex*change in HbA1c, change in Hcy, sex*change in endogenous insulin, and change in HOMA-IR. Throughout the rest of the thesis, change in endogenous insulin will be referred to as change in insulin, unless otherwise noted. All variables that remained either statistically significant or were considered important enough theoretically were kept in the final model. ApoB at baseline (including the sex interaction), HOMA-IR at baseline (including the sex interaction), and change in HOMA-IR did not remain significant in the fully adjusted model and were removed.

Importantly, descriptive analysis also indicated that *magnitude* of weight loss was related to tertiles of change in insulin for men and women (**Table 4.26**). Change in insulin was transformed to tertiles in the final multivariable model to better describe the relationship with weight loss in both sexes. Change in insulin, as a continuous variable, was not associated with weight loss for women but as tertiles it was. It should be noted that only 3 participants reported taking exogenous insulin, none of whom lost weight (n=2) or data on body weight for both time periods was not available (n=1).

Length of time with diabetes was also explored as a predictor of weight loss due to the significant relationship of changes in insulin with weight loss. Length of time with diabetes was categorized as no diabetes, diabetes ≤8 years, and diabetes >8 years. An 8-year cut-off was used because it was close to the median length of time as well as 8 years was the length of follow-up (and time since the last screening). Odds of weight loss were similar between those with short-term diabetes and long-term diabetes (data not shown). Length of time with diabetes was also not related to magnitude of weight loss (**Table 4.27**). Diabetes, regardless of length of time, was not included in the final multivariable model because it did not provide any additional predictive value or superior predictive value over the other variables related to glucose metabolism.

In an effort to understand why change in HbA1c is a predictor of weight loss for men but not women, additional analyses were conducted. It was thought that fasting glucose at follow-up may be higher among men that had the greatest decreases in insulin and greatest increases in HbA1c, which may account for the high odds of weight loss. Although fasting glucose was higher among men compared to women, glucose at follow-up (including the sex*interaction) was not a superior predictor of weight loss as compared to change in HbA1c. However, adding glucose at follow-up (plus the sex*interaction) to the fully adjusted multivariable model resulted in an attenuation in the relationship between change in HbA1c and weight loss. This indicates that the association between change in HbA1c and weight loss among men is partially attributed to a higher fasting glucose at follow-up among men compared to women.

Based on the previously described analysis, the final fully adjusted model was developed (**Table 4.28)**. Estimation of odds of weight loss was also completed for this

model (**Figure 4.12**). Among men with an increase in insulin over time, the odds of weight loss remain low with stable HbA1c, regardless of baseline HbA1c. Whereas, among men with a decrease in insulin, the odds of weight loss are increased more greatly according to change in HbA1c for those that originally had low levels of HbA1c at baseline. A large increase in HbA1c was a more important predictor of weight loss among men with increases in insulin. (panel A, **Figure 4.10**). Among women, the odds of weight loss were higher for increasing levels of baseline HbA1c and the odds were increased among those with decreases in insulin. Women did not experience an increase in odds of weight loss based on change in HbA1c over time. Among those with stable/increases in insulin over time, compared to women, men had lower odds of weight loss among those with stable HbA1c, regardless of baseline HbA1c. However, with increasing HbA1c over time, the odds of weight loss for men with stable/increases in insulin over time surpassed the odds for women with stable/increases in HbA1c over time. Relative to change in insulin and HbA1c at baseline, change in Hcy has a small role in predicting weight loss.

Table 4.25. Predictors of weight loss adjusting for sex, age, and BMI at baseline.

Type	Predictor	Interaction model	Odds ratio (95% CI)	p-value
Baseline	SBP		1.023 (0.995, 1.051)	0.105
	HbA1c		1.509 (1.093, 2.082)	0.012
	HDL-C		0.398 (0.117, 1.352)	0.140
		HDL-C	0.222 (0.027, 1.851)	0.164
		Sex[a]*HDL-C[a]	2.349 (0.202, 27.309)	0.495
	ApoB		2.520 (0.634, 10.026)	0.189
		ApoB	12.937 (1.376, 121.661)	0.025
		Sex[a]*ApoB	0.061 (0.004, 0.963)	0.047
	HOMA-IR		1.115 (0.999, 1.244)	0.051
		HOMA-IR	1.362 (1.063, 1.747)	0.015
		Sex[a]*HOMA-IR	0.779 (0.600, 1.012)	0.061
	HOMA β[b]		0.996 (0.991, 1.001)	0.135
		HOMA β	1.001 (0.992, 1.009)	0.894
		Sex[a]*HOMA β	0.992 (0.981, 1.002)	0.124
	ACR		1.074 (0.966, 1.195)	0.187
		ACR	1.132 (0.958, 1.338)	0.146
		Sex[a]*ACR	0.904 (0.729, 1.122)	0.359
Change in[c]	Glucose		1.078 (0.955, 1.217)	0.226
		Glucose	1.140 (0.968, 1.343)	0.117
		Sex[a]*glucose	0.863 (0.668, 1.115)	0.260

	HbA1c		1.212 (0.966, 1.519)	0.096
		HbA1c	1.461 (1.018, 2.097)	0.040
		Sex[a]*HbAlc	0.661 (0.400, 1.091)	0.105
	TG		0.858 (0.722, 1.019)	0.080
		TG	0.829 (0.640, 1.073)	0.155
		Sex[a]*TG	1.070 (0.750, 1.527)	0.710
	Hcy		1.197 (1.042, 1.376)	0.011
	Insulin		0.993 (0.989, 0.997)	0.002
		Insulin	0.981 (0.969, 0.993)	0.002
		Sex[a]*insulin	1.015 (1.002, 1.028)	0.020
	HOMA β		0.997 (0.993, 1.002)	0.227
		HOMA-β	0.977 (0.958, 0.995)	0.015
		Sex[a]*HOMA-β	1.024 (1.004, 1.045)	0.017
	HOMA-IR		0.907 (0.835, 0.985)	0.020
	HDL-C		126.360 (18.414, 867.129)	<0.001
At follow-	eGFR[c]		1.017 (0.999, 1.035)	0.066
up		eGFR[d]	1.014 (0.991, 1.038)	0.231
		Sex[a]*eGFR	1.005 (0.973, 1.038)	0.652

Binary logistic regression adjusting for age at baseline, sex, and baseline BMI.

ACR, albumin:creatinine ratio; SBP, systolic blood pressure; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA β, homeostatic model assessment for β-cell function; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

[a] Men are the reference group

[b] Adjusted for HOMA-IR; a measure of β-cell function at one point in time must be adjusted for HOMA-IR

[c] "Change in" refers to follow-up value minus baseline value, therefore a positive value denotes an increase in the value over time and a negative value indicates a decrease over time

[d] Adjusted for albuminuria/proteinuria at baseline

Table 4.26. Magnitude of weight loss among men and women according to tertiles of change in insulin over time.

	Men		Women	
Tertiles of change in insulin[a]	Weight loss >5kg n (%)	Weight loss >10k n (%)	Weight loss >5kg n (%)	Weight loss >10k n (%)
<-20.14	18 (69.2)	10 (38.5)	16 (53.3)	8 (26.7)
-20.14-18.00	5 (16.1)	2 (6.5)	6 (25.0)	0 (0)
>18.00	4 (18.2)	3 (13.6)	5 (18.5)	0 (0)

[a] "Change in" refers to follow-up value minus baseline value, therefore a positive value denotes an increase in the value over time and a negative value indicates a decrease over time

Table 4.27. Magnitude of weight loss among men and women according to diabetes status.

Sex	Diabetes status at follow-up	Any weight loss	Weight loss >5 kg	Weight loss >10kg
Men	No Diabetes (n=42)	12 (28.6)	6 (14.3)	2 (4.8)
	Diabetes 0-8 years[a] (n=19)	13 (68.4)	10 (52.6)	7 (36.8)
	Diabetes >8 years (n=18)	14 (77.7)	11 (61.1)	6 (33.3)
Women	No Diabetes (n=50)	20 (40.0)	11 (22.0)	1 (2.0)
	Diabetes 0-8 years[a] (n=23)	12 (52.2)	9 (39.1)	4 (17.4)
	Diabetes >8 years (n=14)	10 (71.4)	7 (50.0)	3 (21.4)

Data are presented as n (%)

[a] Includes those newly diagnosed through the screening.

Table 4.28. Multivariable model of weight loss.

Variable	Odds ratio (95% CI))	p-value
Sex[a]	0.667 (0.126, 3.541)	0.634
Age at baseline	1.038 (0.988, 1.089)	0.136
BMI at baseline	1.017 (0.950, 1.088)	0.634
HbA1c at baseline	2.144 (1.303, 3.527)	0.003
Change in[c] insulin		
<-20.14	Reference	
-20.14-18.00	0.156 (0.034, 0.722)	0.017
>18.00	0.038 (0.005, 0.280)	0.001
Sex[a]*Change in[c] insulin		
<-20.14	Reference	
-20.14-18.00	3.858 (0.531, 28.043)	0.182
>18.00	10.931 (1.017, 117.466)	0.048
Change in[c] Hcy	1.181 (1.020, 1.368)	0.026
Change in[c] HbA1c	1.918 (1.149, 3.202)	0.013
Sex[a]*change in[c] HbA1c	0.493 (0.243, 0.999)	0.050

Binary logistic regression with weight loss as the outcome.

BMI, body mass index; HbA1c, hemoglobin A1c

[a] Men are the reference group

[b] Categorical variable where "change in insulin <0" is the reference group

[c] "Change in" refers to follow-up value minus baseline value, therefore a positive value denotes an increase in the value over time and a negative value indicates a decrease over time

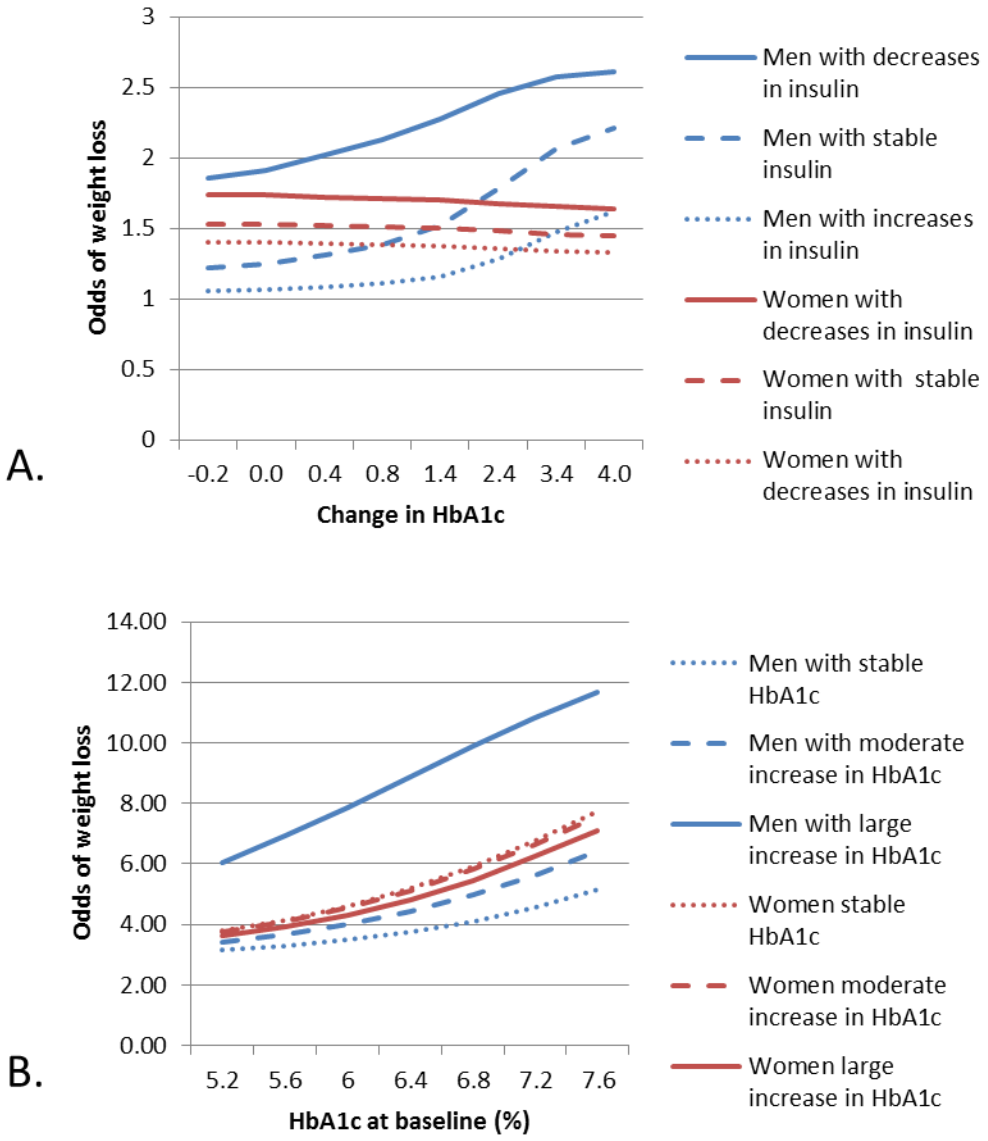


Figure 4.12. Odds of weight loss according to tertiles of change in[a] insulin and change in HbA1c (panel A); and odds of weight loss according to HbA1 at baseline and change in HbA1c (panel B).

Based on Table 6.32, for person 30 years of age, BMI at baseline=30, HbA1c at baseline = 6.0, stable insulin (-20.14-18.00), and change in Hcy = 0 where applicable.

Change in insulin is divided into tertiles; stable HbA1c is change in HbA1c =0; moderate increase in HbA1c is change in HbA1c = 0.8; and large increase in HbA1c is change in HbA1c = 3.4

Objective 3b: Predictors of change in apoB. Correlations of change in apoB with baseline cardiometabolic markers and change in cardiometabolic markers was first completed (Appendix 8.8). Change in apoB was not normally distributed and coefficients in univariate analysis were very small; mean change in apoB was -0.014 g/L and did not differ between men and women. Therefore, it was decided to model apoB at follow-up as the outcome rather than change in apoB. This allowed for the use of a general linear model as well as produced larger coefficients, which eased interpretation. Mean apoB at baseline and follow-up was 0.9 g/L and normally distributed. All variables that were significant in correlation analysis were further tested in GLM analysis, adjusted for age, sex, and apoB at baseline (**Table 4.29**).

Based on the partially adjusted analysis, the following variables were included in a multivariable model: TG at baseline (plus the sex-interaction), change in BMI (plus sex interaction), change in glucose (plus the sex interaction), change in apoA (plus sex interaction), eGFR (plus sex interaction and albuminuria at baseline for control) in addition to the control variables: age, sex, and apoB at baseline. All variables remained significant in multivariable analysis, with the exception of eGFR (plus the sex interaction), which was removed (**Table 4.30**). Change in BMI was explored as tertiles, which confirmed its dose-response relationship with apoB at follow-up. Therefore, change in BMI was kept as a continuous variable. The results from the final model are illustrated in **Figure 4.13**. In general, apoB for men changed substantially in conjunction with changes in other cardiometabolic variables. Specifically, apoB decreased in response to decreases in BMI among men but not women. Importantly, there was a near significant (p=0.05) main effect of sex on apoB at follow-up, such that women had higher apoB at

follow-up compared to men. While women experienced a significant positive change in apoB in response to changes in glucose, the magnitude of this relationship was small in comparison to the main effect of sex.

Table 4.29 Partially adjusted predictors of apoB at follow-up.

Type	Variable	Interaction model	β (SE)	p-value
Baseline	SBP		0.000 (0.0011)	0.746
		SBP	-0.001 (0.0016)	0.686
		Sex[a]*SBP	0.002 (0.0022)	0.362
	BMI		-0.002 (0.0024)	0.380
		BMI	-0.004 (0.0039)	0.349
		Sex[a]*BMI	0.002 (0.0048)	0.616
	HbA1c		-0.003 (0.0104)	0.753
		HbA1c	-0.004 (0.0130)	0.781
		Sex[a]*HbA1c	0.001 (0.0190)	0.965
	TG		0.014 (0.0058)	0.016
		TG	0.015 (0.0059)	0.012
		Sex[a]*TG	-0.013 (0.430)	0.430
	HOMA-IR		0.000 (0.0004)	0.577
		HOMA-IR	0.000 (0.0009)	0.863
		Sex[a]*HOMA-IR	9.799E-5 (0.0010)	0.923
	ACR		0.006 (0.0041)	0.128
		ACR	0.003 (0.0054)	0.521
		Sex[a]*ACR	0.006 (0.0080)	0.424
Change in[b]	DBP		0.001 (0.0011)	0.295
		DBP	0.002 (0.0016)	0.125
		Sex[a]*DBP	-0.002 (0.0021)	0.263
	BMI		0.005 (0.0031)	0.110
		BMI	0.012 (0.0060)	0.048
		Sex[a]*BMI	-0.009 (0.0070)	0.182
	Glucose		0.000 (0.0047)	0.917
		Glucose	-0.013 (0.0058)	0.028
		Sex[a]*Glucose	0.034 (0.0093)	<0.001

	TG		0.002 (0.0062)	0.753
	ApoA		0.153 (0.0680)	0.025
		ApoA	0.234 (0.0908)	0.010
		Sex[a]*ApoA	-0.181 (0.1357)	0.181
At follow-up	eGFR[c]		0.0009 (0.0007)	0.904
		eGFR[c]	-0.002 (0.0010)	0.082
		Sex*eGFR	0.004 (0.0013)	0.008

General linear model with apoB at follow-up as outcome and adjusting for age, sex, baseline apoB

ACR, albumin:creatinine ratio; apoA, apolipoproteinA; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate.

[a] Men are the reference group

[b] "Change in" refers to follow-up value minus baseline value, therefore a positive value denotes an increase in the value over time and a negative value indicates a decrease over time

[c] adjusted by albuminuria/proteinuria at baseline

Table 4.30. Final multivariable model predicting apoB at follow-up.

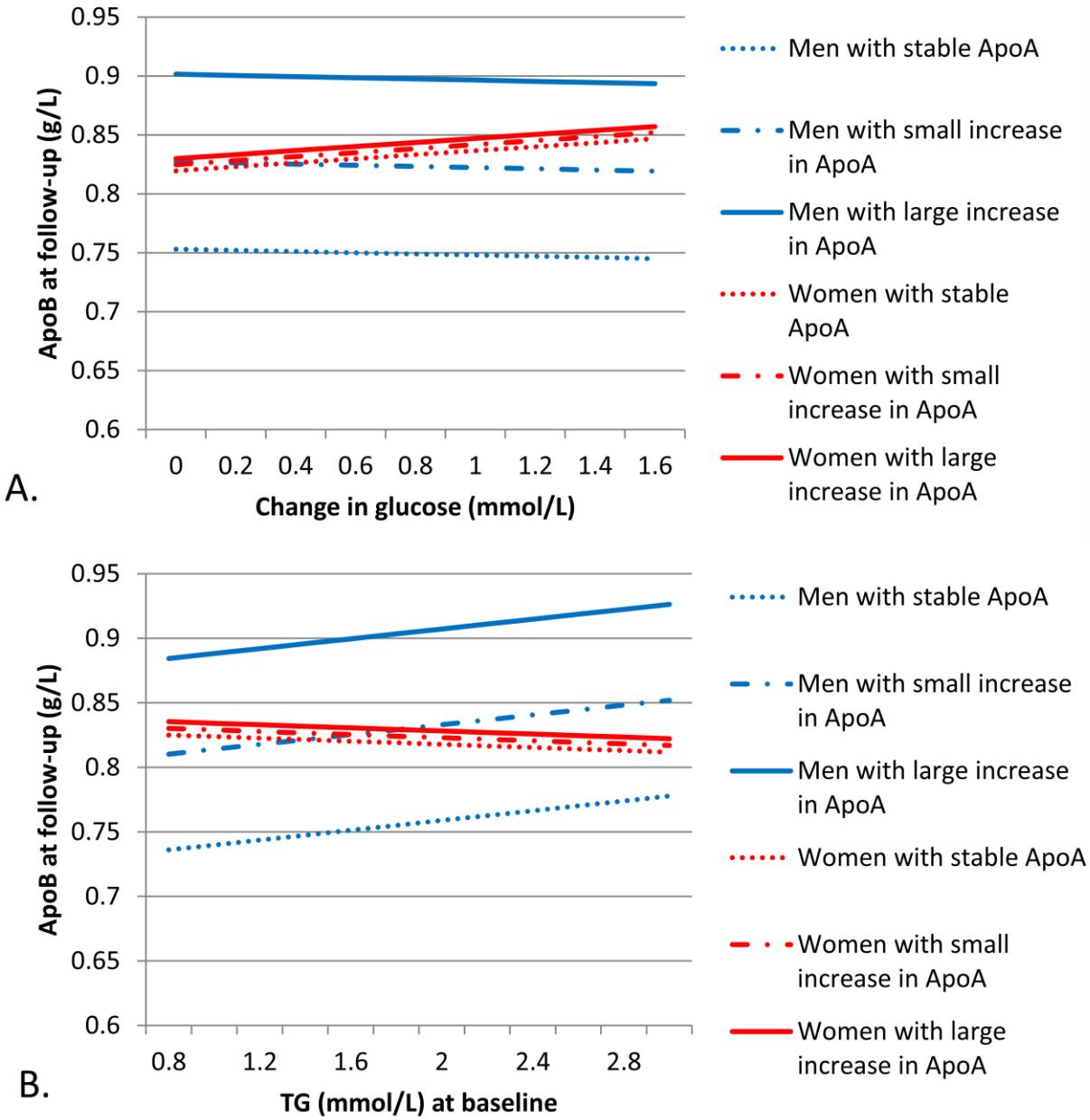
Variable	β (SE)	p-value
Age at baseline	-0.002 (0.0016)	0.152
Sex[a]	0.109 (0.0555)	0.050
ApoB at baseline	0.666 (0.0601)	<0.001
TG at baseline	0.019 (0.0056)	0.001
Sex[a]*** TG at baseline**	-0.025 (0.0155)	0.102
Change in glucose	-0.005 (0.0057)	0.386
Sex[a]*** Change in glucose**	0.022 (0.0098)	0.028
Change in BMI	0.022 (0.0064)	0.001
Sex[a]*** Change in BMI**	-0.020 (0.0072)	0.006
Change in apoA	0.371 (0.0898)	<0.001
Sex[a]*** Change in apoA**	-0.345 (0.1288)	0.007

General linear model with apoB at follow-up as outcome, intercept = 0.248

ApoB, apolipoproteinB,; TG, triglycerides; BMI, body mass index; apoA, apolipoproteinA

[a] Men as the reference group

[b] "Change in" refers to follow-up value minus baseline value, therefore a positive value denotes an increase in the value over time and a negative value indicates a decrease over time


A.
ApoB at follow-up (g/L)
0.95
0.9
0.85
0.8
0.75
0.7
0.65
0.6
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
Change in glucose (mmol/L)
Men with stable ApoA
Men with small increase in ApoA
Men with large increase in ApoA
Women with stable ApoA
Women with small increase in ApoA
Women with large increase in ApoA
B.
ApoB at follow-up (g/L)
0.95
0.9
0.85
0.8
0.75
0.7
0.65
0.6
0.8
1.2
1.6
2
2.4
2.8
TG (mmol/L) at baseline
Men with stable ApoA
Men with small increase in ApoA
Men with large increase in ApoA
Women with stable ApoA
Women with small increase in ApoA
Women with large increase in ApoA

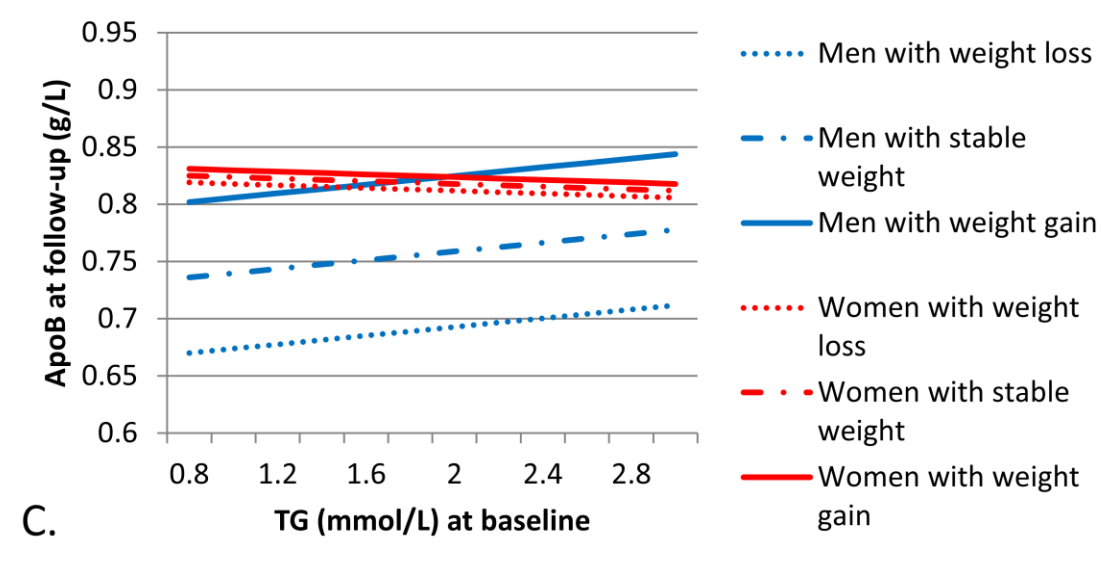


Figure 4.13. ApoB (g/L) at follow-up according to predictors determined in multivariate analysis (Table 6.37). Panel A. ApoB at follow-up (g/L) according to sex, change in glucose, and change in apoA ; Panel B. ApoB at follow-up (g/L) according to sex, TG at baseline, and change in apoA; and Panel C. ApoB at follow-up (g/L) according to sex, TG at baseline, and weight change.

Based on Table 6.37 for person aged 30 years, TG at baseline = 1.7 mmol/L, change in BMI = 0, change in glucose = 0, change in apoA = 0, and apoB at baseline = 0.08 g/L (where applicable). Weight loss is change in BMI = -3, stable weight is change in BMI= 0, weight gain is change in BMI = 3, stable apoA is change in apoA = 0 , small increase in apoA is change in apoA = 0.2, large increase in apoA is change in apoA = 0.4.

Objective 3c: Predictors of change in Hcy. Correlation analysis of change in Hcy with baseline cardiometabolic measures and changes in cardiometabolic measures was first completed (Appendix 8.9). Generalized linear models with gamma distribution and a linear transformation were used to determine univariate predictors of change in hcy, independent of sex, age, and hcy at baseline (data not shown). Only glucose at baseline was statistically significant in its relationship with change in hcy, likely due to the large variability in change in hcy. Therefore, logistic regression models with increase in hcy as the outcome were completed adjusting for age at baseline, sex, and hcy at baseline (**Table 4.31**). An increase in hcy is defined as change in hcy > 0; change in hcy ≤ 0 is the reference group.

Those variables that were statistically significant in the partially adjusted analysis were: glucose at baseline, ACR at baseline, HOMA β-cell function at baseline, change in BMI, change in glucose, and eGFR at follow-up (including the sex interaction adjusting for albuminuria). Glucose at baseline and HOMA β-cell function at baseline are strongly correlated therefore only one of the variables could be included in the final multivariable model. It was decided to keep HOMA β-cell function at baseline (and its adjustment by HOMA-IR at baseline) because it contributed more specific information with regards to diabetes progression than glucose alone. Although ACR was more strongly associated with increases in hcy as compared to albuminuria, there was a greater degree of missing data for ACR due to the exclusion of participants with proteinuria (hence no measure of urinary albumin or creatinine). For this reason, the dichotomous variable, albuminuria, was included in the final model. Although albuminura was not statistically significant in the final multivariate model, it was important to include some measure of kidney function

at baseline as a control for eGFR at follow-up. Lastly, sex-stratified analysis revealed a substantially different relationship between change in BMI and increased hcy, therefore a sex-interaction was added to the final model.

Change in BMI was also explored using tertiles to determine whether there was a dose-response relationship. In fact, there was not a dose-response relationship, rather, change in BMI less than -1.9 kg/m^2 was associated with a similarly increased odds of an increase in hcy as compared to both change in BMI between -1.9 and 1.5 kg/m^2 and change in BMI >1.5 kg/m^2. For this reason, the tertiles were merged to produce a dichotomous variable for change in weight, change in BMI <-1.9032 kg/m^2 and change in BMI ≥ -1.9032 kg/m^2 (**Table 4.32**). The final model and the model for which prediction estimation was completed are described in Table 6.36.

For women, eGFR at follow-up did not predict increases in hcy, whereas there was a strong relationship among men (**Figure 4.14**). Of note, hcy at baseline, hcy at follow-up, change in hcy, and eGFR were all not significantly higher among men compared to women (data not shown). HOMA β-cell function is a stronger predictor of increases in hcy among those with stable or weight gain and with higher levels of kidney function.

Table 4.31. Predictors of increased homocysteine adjusting for age, sex, and homocysteine at baseline.

Type	Variable	Interaction model	AOR (95% CI)	p-value
Baseline	Glucose		1.501 (1.106, 2.037)	0.009
	HOMA β-cell function[a]			0.002
	Current smoke exposure at baseline		1.009 (0.954, 1.067)	0.748
		Current smoke exposure at baseline	1.015 (0.942, 1.093)	0.693
		Sex[b]*Current smoke exposure at baseline	0.986 (0.882, 1.103)	0.811
	ACR		1.678 (1.117, 2.522)	0.013
		ACR	1.235 (0.897, 1.700)	0.195
		Sex[b]*ACR	2.182 (0.915, 5.205)	0.079
Change in[c]	BMI		0.893 (0.816, 0.978)	0.015
	Glucose		0.875 (0.776, 0.986)	0.029
		Glucose	0.892 (0.770, 1.033)	0.128
		Sex[b]*Glucose	0.949 (0.746, 1.208)	0.672
	HDL-C		2.438 (0.723, 8.228)	0.151
		HDL-C	4.774 (0.836, 27.270)	0.079
		Sex[b]*HDL-C	0.216 (0.018, 2.656)	0.231
	TG		0.848 (0.707, 1.016)	0.074
		TG	0.723 (0.481, 1.088)	0.120
		Sex[b]*TG	1.279 (0.794, 2.060)	0.312

HOMA-IR		0.997 (0.989, 1.006)	0.532
	HOMA-IR	1.001 (0.990, 1.013)	0.841
	Sex[b]*HOMA-IR	0.990 (0.971, 1.009)	0.279
At follow-up			
eGFR[d]		0.975 (0.995, 0.996)	0.019
	eGFR[d]	0.951 (0.922, 0.981)	0.001
	Sex[b]*eGFR	1.049 (1.009, 1.091)	0.015

Binary logistic regression with gain in Hcy as the outcome, adjusting for age sex and baseline Hcy

ACR, albumin:creatinine ratio; HbA1c, glycated hemoglobin; Hcy, homocysteine; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA β, homeostatic model assessment for β-cell function; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate.

[a] Adjusted for HOMA-IR at baseline

[b] Men are the reference group

[c] "Change in" refers to follow-up value minus baseline value, therefore a positive value denotes an increase in the value over time and a negative value indicates a decrease over time

[d] Adjusted for albuminuria/proteinruia at baseline

Table 4.32. Multivariable model for predicting increases in Hcy.

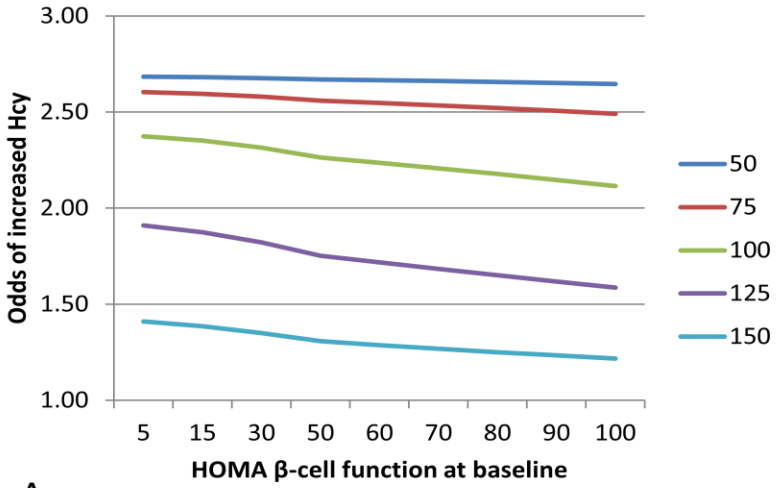
Variables	Odds ratio (95% CI)	p-value
Age at baseline	1.017 (0.966, 1.070)	0.526
Sex[a]	0.040 (0.000, 8.728)	0.241
Hcy at baseline	0.703 (0.582, 0.848)	<0.001
Albuminuria[b]	2.859 (0.781, 10.463)	0.113
eGFR at follow-up	0.951 (0.919, 0.985)	0.004
Sex*eGFR at follow-up	1.055 (1.005, 1.107)	0.030
HOMA β at baseline	0.992 (0.985, 0.999)	0.029
HOMA-IR at baseline	1.029 (0.875, 1.210)	0.730
Change in BMI:		
<-1.9032	Reference	
≥ -1.9032	0.343 (0.086, 1.363)	0.129
Sex*change in BMI		
Sex*<-1.9032	Reference	
Sex*≥ -1.9032	0.159 (0.012, 2.166)	0.168

Binary logistic regression

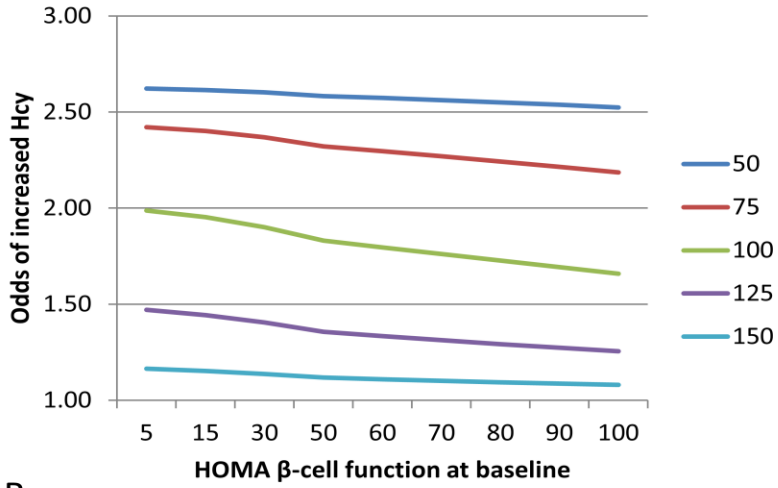
BMI, body mass index; Hcy, homocysteine; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA β, homeostatic model assessment for β-cell function; eGFR, estimated glomerular filtration rate.

[a] Men are reference group

[b] Those without albuminuria are the reference group


3.00
2.50
2.00
1.50
1.00
Odds of increased Hcy
5 15 30 50 60 70 80 90 100
HOMA β-cell function at baseline
50
75
100
125
150

A.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2.00
1.50
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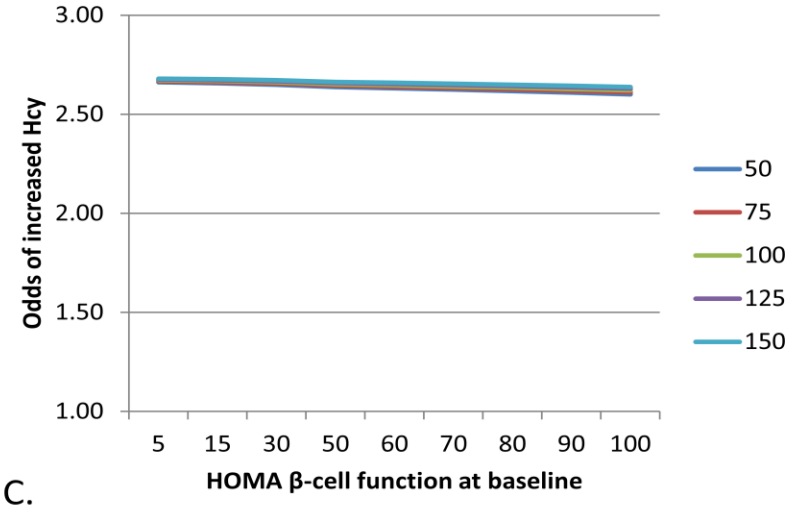
Odds of increased Hcy
5 15 30 50 60 70 80 90 100
HOMA β-cell function at baseline
50
75
100
125
150

B.


3.00
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2.00
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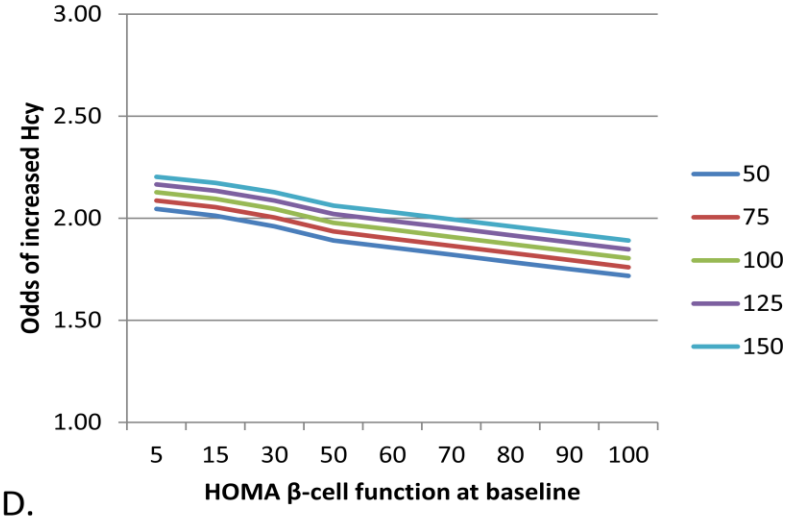
Odds of increased Hcy
5 15 30 50 60 70 80 90 100
HOMA β-cell function at baseline
50
75
100
125
150

C.


3.00
2.50
2.00
1.50
1.00
Odds of increased Hcy
5 15 30 50 60 70 80 90 100
HOMA β-cell function at baseline
50
75
100
125
150

D.

Figure 4.14. Odds of increased hcy according to HOMA β-cell function at baseline and levels of eGFR. **Panel A:** Men with weight loss; **Panel B:** Men with stable or weight gain; **Panel C:** Women with weight loss; **Panel D.** Women with stable or weight gain.

Predicted odds based on the final multivariable model (Table 6.36), assuming age at baseline=30, hcy = 8 μmol/L, HOMA-IR at baseline = 2, and albuminuria=0.

Hcy, homocysteine; HOMA β, homeostatic model assessment for β-cell function; eGFR, estimated glomerular filtration rate.

Objective 3: Summary of results.

●Approximately half the cohort lost weight, including two-thirds of those with diabetes at follow-up.

●Among those with diabetes at follow-up, 35.1% of men, and 18.9% of women lost greater than 10kg.

●Both men and women lost weight in association with decreases in fasting blood insulin, while men also lost weight in association with uncontrolled glucose (increases in HbA1c over time).

●There are significant sex differences in progression of cardiometabolic disease; women experienced significantly greater increases in apoB in association with increases in fasting glucose as well as a very strong trend toward an independent effect of sex on apoB such that women had greater increases in apoB compared to men, independent of changes in other cardiometabolic markers.

●Change in apoB was strongly associated with change in BMI for men, but not women.

● eGFR was significantly and inversely associated with increases in hcy among men but not women, such that decreases in kidney function predicted increases in hcy in a dose-response manner.

●Weight loss was also associated with increases in hcy. For men, weight loss was a stronger predictor among those with better kidney function.

5. DISCUSSION

5.1 Time period trends

Overall, there were few major changes at the population level in terms of cardiometabolic burden from 2002/2003 to 2011/2012. The sex- and age-standardized prevalence of diabetes was not significantly different between time periods. While the sex- and age-standardized prevalence of obesity was significantly lower in 2011/2012 compared to 2002/2003, this was mostly accounted for by middle-aged men. Additionally, the sex- and age-standardized prevalence of abdominal obesity, dyslipidemia, and metabolic syndrome were also not significantly different between time periods. The lack of any radical changes in many cardiometabolic conditions over time may indicate the slowing or plateau of the epidemic, though it is difficult to make conclusions based on two time periods. Several noteworthy findings that are discussed are 1) the progression of the diabetes epidemic; 2) sex-differences; 3) improved cardiometabolic profile among middle-aged men; and 4) higher prevalence of current smoking status in 2011/2012.

5.1.1 Diabetes

Although the sex- and age-standardized prevalence of diabetes, at 39% during both time periods, is high, the rates were not significantly different between time periods. This may indicate a plateau in the diabetes epidemic as well as evidence to support that there has not been any significant improvement in the epidemic. Our findings are in conflict with previous reports, which suggest the epidemic is increasing and will continue to increase (Dyck et al., 2010; Green et al., 2003; Johnson et al., 2009). Due to the high prevalence of diabetes in the study community, it is likely that the epidemic may be more

advanced compared to other communities and other provinces. The plateau could also be viewed as heartening given that there was not an increase in prevalence. Nevertheless, the age-standardized prevalence is one of the highest reported in any population, which is not encouraging regardless of the direction of the epidemic.

A closer look at glucose status revealed a significant increase in fasting glucose among those without diabetes from 2002/2003 to 2011/2012; this increase was similar among men and women and more pronounced in the younger age groups, partly because there are many more individuals without diabetes in the younger age groups. Similarly, HbA1c was also significantly higher among those without diabetes in 2011/2012 compared to 2002/2003, independent of age group and sex. This is concerning because fasting glucose may be considered a more acute measure of glucose metabolism compared to diabetes status and this perhaps indicates a decrease in health status among those without diabetes, many of whom are young. While both glucose and HbA1c were statistically significantly higher in 2011/2012, an increase in glucose by 0.18 mmol/L (and 0.07% in HbA_{1c}) is of questionable clinical significance on an individual level. However, because these are mean values for a population, this probable shift in glucose tolerance is significant in terms of population health.

We hypothesized that the higher glucose among those without diabetes may indicate the beginning of a downward shift in the age of diagnosis of diabetes. However, the mean age at diagnosis remained at approximately 37 years of age among men and women in both time periods, which, although very young, was not significantly different between time periods. It should be noted though that age of diagnosis is a somewhat arbitrary measure since it is greatly affected by delays in diagnosis.

Another note on the diabetes epidemic in Sandy Bay is the persistence of a high prevalence of undiagnosed diabetes. Approximately a quarter of those found to have diabetes during both study periods were previously undiagnosed. In Sandy Lake First Nation, 41% of those with diabetes were previously undiagnosed (Harris et al., 1997). Importantly though, the data from Sandy Lake are over 20 years old and therefore not necessarily comparable. Diagnosis of diabetes is critical in managing blood glucose and preventing/delaying complications (Young & Mustard, 2001). Undiagnosed diabetes may be partly attributed to the healthcare services available in the study community. Sandy Bay First Nation operates a health centre, which does not offer primary medical care as its main focus. The mandate of the health centre involves community care and public health, with physician services following a "walk-in clinic" model, which is not suitable for management of chronic disease. Furthermore, travel to surrounding communities for regular physician services is difficulty for many. There may also be issues related to cultural safety in the relationships between medical professionals and community members that affect willingness to visit a physician. Lastly, several participants expressed fear regarding diabetes, such that they did not want to know their risk factor profile.

5.1.2 Sex difference

There was a sex difference in prevalence of hypertension in 2011/2012 that was not detected in 2002/2003. This sex difference may be partly explained by a strong trend in difference of incidence of hypertension between men and women found in the longitudinal component of this study; men had a 50% higher risk of developing hypertension compared to women. Interestingly, this finding contradicts that of the other findings that suggest significant cardiometabolic improvement among middle-aged men

and lack of improvement in any other cardiometabolic measure in women between time periods. Given the inconsistency of this finding with the larger picture, the public health significance of this change is questionable.

On the other hand, this finding is congruent with longitudinal data and the apparent lack of association of changes in blood pressure with changes in any other cardiometabolic measures. It appears as though, changes in blood pressure operate independently of adiposity and lipid metabolism in this population. It is also possible that the changes in prevalence of hypertension may reflect changes in lifestyle habits in the population. Specifically, incidence of hypertension is sensitive to alcohol consumption such that increased intake may induce hypertension (Peng et al., 2013). Results from the larger Stress and Diabetes Study suggest that alcohol is a problem for many community members. However, we are unaware of any changes in alcohol intake over time as well as any differences in alcohol intake between men and women; detailed data regarding alcohol intake were not collected. We are not aware of any other change in lifestyle in the community or sex difference to explain this phenomenon.

Crude prevalence of dyslipidemia, obesity, abdominal obesity and metS were significantly higher among women compared to men in both time periods but diabetes prevalence did not differ by sex. The literature has consistently reported higher prevalence of diabetes among First Nations women compared to First Nations men (Dyck et al., 2010; Green et al., 2003; Johnson et al., 2009). Again, the lack of sex difference for diabetes prevalence in this community may be a feature of a more advanced epidemic given the reported reduction in the diabetes gap between men and women over time in Saskatchewan (Dyck et al., 2010). Similarly, Green and colleagues (2003) reported an

increasing incidence of diabetes over time for First Nations men compared to a plateau for First Nations women in Manitoba during the 1990's.

With respect to higher prevalence of other cardiometabolic conditions among women compared to men in the present study, this may partially explain the higher risk associated with diabetes on CV outcomes for women compared to men reported in other populations (Natarajan et al., 2003; Huxley et al., 2006). This is also consistent with previous reports suggesting that women experience more pronounced adverse changes in lipid profile in response to diabetes compared to men (Howard et al., 1998; Bittner, 2002). This sex difference may also partially explain the greater gap in CV mortality observed between Canadian First Nations women and non-First Nations women compared to their male counterparts (Tjepkema et al., 2012). Additional research is required to determine the contribution of sex-based biological influences and gender-based social/cultural influences to this sex difference in disease and intermediate outcomes. Specifically, the role of pregnancy and gestational diabetes is unclear and may contribute to these differences.

5.1.3 Cardiometabolic improvements in middle-aged men

Men aged 40-49 years old had significantly lower odds of obesity in 2011/2012 compared to 2002/2003. Additionally, men in the same age group had significantly lower BMI, waist circumference, TG, and apoB in 2011/2012 compared to 2002/2003. They also had significantly higher HDL-C and apoA (observed in the entire sample) in 2011/2012. These metabolic improvements were not consistently observed in any other age or sex group and the lower odds of obesity were independent of diabetes. This finding could be considered a step in the right direction, although glucose and HbA1c

were also observed to be higher among those without diabetes in 2011/2012, independent of age group and sex. For this reason, the cardiometabolic improvements among middle-aged men should be interpreted with caution. It is also possible that the male sample aged 40-49 in 2002/2003 and/or 2011/2012 was either more or less healthy than the population from which it was drawn.

5.1.4 Smoking status

The prevalence of current smoking is important from a public health perspective because smoking is a major lifestyle factor that influences disease risk. Both current smoking and passive tobacco smoke exposure (including in utero) are associated with risk of developing diabetes (Sun et al., 2014; Jaddoe et al., 2014) and glucose intolerance (Houston et al., 2006; Piatti et al., 2014), not to mention many other adverse health outcomes (Blanchard et al., 2012; Burke et al., 2012; Dossus et al., 2014). Specifically, we have previously shown that pack-years was significantly associated with neuropathy in the community, independent of age, sex, education, HbA1c, and Hcy (Bruce & Young, 2008). This is important given that Dakota Ojibway Tribal Council has the highest rates of diabetes-related lower limb amputations in the province (Martens et al., 2007).

The proportion of current smokers in the study community, at 80.0%, is considerably higher than the Canadian prevalence, at 19.9% in 2011 (Janz, 2012), and also higher compared to the general First Nations population; according to the Assembly of Manitoba Chiefs' review of the First Nations Regional Longitudinal Health Survey, 62.4% of First Nations adults are current smokers (Elias & LaPlante, 2006). Community-specific data from Sandy Lake First Nation, indicated that 82% of youth aged 15-19 were

current smokers (data collected between 1993 and 1995) (Retnakaran et al., 2005). This prevalence is similar to the prevalence reported here for those 18-29 years old.

Godel and colleagues (2006) reported that the rate of smoking is slowly decreasing among the Canadian Aboriginal population. In contrast, the prevalence of current smoking was significantly higher in 2011/2012 compared to 2002/2003 in the study community. The largest increase in prevalence of smoking was seen in the 50+ age group. Among men in this age group, the crude prevalence increased from 60.5% to 77.6% and among women the crude prevalence increased from 50.0% to 67.3%. The highest increase in any other age and sex group was among men aged 18-29 years, where the crude prevalence of current smoking went from 73.6% to 83.7%. Therefore, this increase in current smoking prevalence was likely driven by a cohort effect; that is, those previously in the 40-49 year age group in 2002/2003 have now moved into the 50+ age range, along with their high smoking prevalence. A second driving force to this increase in current smoking is likely an increased number of young men beginning smoking, as evidenced by the third largest increase in any one age/sex group. In addition, over half of smokers on-reserve start smoking between the ages of 13 and 16 (Health Canada, 2011). Therefore, the increase in smoking prevalence is likely not driven by individuals over 18 years old that have now started smoking.

The increase in smoking among young men may be due to increased social pressures to smoke. While parent and sibling smoking were not associated with youth smoking, having friends that smoked was (Lemstra et al., 2011). A qualitative study among BC First Nations women also reported that smoking has an important social dimension, which increases the pressure to smoke (Bottorff et al., 2010). Specifically,

Bingo halls were identified as a social gathering, which promoted group smoking (Bottorff et al., 2009). While social support and social pressures can have strong positive influences on health behaviors, they can also influence behaviours negatively (Richmond & Ross, 2008), as observed with smoking here.

Lemstra and colleagues (2011) report that smoking youth in a Saskatchewan First Nation were more likely to report stress as reasons to start smoking compared to non-smoking youth. Previous qualitative research in the study community also indicates stress as a major contributor to smoking. In addition, qualitative data from a nutrition study in this study community suggest smoking may be used as a coping strategy for dealing with hunger and food insecurity. Therefore, aside from addiction, these factors must also be taken into account when attempting to address smoking rates in the community.

Policy strategies employed in the general population such as media campaigns, smoking cessation services, community awareness initiatives, smoke-free spaces, litigation, and taxation of tobacco products have proven effective in reducing population smoking rates (Samil & Wardman, 2009). However, in Canada as well as other developed countries, smoking rates have decreased over time to a much greater extent among those with higher levels of education compared to those with less education (Smith et al., 2009; Pierce, 1989). Recently, Dwyer-Lindgren and colleagues (2014) also report a greater decline in smoking rates among American counties in the top income quintile, with many low income counties experiencing no reduction in smoking rates from 1996-2012. These authors also report the persistence of higher rates of smoking among counties with large Native American populations. These results indicate that the

previously mentioned policy strategies have been much less effective in low socioeconomic groups, including indigenous populations.

The difference in effectiveness of policy interventions targeting smoking may be responsible for increasing or maintaining the health equity gap. Tjepkema and colleagues have recently reported disease-specific variation in the association between measures of socioeconomic status and age-standardized mortality rates of various causes of death. Many of the largest gaps were for causes of death closely associated with smoking (Tjepkema et al., 2013a). Among women, the hazard ratios for education and income were largest for death due to chronic obstructive pulmonary disease (COPD), diabetes, ischemic heart disease, and cirrhosis. Among men, the hazard ratios were largest for deaths due to lung cancer, COPD, cirrhosis, unintentional injuries, and diabetes (Tjepkema et al., 2013b). This paper supports the pivotal role for smoking in contributing to healthy equity gap.

Another important consideration in the discussion regarding smoking among First Nations is the issue of sovereignty. Tobacco sales are an important contribution to the First Nations economy and source of self-determination. Also, most of the previously listed policies are not in effect on reserve due to jurisdictional differences with regard to tobacco. Tobacco products are exempt from taxation on reserve, making the average cost for a carton of cigarettes sold on reserve to a First Nations person 44% less compared to a carton purchased off-reserve. According to Bill C-93, First Nation communities have the authority to tax tobacco products sold to First Nations and non-First Nations people (Samji & Wardman, 2009). However, as reported by the Canadian Revenue Agency in 2006, fewer than 2% of bands tax tobacco (Samji & Wardman, 2009). A detailed

commentary on the implementation, benefits, and challenges of a tobacco tax in a First Nation community has previously been reported (Samji & Wardman, 2009). However, what is not discussed by Samji & Wardman is the close geographical proximity between First Nations communities, particularly for the study community. For any policy to be effective there must be buy-in by more than individual communities. Importantly, Joseph and colleagues (2012) reported that only 3% of participants in their study from Six Nations reported being in favour of tobacco taxation, despite over 90% of participants reporting that tobacco use is a problem in their community. Policies to address smoking on reserve must also acknowledge the important traditional use of tobacco for First Nations people.

Lastly, in any public health intervention to address smoking in this population, consideration must be given to the unintended consequences. While action is needed, if policies or interventions do not take into account the previously described factors, outside of just addiction, we risk either making the problem worse or replacing the problem with another problem.

5.2 Incidence of intermediate chronic disease outcomes

5.2.1 Diabetes

In the present study, the incidence of diabetes among those without diabetes was 27% after a mean follow-up of 8.2 years. The higher rate among those 50 years and older reported here is consistent with the previous report in Manitoba First Nations (Green et al., 2003). Comparisons of incidence rates of diabetes to other populations are summarized in **Table 5.1**. The incidence rate appears to be highest in the study community; however all comparisons between studies are biased due to different length

of follow-up, dates surveyed, age groups included, age structure of the population, and/or method of diagnosis. In addition, the longitudinal sample may not necessarily be representative of population incidence in Sandy Bay. The longitudinal sample may be healthier compared to the population; therefore, the incidence rate of diabetes may in fact be underestimated.

Diabetes incidence among those with IFG at baseline was 69% over 8.2 years in the present study. In the Finnish population, 38% and 50% of individuals with impaired glucose tolerance, with no active intervention, will develop diabetes during 6 and 10 years follow-up, respectively (Lindstrom et al., 2006; Wikstrom et al., 2009). In the Diabetes Prevention Program, the diabetes incidence among those with impaired glucose tolerance was 11.0 per 100 person-years in the placebo group (Diabetes Prevention Program Research Group, 2002). In the present study, the rate was 14.6 per 100 person-years of follow-up. Therefore the conversion rate of "pre-diabetes" to diabetes may also be higher in this First Nation population compared to other high risk individuals from other populations.

Similar to prevalence, incident diabetes was not significantly different between men and women in the present study. In contrast, Green and colleagues (2003) reported a higher diabetes incidence among First Nations women compared to First Nations men in Manitoba. However, the authors also reported an increasing incidence of diabetes over time for First Nations men compared to a plateau for First Nations women in Manitoba during the 1990's; this finding also supports the reduction in the diabetes gap between First Nations men and women over time and as the epidemic advances.

Table 5.1. Comparison of diabetes incidence rates in Indigenous populations.

Population	Incidence rate/density	Reference
Sandy Bay First Nation	27% over 8.2 years 3% per year 38.6 cases/1000 person-years	Present study
Australian Aboriginal communities	20.3 cases/ 1000 person-years	Daniel et al., 1999
Manitoba First Nations population		Green et al., 2003
Men	21.1 per 1000	
Women	21.1 per 1000 [estimated based on other data provided]	
Albertan First Nations population		Oster et al., 2011
Men	10.3 per 1000 per year or 1.03%	
Women	11.9 per 1000 per year or 1.19%	
Saskatchewan First Nations population		Dyck et al., 2010
Men	17.80 per 1000 per year or 1.78%	
Women	17.95 per 1000 per year or 1.795%	
Sandy Lake First Nation (aged 10-79 years at baseline)	17.5% over 10 years	Ley et al., 2008
Kahnawá:ke First Nation		Horn et al., 2007
1986-88		
Men	8.8 per 1000	
Women	8.8 per 1000	
2001-03		

Men	7.0 per 1000
Women	5.2 per 1000

5.2.2 Weight change

Risk of weight gain was highest among those 18-29 years old compared to all other age groups. Heitmann & Garby (2002) also reported that in a Danish population, those that gained weight were younger on average. There are also age-related changes in body composition that should be taken into account in the interpretation of this age association. Typically, individuals experience a loss of fat-free mass and gain in body fat with age (Heitmann et al., 2002). Unfortunately, data on body composition is not available for the present study. In terms of magnitude of weight gain among young adults in the present study, it appears as though the rate of weight gain is similar to that of young adults in the African American population (**Table 5.2**). The rate of weight gain is just over 1 kg per year in the present study as well as in the African American population. However, this rate is substantially higher compared to the rate of weight gain in white samples, regardless of sex. Unlike the other populations though, rate of weight gain was identical among men and women aged 18-29 years old in present study. Among the African American populations rate of weight gain was higher among women compared to men, whereas the rate was high among men compared to women in the white population. The higher rate of weight gain among women in the African American population may be pregnancy-related (Hediger et al., 1997).

Description of weight gain is important because of the high prevalence of obesity as well as the well-documented associations between BMI and chronic disease, including diabetes. Importantly, weight gain is a risk factor for developing metS among young adults, independent of diet, physical activity, and other risk factors (Carnethon et al., 2004). However, ethnicity may be an important modifier in the relationship between

weight change and CV risk (Tybor et al., 2011), which has not been explored in a First Nations population. Additional future research of this cohort will include exploring the contribution of nutritional factors to weight gain. While controversial, the wider body of literature seems to suggest weight maintenance may be better for long-term health as compared to recommendations for weight loss, which is difficult to sustain and could result in weight cycling (Bombak, 2014; French et al., 1996).

Table 5.2. Weight change among young adults.

Population	Rate of weight gain	Reference
Sandy Bay First Nation (18-29 years old)		Present study
Men	1.05 kg/year	
Women	1.05 kg/year	
CARDIA Study (Americans 18-30 years old)		Norman et al., 2003
Black women	1.18 kg/year	
White women	0.72 kg/year	
Black men	1.05 kg/year	
White men	0.77 kg/year	
Princeton School Study of the Cincinnati Lipid Research Clinic (18 years old at baseline)		Khoury et al., 1983
Black women	1.11 kg/year	
White women	0.42 kg/year	
Black men	0.90 kg/year	

White men	0.69 kg/year	
Iowa Women's Health Study **Mostly white (>99%) women (weight change from 18 to 30 years old)**	0.51 kg/year	French et al., 1996
Pitt County Study (African Americans age 25-39 years old)		Curtis et al., 1998
Men	0.84 kg/year	
Women	1.34 kg/year	

Some values were calculated based on the data provided; the values were calculated from all members of each group, including those who lost weight;

5.3 Disease progression

5.3.1 Diabetes-related weight loss

General interpretation. Among those with diabetes at follow-up, 35.1% of men, and 18.9% of women lost greater than 10kg. These results are congruent with anecdotal reports from the community regarding men with diabetes becoming "ghosts of themselves". We hypothesize that this weight loss is unintentional. Our rationale for this is that intentional weight loss has consistently been associated with improvements in glucose measures (Aguiar et al., 2014) whereas weight loss in the current study was associated with uncontrolled glucose (HbA1c).

Despite the emphasis in public health on optimal body weight and weight loss, there is relatively little research on weight change, particularly intentional vs unintentional, among those with diabetes. Gregg and colleagues (2004) report that 45% of overweight individuals with diabetes experienced a weight loss (>1 lb) during 9 years of follow-up, compared to approximately 66% over 8.2 years in the current study. Compared to those with stable weight, Gregg and colleagues also report that those who lost weight were younger, more likely to be women, more likely to have been diagnosed with diabetes more recently. In contrast, we did not find a sex difference with weight loss (presence or absence), a significant relationship with age, nor length of time with diabetes. Furthermore, in a Japanese 20-year follow-up study, participants who lost ≥10kg were more likely to have hypertension, diabetes and be a current smoker (Chou et al., 2013). While diabetes was associated with weight loss in the present study, hypertension and current smoking were not. However, the high prevalence of smoking (hence little variation) and high prevalence of hypertension among those with diabetes,

may have precluded the detection of significant relationship. However, these factors may explain the apparent higher rate of weight loss in this population.

Additional explanations for the reported weight losses include: large increases in glucose, and decreases in fasting insulin, may have resulted in significant glucosuria; and/or uncontrolled glucose may have contributed to autonomic dysfunction of the digestive system or diabetic gastroparesis (leading to reduced intake); and/or widowhood. In regards to the second explanation of gastroparesis, we noted many participants, particularly men with diabetes, were on medications to control stomach acid production (omeprazole, ranitidine) and improve stomach motility (domperidone). These data were not systematically collected in the 2011/2012 study but some participants provided it because they were unsure of which medications were prescribed for which conditions and we asked about medications for diabetes and heart disease. However, as part of the Sandy Bay Nutrition Study, data regarding these medications were collected as well as a description of any health-related problems that affected food intake. Anecdotally, I can say that dyspepsia is a significant problem in the community, particularly among those with diabetes. This is an area of further investigation which may aid in determining additional contributing factors to these weight losses.

The positive relationship between change in fasting insulin and change in body weight has been previously described. For example, in the Diabetes Prevention Program (DPP), a 3-7% weight loss was associated with a decrease in insulin, especially among men (Perreault et al., 2008). The differences between the DPP and the present study is that in the DPP most of the participants have their beta-cell function preserved and weight loss was intentional whereas in the current study, the decrease in fasting insulin is

likely reflection of decreased beta-cell function and weight loss was likely unintentional. In this regard, in the present study, change in HOMA β-cell function was also inversely associated with weight loss among men in the partially adjusted analysis, independent of age and BMI at baseline. In other words, in the DPP, the participants likely had decreased insulin because of better glucose control while in the current study participants likely had decreased insulin due to β-cell exhaustion. Therefore, while the relationship between change in insulin and weight change is similar, it is unclear if it is appropriate to compare the cohorts.

With respect to the contribution of widowhood to unintentional weight loss, Meltzer & Everhart (1995) have previously reported that unintentional weight loss was associated with widowhood among men but not among women. Also, there is some data from the Sandy Bay Nutrition Study to suggest that widowhood may have contributed to greater weight losses among men in the study; however, this requires further research and analysis of that data. Additional data regarding food intake among those that lost weight will also be explored. Lastly, there have been no major changes in the community regarding diabetes programming, access to exercise facilities, or access to food that could explain these results.

Risk of unintentional weight loss. There is a considerable amount of literature supporting a high risk of CV outcomes and CV-related mortality for those experiencing unintentional weight losses. Gregg and colleagues (2004) report a 22% and 40% higher mortality rate among those who lost any weight and those losing at least 20 lbs (regardless of intention) compared to those having no weight change, respectively, independent of age, sex, BMI, smoking and education. When specifying further by

weight loss intention, it was found that compared to those with stable weight or weight gain and not trying to lose weight, those with unintentional weight loss of any amount, had a 58% higher mortality rate. Additionally, those that lost weight were more likely to report neuropathy and hypertension (Gregg et al., 2004). Stevens et al. (2013) also report that a weight loss >3% in 3 years was associated with an increased CHD risk (HR: 1.46) and stroke risk (HR: 1.45), indicating that even a short-term weight loss could be a sign of a looming CV event. In a study investigating weight change since age 20 among participants 40-79 years old followed for 13.3 years, participants that lost ≥10 kg had a significantly higher risk of death from all forms of stroke (Chou et al., 2013). The adjusted hazard ratio was slightly higher for women compared to men at 1.62 vs 1.52, respectively. This relationship persisted even when deaths in the first 3 years of follow-up were excluded.

As diabetes prevention programs stress weight loss and we are currently trying to develop an intervention in the community it is important to report that among men, ***intentional*** weight loss of 1-19 lbs was associated with a 22% reduction in diabetes-related mortality; however, a weight loss >20 lbs was associated with a 48% increase in mortality (Williamson et al., 1999). Of note, these analyses were not adjusted for measures of glucose control. While the preceding comparison to the literature is based on observational studies, we must be cautious in recommendations for weight loss in the community for the prevention of diabetes. Additionally, it is crucial in future research with the community to distinguish between intentional vs unintentional weight loss, as well as better understand the determinants of weight loss among those with diabetes.

Sex differences. The descriptive analysis seems to indicate that there is a difference in the magnitude of weight loss between men and women. This may be related to the type of weight lost (Yamashita et al., 2012), with women being more likely to lose fat mass as opposed to lean body mass. Additionally, women may have gained more weight prior to losing weight due to changes in fasting insulin or HbA1c, resulting in more women with net weight gain rather than net weight loss or less net weight loss. This may have limited the ability to detect more predictors of weight loss among women in the multivariable model. Lastly, some women retain a significant amount of weight following pregnancy (Grunderson & Abrams, 2000), which could further influence sex differences in diabetes-related weight loss and/or its predictors.

Another sex difference that was noted was the significant interaction between sex and change in HbA1c on odds of weight loss. This relationship was partially attributed to the higher HbA1c and fasting glucose among men compared to women. However, there were still several women in the sample with large increases in HbA1c. This leads to two questions: 1) why do men with diabetes have more poorly controlled glucose compared to women?; and 2) why are men more likely to lose weight in response to changes in HbA1c compared to women? First, it has previously been reported in other populations that men have higher fasting glucose levels compared to women (Perrault et al., 2008; Williams et al., 2003). We speculate that there are multiple factors that contribute to these differences that are both biological and social. Diet, physical activity, adherence to medication, stress, and care-seeking may be different between men and women. While blood pressure was not significant in the multivariable model, there may still be a mediating role for blood pressure in weight loss; we have previously reported that the risk

of incident hypertension in the longitudinal sample was significantly higher among men. Due to the small sample size, we may not have been able to detect a relationship. Lastly, these results also suggest that the underlying causes of weight loss among men and women may be different despite sharing some of the same predictors.

Implications for intervention. The Diabetes Prevention Program – lifestyle arm, generally considered the current gold standard for prevention of diabetes, has indicated that weight loss is an important part of reducing diabetes risk (Hamman et al., 2006). Based on the current literature and the high number of individuals with diabetes in the study community with the goal of preventing secondary complications, interventions focussing on health-related behaviours such as diet and exercise rather than weight loss specifically, may be more prudent.

5.3.2 Predictors of change in apoB

General interpretation. The Canadian Cardiovascular Society recommends an apoB goal of ≤0.8 g/L for those with CHD. The American Diabetes Association also recommend a goal of ≤0.8 g/L for those with established CVD or diabetes plus one other risk factor and ≤0.9 g/L for those without CVD disease plus 2 cardiometabolic risk factors (Brunzell et al., 2008). At baseline and follow-up, mean apoB was 0.9 g/L among both men and women in the current study. This is consistent with the high CV burden according to apolipoproteins previously reported in this population (Riediger et al., 2011).

The advantages of apoB as a predictor of CV outcomes have been previously described in the introduction chapter. Additional practical advantages of measuring apoB are that it does not require a fasting sample and is measured directly as opposed to LDL-

cholesterol, which is calculated from other values. However, as apoB is a somewhat newer CV risk factor, not all provinces fund apoB laboratory tests (Anderson et al., 2013).

Sex differences. There are significant sex differences in change in apoB over time; women experienced significantly greater increases in apoB in response to increases in fasting glucose as well as a very strong trend toward an independent effect of sex on apoB such that women had greater increases in apoB compared to men, independent of changes in other cardiometabolic markers. Also, change in BMI was positively associated with apoB at follow-up for men, but not women.

In terms of death from CHD, diabetes is a stronger predictor among women compared to men (Natarajan et al., 2003; Huxley et al., 2006). Kannel and McGee (1979) also reported significantly greater CV morbidity and mortality among women with diabetes compared to men with diabetes. However, for coronary heart disease, peripheral vascular disease, and stroke the sex difference for the impact of diabetes on these outcomes was lost after adjustment for traditional CV risk factors; nevertheless, even after this adjustment, the impact of diabetes on CV mortality was still greater for women. The adjusted relative risk of diabetes for women was 3.3 compared to 1.7 for men. Importantly though, apoB was not adjusted for. A recent meta-analysis on the sex difference in risk of stroke associated with diabetes also indicated that diabetes is a stronger risk factor for stroke among women than for men (Peters et al., 2014). This finding was also independent of other CV risk factors in many of the reviewed studies, but never adjusted for apoB. It is widely thought that differences in risk factors do not

fully account for this sex difference and that gender differences in health care in the prediabetic state may also play a role.

While similar research regarding the sex difference for diabetes in risk of CV outcomes has not been completed for First Nations populations, the available research generally supports this phenomenon. CV disease mortality rate ratios comparing First Nations men and women to non-First Nations Canadians from the Canadian census mortality follow-up study (1991-2001) indicated significantly higher CVD mortality rates among First Nations, especially among women and in younger age groups, compared to non-First Nations. Specifically, among those 25-34 years old at baseline, the risk of CV mortality for First Nations men was 62% higher and 217% higher for First Nations women, compared to their non-First Nation counterparts (Tjepkema et al., 2012). Lastly, out of all Canadian provinces and territories, First Nations men and women in Manitoba had the highest CV mortality rate, with the exception of Atlantic Canada (grouped) (Tjepkema et al., 2012), which mirrors the available provincial diabetes prevalence statistics (Dyck et al., 2010; Green et al., 2003; Oster et al., 2011).

As previously discussed, risk factors do account for at least some of the sex difference in risk of diabetes for CV outcomes. It is hypothesized that the most important risk factors in accounting for this sex difference are lipids (Carnevale Schianca et al., 2012). Our results support this hypothesis in that apoB at follow-up was nearly significantly higher among women compared to men, independent of other risk factors, as well as significantly higher in response to changes in fasting glucose. Similarly, among American Indians in the Strong Heart Study, women with diabetes had worse lipid changes compared to men with diabetes, specifically the women had greater decreases in

HDL cholesterol and apoA, and greater increases in apoB (Howard et al., 1998). Bittner has also reported that TG are much higher and HDL cholesterol is much lower for women with diabetes compared to women without diabetes (Bittner, 2002). It is thought that sex hormones may play a role and there is some evidence to support this (Pérez-López et al., 2010). Again, while there is likely a significant role for gender, that is social and cultural roles of women, in lipid changes and CHD, there is substantially less literature on this topic.

The other important sex difference noted in the analysis of apoB at follow-up is the significant sex interaction with weight change, such that weight change was associated with apoB among men but not women. Sex differences in weight change with changes in other cardiometabolic risk factors have been previously reported. Norman and colleagues (2003) reported a significantly stronger relationship between weight gain and LDL-C, triglycerides, and fasting insulin in men than in women. Our findings are also in agreement with those from the Framingham Study, where the positive relationship between weight change and changes in total cholesterol, systolic blood pressure, and blood glucose were all stronger in men than in women (Ashley & Kannel, 1974). This may be related to differences in the type of weight lost/gained between men and women, for example, lean body mass vs. adipose tissue.

Implications for intervention. There are two important implications with respect to the apoB analysis. The first being the sex difference in apoB with changes in fasting glucose. It may be more important to reach and/or maintain target apoB levels for women compared to men to reduce CV risk. Since research relating to apoB is emerging, there is a paucity of research into interventions to reduce apoB and its relationship to long-term

outcomes. The available research however does suggest a role for lifestyle intervention. Specifically, weight loss, through a low-fat diet, has been directly associated with a reduction in apoB among Caucasian men with the metabolic syndrome (Chan et al., 2008). To my knowledge there are neither available medications targeting apoB nor have currently available medications been shown to reduce apoB. Notably, among those taking statins, apoB was still more closely associated with CV outcomes compared to LDL-cholesterol (Kastelein et al., 2008). Among patients "successfully" treated with statins (ie. target LDL-cholesterol reached), half had not reached the apoB goal (Ballantyne et al., 2006).

The role for lifestyle intervention in reducing apoB then leads to a discussion regarding the sex difference in effectiveness of lifestyle intervention in reducing diabetes risk and CV risk. Again, while not comprehensively researched to date, the available research suggests an important sex difference. Investigators for the Finnish Diabetes Prevention Study report a 63% and 54% reduction in diabetes incidence for men and women, respectively, randomized to the lifestyle intervention compared to the control group; the authors do not report whether this difference in statistically significant (Tuomilehto et al., 2001). In the Diabetes Prevention Program, men and women did not differ in their reduction in incidence of diabetes in the lifestyle group compared to control (Knowler et al., 2002). However, in response to the lifestyle intervention, men lost more weight, were more physically active, and met more lifestyle goals compared to women (Perrault et al., 2008). Importantly, in the lifestyle intervention group weight loss of 3-7% resulted in significantly greater decreases in 2-hour glucose, fasting insulin, and insulin resistance among men compared to women. Additionally, weight loss>7% resulted in

significantly greater decreases in TG, 2-hour glucose, and HbA1c among men compared to women (Perrault et al., 2008). The association between weight loss and apoB was not reported. It should be noted though that men had significantly higher fasting glucose and more adverse cardiometabolic risk factors at baseline compared to women. Lastly, in a study of the metabolic effects following gastroplasty, with 49 of 53 participants being female, many cardiometabolic measures improved with weight loss (mean BMI loss was 12 kg/m^2), whereas apoB did not (Borson-Chazot et al., 1999). These results suggest a more limited direct role of weight loss in influencing apoB levels among women.

5.3.3 Predictors of increased homocysteine

General interpretation. In the present study, HOMA β-cell function at baseline, weight change, and eGFR (kidney function) at follow-up were inversely associated with increased hcy at follow-up, independent of age, sex, hcy at baseline, HOMA-IR at baseline, and albuminuria status at baseline. There were also significant sex interactions with weight loss and eGFR on increased hcy; specifically, eGFR was a much stronger negative predictor of increased hcy among men compared to women and weight loss was a stronger positive predictor of increased hcy among women compared to men.

The role of β-cell function in driving changes in hcy has been previously reported. Hcy is higher among those with diabetes compared to those without. Importantly, the authors report that HbA1c was more closely associated with hcy among those with diabetes, indicating that hcy may increase following the onset of diabetes, which usually results from β-cell exhaustion (Masudaet al., 2008). Lastly, hcy is a stronger predictor of CVD among those with diabetes than patients with normal glucose tolerance (Audelin & Genest, 2001).

Similar to β-cell function, weight loss has also been previously implicated in increases in hcy. In an RCT with patients randomized to either an energy-restricted very-low carbohydrate diet or isocaloric conventional high carbohydrate diet, hcy increased after weight loss but increased more greatly in the very-low carbohydrate group (Keogh et al., 2008). While not directly comparable, several studies have shown that hcy increases as a result of surgery for weight loss (gastroplasty, lap-band surgery) (Borson-Chazot et al., 1999; Dixon et al., 2001; Sheu et al., 2001). Dixon and colleagues (2001) also conclude that even greater folate intake is required to maintain hcy levels during weight loss as compared to weight maintenance. Lastly, Lobrano and colleagues (2006) reported a higher prevalence of hyperhomocysteinemia among a sample of patients with gastroparesis (including diabetic gastroparesis) compared to the general population. This finding is especially relevant to our study population given that diabetic gastroparesis may be implicated in the weight loss observed.

Renal disease is a well-known predictor of plasma hcy due to the impairment of renal clearance of hcy (van Guldener, 2006). Specifically, Ruan and colleagues (2009) reported that hcy was significantly associated with eGFR in a multi-ethnic sample, independently of other risk factors; however, the authors did not report a sex difference in this relationship. Similarly, among both Japanese men and women, there was a significant association between eGFR and hcy (Masuda et al., 2008). The relationship between hcy and eGFR was stronger among those without diabetes compared to those with diabetes; this finding is similar to our findings, in that prediction analysis revealed that HOMA β-cell function was a more important predictor of increased hcy with better kidney function. While there is controversy surrounding hcy as a risk factor as opposed to risk marker for

CVD because of its relationship with kidney function (Rodionov & Lentz, 2008), hcy has been associated with myocardial infarction independently of renal function (Van Guelpen et al., 2009).

Sex differences. Some sex differences in hcy and its relationships with various other CV risk factors and outcomes have been documented. (Boushey et al., 1995; Graham et al., 1997; Hornstra et al., 2014). However, most have not been extensively studied, though it is accepted that hcy is higher in men compared to women (Nygård et al., 1995). Women in the present study may have experienced the protective CV effect of estrogen on hcy metabolism. While we did not collect age of menopause, based on the age of female participants, we can assume that many of them were premenopausal at baseline and may have progressed through menopause at follow-up. Potential mechanisms for the estrogen-effect on hcy and CV risk have been postulated by others (Smolders et al., 2004; Spencer et al., 2004). However, the relationship between estrogen and hcy has mostly been studied in the context of hormone-replacement therapy among post-menopausal women (Hak et al., 2001; Mijatovic et al., 1998; Van Baal et al., 1999)

Implications for intervention. Hcy is not currently an accepted CV risk factor because trials to lower hcy through vitamin B supplementation have not resulted in reduced CV risk. For this reason, the implications of this analysis for intervention are difficult to assess. However, the inverse relationship between weight change and increased hcy indicates that the weight loss described throughout the discussion may be caused by reduced food intake, given that folate status is the main predictor of homocysteinemia (Kang et al., 1987; Selhub et al., 1993; Verhoef et al., 1997).

Interestingly, heavy coffee consumption raises hcy in healthy individuals as evidenced by several randomized controlled trials (Verhoef et al., 2002; Urgert et al., 2000; Grubben et al., 2000). Anecdotally, I can say that coffee intake is very high in Sandy Bay and may offer a target for intervention; this will be investigated further in the Sandy Bay Nutrition Study. However it remains to be seen whether reducing coffee intake would reduce CVD or CV mortality.

Nevertheless, the effects of diabetes-related weight loss reported in all analyses here may support the hypothesized mechanisms of obesity-related conditions presented by Bombak (2014). She describes a direct pathway involving adipose tissue as well as the direct role of diet, independent of body size. Here, the relationship between change in body weight and apoB (among men) may be an example of a direct role for adipose tissue, and the relationship between weight change and increases in hcy may be an example of a direct role of diet (here, B vitamins), independent of body size.

5.4 Strengths

There are several important strengths of this research project, including the participatory framework, richness of the data, unique population, use of both a repeated-cross-sectional and prospective cohort design to describe the epidemic, and a sex- and gender-based analysis.

5.4.1 Framework

The most important strength of CBPR is that the research question is of importance to the community and that the community is expected to benefit from the completion of the research. Specifically, the community was very interested in

comparing the prevalence of cardiometabolic conditions between study periods (objective 1). This data provides the community with evidence to advocate for greater resources with respect to primary health care and public health. Secondly, the issue of unintentional diabetes-related weight loss among men in the community has been a concern for some time (objective 3). This work sheds light onto the causes of unintentional weight loss among those with diabetes.

Not only does the community benefit from the results of the research project but they also received benefits from the research process. Those involved in the conception and implementation of the project benefit from the research knowledge and experience in carrying out a research study. In this way, the members of the CDAG may feel empowered to make their own changes. Community Research Assistants also gained research skills by being involved in the study.

5.4.2 Richness of data

Currently, population-level data (in any population) is often restricted to administrative health data, which has several limitations. A rich dataset including cardiometabolic risk factors can only be obtained by meticulous, labour-intensive, and resource-intensive data collection. An important strength of this dataset is the inclusion of a representative number of young males; many population-based studies struggle with recruitment of this age/sex demographic. Another source of richness that aids in the interpretation of the analysis is that not only did I conduct the analysis but I was also heavily involved in the data collection of the 2011/2012 study as well as the follow-up Sandy Bay Nutrition Study. Specifically with regard to the analysis on weight loss, data on height and weight in each time period was collected rather than self-report, as used in

many studies on weight loss. Lastly, the First Nations population is unique in many ways. Therefore the combination of the richness of data with the unique population, make for a major strength.

5.4.3 Design

The use of both a repeated-cross-sectional and a prospective cohort design is also a major strength, as they capitalize on each other's limitations. With respect to the repeated cross-sectional design, the sample can be representative of the total population at each wave of the study. In this way, the repeated cross-sectional design is appropriate for assessing period trends. In the current study, it should be noted that convenience sampling was used during both time periods rather than random or probability-based sampling. However, the 2002/2003 and 2011/2012 samples were both representative of the populations according to age and sex. Lastly, lost-to-follow up or attrition is not an issue in this design. With regard to the prospective cohort design, this design can be used to assess temporality and therefore is better for determining causation as compared to the cross-sectional design (Menard, 2002).

5.4.4 Sex and Gender-based analysis

Sex considerations are very important, particularly in CV research, where numerous sex differences are already known. Not taking a sex- and gender-based approach may result in missing relationships when sex-specific associations are in the opposite direction or detecting relationships when only one sex is driving the association. Using this approach I was able to detect many sex-specific relationships, which may have implications regarding intervention. Importantly, gender was considered in the interpretation and discussion of the results.

5.5 Limitations

There are of course several limitations in the present study:

Age-period-cohort effects. Although the repeated cross-sectional design allows for assessment of differences/changes across different age groups, the issue of cohort effects may confound the interpretations of the results if any data collection period is looked at in isolation. Cross-sectional analysis may give additional information about a pattern or relationship that longitudinal data may not capture or vice versa, even though both patterns may be correct (Menard, 2002). For this reason, it is difficult to fully understand trends over time with only two time points, such as in the present study. This may be especially problematic in the interpretation of the changes in risk of middle-aged men in the repeated cross-sectional results.

Limited data points in longitudinal design. A longitudinal design with only two time points was utilized. With limited time points we are unable to assess changes in incidence over time as well as accurately assess time of diabetes diagnosis or timing with regard to any aspect of progression of cardiometabolic disease. Also, disease progression is not necessarily linear, which could not be captured using this design.

Lost to follow-up. Attrition is the loss of participants beyond those lost to death or in the case of the present study, including those lost to death. This can affect power (n) and if severe enough may impede analysis when there are insufficient numbers per cell. Attrition has 3 main causes: 1) moving, resulting in being unable to contact participants; 2) researcher unable to contact participant at correct address; 3) Refusal for further participation (Menard, 2008). While some degree of attrition is inevitable, if attrition is

non-random it could be a biased sample. With the exception of age, the longitudinal sample was representative of the original 2002/2003 cross-sectional sample based on sex, marital status, education, employment, diabetes status, and hypertension status. Therefore, the data do not indicate a biased longitudinal sample. However, the small sample size may impair the detection of significant differences in the longitudinal analysis. The high degree of attrition may be partially attributed to a longer time period of follow-up.

Mortality outcomes. No data was collected regarding death or cause of death. For the 2011/2012 sample, Manitoba Health numbers were collected to ensure that date and cause of death could be examined in the future.

Self-report. Previous diagnosis of diabetes and hypertension as well as number of years with diagnosis is self-reported.

Underlying conditions. We are not aware of any other conditions which may affect the markers investigated in the analysis. Specifically, we are not aware of genetic defects in metabolism of hcy in the population that would influence the hcy analysis.

Unavailable data. Several variables that may be helpful in the interpretation of the findings were not available. Specifically, data regarding weight loss intention were not collected. However, this is an area of further investigation as part of the Sandy Bay Nutrition Study. Complete data on renal health were also not collected. While measures of renal function were collected in both time periods, they are different (ACR in 2002/2003 and eGFR in 2011/2012), and therefore we could not ascertain changes in renal function over time. Medications for lipid-lowering were not collected reliably,

partially due to self-report. However, further research linking participants to administrative data could be undertaken to ascertain medication use.

Missing data. In both the repeated cross-sectional design and the prospective cohort design there was little missing data. For the repeated cross-sectional analysis, <3% of the data was missing for all the analysis and <1% for most of the analysis. With respect to the prospective cohort analysis, the multivariate model with hcy had the most missing data. However, <7% of the participants could not be included (160 of 171 included). This was mostly accounted for by missing urinary data at baseline. There is no indication that this data is not missing randomly.

Analysis. With respect to objective 1, with the repeated cross-sectional design, multiple time period comparisons were made for continuous variables. In addition, we did not adjust the level of significance to account for this multiple comparison issue. However, it should be noted that the majority of the findings were not discussed in an individual manner; rather the interpretation was of the "bigger picture".

External validity. The results for the present study represent one First Nation community. There is likely somewhat limited external validity with respect to other Canadian First Nations, especially those outside of Manitoba. However, it is also unlikely that the results presented are unique to just this community. There is likely better external validity with other communities within the Dakota Ojibway Tribal Council of Manitoba. Specifically, communities with a similar health care model (ie. Health Centre) and social determinants of health (ie. lack of economic development, limited employment opportunities, etc) will have improved comparability with the study population.

5.6 Knowledge translation

5.6.1 Diabetes Advisory Group

Frequent meetings between the researchers and the Diabetes Advisory Group occurred **(Table 5.3).** Content of the meetings included study planning, study logistics, hiring of community research assistants, dissemination of results, and workshop planning.

Table 5.3.Summary of meetings attended with Community Diabetes Advisory Group (CDAG).

Date	Group	Purpose
April 17, 2014	CDAG	Present thesis results and plans for publication
March 13, 2013	CDAG and extended Research Team	Update study progress and begin planning for intervention
September 14, 2012	CDAG and Dept of Community Health Sciences	Colloquium presentation in the Department of Community Health Sciences – presentation of Nutrition Study and how it will connect to the Stress Study
June 5, 2012	CDAG	Presentation of preliminary results of Stress and Diabetes Study
May 8, 2012	CDAG	Presentation of progress in Nutrition Study and Stress and Diabetes Study
December 7, 2011	CDAG	Presentation of proposed nutrition study, Diabetes Advisory Group meeting
October 5, 2011	CDAG	Presentation of study results
April 16, 2011	Health Advisory Board	Presentation for approval of study protocol

5.6.2 Participant knowledge translation

The study team prepared individual results letters during each study period for every participant outlining their fasting glucose, HbA1c, Total cholesterol, TG, HDL-C, LDL-C, Total cholesterol:LDL-C ratio, and blood pressure. Reference values for each measure were also provided. Importantly, a lay summary was provided of the results, including a suggestion for participants to visit their physician if their results indicated a high suspicion of diabetes, hypertension, or dyslipidemia.

The study team attempted to return letters to all participants via home-drop off or pick-up. If participants could not be located at a residence, we attempted to reach them by phone. In 2011/2012, 30 letters (of 596) were left undelivered; twenty-three participants had moved, 2 were deceased, and 5 we were unable to locate.

All participants were encouraged to provide their results to their physician at the community Health Centre. Informal conversations with a nurse at the Health Centre indicated that for the 2003 study, approximately three quarters of participants provided their results. Anecdotally, I can report that in 2011/2012, many participants did provide their results to their physician. In addition, I personally spoke with many participants regarding their results, including what the measures represented and lifestyle strategies to improve test results for those that were interested. Canada's Food Guide's (both Canadian and First Nations versions, including copies in Ojibway) were offered to participants.

5.6.3 Workshops, newsletters, radio

On March 15, 2012 a Nutrition Workshop was held from 10 AM- 3 PM at the Sandy Bay First Nation, Community Complex. I coordinated the planning of the workshop with the Aboriginal Diabetes Initiative worker. Study results to date were

presented and I gave an interpretation of the results letters. Individual participants were also given the opportunity to meet privately with a member of the study team, including a physician, Dr. Barry Lavallee, to discuss their study results. Lastly, we presented on nutrition education for diabetes prevention and treatment, including a segment on reading food labels, as requested by the Aboriginal Diabetes Initiative worker.

Other community initiatives included hosting a booth at the Sandy Bay First Nation Health Fair in November 2011 to promote the study and answer questions about the study and diabetes in general. I, along with another Research Assistant, was interviewed live on Sandy Bay Radio on October 13th, 2011 to promote the study as well. Lastly, we regularly recorded advertisements regarding the study on Sandy Bay Radio.

6.0 CONCLUSIONS

Results from this study contribute new findings to the body of literature on First Nations health. We now have a deeper and more current understanding of the diabetes and related chronic disease epidemic in this First Nation community. Specifically, the diabetes epidemic has appeared to have reached a plateau in this population. This study may also forecast the diminished sex differences in diabetes prevalence as the epidemic progresses in other First Nations populations. However, CV risk factors such as current smoking status have increased and a higher burden of obesity, dyslipidemia, and metabolic syndrome continue to plague women in the community. While this study is not a direct evaluation of the resources or programs directed to the problem, this study does provide data for the community to assist in advocating for additional resources/programs to address the burden of diabetes and the underlying social determinants of health. This study also provides rationale for additional efforts at the provincial and federal level to address the burden of chronic disease among First Nations people if improvement is sought. Lastly, the results from objective 1 provide a detailed description of population disease burden and the direction of the epidemic to assist in evaluating future programs and interventions.

Generally, the results from this study regarding progression of cardiometabolic disease confirm that several relationships observed in other populations are similar in this First Nation population. On the other hand, the burden of diabetes-related weight loss appears to be disproportionately high in this First Nation population, and several potentially important correlates of diabetes-related weight loss were observed. These results should be taken into consideration when designing interventions and defining sub-

populations for these interventions, specifically related to weight loss for prevention of diabetes. Furthermore, the implications of these findings for interventions would be further clarified with research to correlate diabetes-related weight loss with long-term mortality outcomes.

7.0 REFERENCES

Aguiar, E.J., Morgan, P.J., Collins, C.E., Plotnikoff, R.C., & Callister, R. (2014). Efficacy of interventions that include diet, aerobic and resistance training components for type 2 diabetes prevention: a systematic review with meta-analysis. *International Journal of Behavioral Nutrition and Physical Activity*, 11, 2.

Alberti, K.G.M.M., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.L., Donato, K.A., … Smith, S.C. Jr. (2009). Harmonizing the metabolic syndrome. A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*, 120, 1640-1645.

American Diabetes Association (2013). Executive summary: standards of medical care in diabetes – 2013. *Diabetes Care*, 36, S4-S10.

Anand, S.S., Razak, F., Yi, Q., Davis, B., Jacobs, R., Vuksan, V., ... Yusuf, S. (2004). C-reactive protein as a screening test for cardiovascular risk in a multiethnic population. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 24, 1509-1515.

Anand, S.S., Razak, F., Davis, A.D., Jacobs, R., Vuksan, V., Teo, K., Yusuf, S. (2006). Social disadvantage and cardiovascular disease: Development of an index and analysis of age, sex, and ethnicity effects. *International Journal of Epidemiology*, 35, 1239-1245.

Anand, S.S., Yusef, S., Jacobs, R., Davis, A.D., Yi, Q., Gerstein, H., ... Lonn, E. (2001). Risk factors, atherosclerosis, and cardiovascular disease among aboriginal people in Canada: The study of health assessment and risk evaluation in aboriginal peoples (SHARE-AP). *Lancet*, 358, 1147-1153.

Anderson, J.L.,Muhlestein, J.B.,Horne, B.D., Carlquist, J.F., Bair, T.L.,Madsen, T.E., & Pearson, R.R. (2000). Plasma homocysteine predicts mortality independently of traditional risk factors and C-reactive protein in patients with angiographically defined coronary artery disease. *Circulation*, 102, 1227–1232.

Anderson, T.J., Grégoire, J., Hegele, R.A., Couture, P., Mancini, J., Mcpherson, R., … Ur, E. (2013). 2012 update of the Canadian Cardiovascular Society Guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Canadian Journal of Cardiology*, 29, 151-167.

Arnesen, E., Refsum, H., Bonaa, K.H., Ueland, P.M., Forde, O.H., & Nordrehaug, J.E. (1995) Serum total homocysteine and coronary heart disease. *International Journal of Epidemiology*, 24, 704–709.

Ashley, F.W. & Kannel, W.B. (1974). Relation of weight change to changes in atherogenic traits: the Framingham Study. *Journal of Chronic Disease*, 27, 103-114.

Assembly of First Nations (2007). OCAP: Ownership, control, access and possession. First Nations Inherent Right to Govern First Nations data. Sanctioned by the First Nations information governance committee, Assembly of First Nations. Ottawa: National Aboriginal Health Organization. Accessed February 27, 2014 from http://64.26.129.156/misc/ocap.pdf

Audelin, M.C., & Genest Jr., J, (2001). Homocysteine and cardiovascular disease in diabetes mellitus. *Atherosclerosis,* 159, 497-511.

Ballantyne, C.M., Bertolami, M., Hernandez Garcia, H.R., Nul, D., Stein, E.A., Theroux, P., … Raichien, J.S. (2006). Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY (MERCURY) II. *American Heart Journal*, 151, 975.e1-975.e9

Benjamin, E.J., Levy, D., Vaziri, S.M., D'Agostino, R.B., Belanger, A.J., & Wolf, P.A. (1994). Independent risk factors for atrial fibrillation in a population-based cohort: The Framingham heart study. *The Journal of the American Medical Association*, 271, 840-844.

Bittner, V. (2002). Lipoprotein abnormalities related to women's health. *American Journal of Cardiology*, 90, 77i-84i.

Blanchard AK, Wang X, El-Gabalawy H, Tan Q, Orr P, Elias B, ... Bernstein, C (2012). Oral health in a First Nations and non-Aboriginal population in Manitoba. *International Journal of Circumpolar Health*, 71, 17394.

Bombak, A. (2014). Obesity, health at every size, and public health policy. *American Journal of Public Health*, 104, e60-e67.

Bonora, E., & Muggeo, M. (2001). Postprandial blood glucose as a risk factor for cardiovascular disease in Type II diabetes: The epidemiological evidence. *Diabetologia*, 44, 2107-2114.

Borson-Chazot, F., Harthe, C., Labrousse, F., Gaume, C., Guadagnino, L., Claustrat, B., … , Moulin, P. (1999). Occurrence of hyperhomocysteinemia 1 year after

gastroplasty for severe obesity. *Journal of Clinical Endocrinology and Metabolism,* 84, 541-545.

Bottorff, J.L., Carey, J., Mowatt, R., Varcoe, C., Johnson, J.L., Hutchinson, P., ... Wardman, D. (2009). Bingo halls and smoking: perspectives of First Nations women. *Health & Place,* 14, 1014-1021.

Bottorff, J.L., Johnson, J.L., Carey, J., Hutchinson, P., Sullivan, D., Mowatt, R., & Wardman, D. (2010). A family affair: Aboriginal women's efforts to limit second-hand smoke exposure at home. *Canadian Journal of Public Health,* 101, 32-35.

Boushey, C.J., Beresford, S.A., Omenn, G.S., & Motulsky, A.G. (1995). A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *Journal of the American Medical Association,* 274, 1049-1057.

Brassard, P., & Robinson, E. (1995). Factors associated with glycemia and microvascular complications among James Bay Cree Indian diabetics of Quebec. *Arctic Medical Research,* 54, 116-124.

Brassard, P., Robinson, E., & Dumont, C. (1993a). Descriptive epidemiology of non-insulin dependent diabetes mellitus in the James Bay Cree population of Quebec, Canada. *Arctic Medical Research,* 52, 47-54.

Brassard, P., Robinson, E., & Lavallee, C. (1993b). Prevalence of diabetes mellitus among the James Bay Cree of northern Quebec. *Canadian Medical Association Journal,* 149, 303-307.

Bruce, S.G., & Young, T.K. (2008). Prevalence and risk factors for neuropathy in a Canadian First Nation community. *Diabetes Care,* 31, 1837-1841.

Bruce, S.G., Riediger, N.D., Zacharias, J.M., & Young, T.K. (2011). Obesity and obesity-related co-morbidity in a Canadian First Nation population. *Preventing Chronic Disease*, 8, A03.

Bruno, G., Merletti, F., Biggeri, A., Bargero, G., Prina-Cerai, S., Pagano, G., Cavallo-Perin, P. (2006). Effect of age on the association of non-high-density-lipoprotein cholesterol and apolipoprotein B with cardiovascular mortality in a Mediterranean population with type 2 diabetes: the Casale Monferrato study. *Diabetologia*, 49, 937-944.

Brunzell, J.D., Davidson, M., Furberg, C.D., Goldberg, R.B., Howard, B.V., Stein, J.H., Witztum, J.L. (2008). Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *Journal of the American College of Cardiology*, 51, 1512-1524.

Burke, H., Leonardi-Bee, J., Hashim, A., Pine-Abata, H., Chen, Y., Cook, D.G., ... McKeever, T.M. (2012). Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics*, 129, 735-744.

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee (2013). Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. *Canadian Journal of Diabetes* 37, S8-S11.

Carnethon, M.R., Loria, C.M., Hill, J.O., Sidney, S., Savage, P.J., & Liu, K. (2004). Risk factors for the metabolic syndrome: The Coronary Artery Risk Development in Young Adults (CARDIA) study, 1985-2001. *Diabetes Care*, 27, 2707-2715.

Carnevale Schianca, G.P., Fra, G.P., Colli, E., Bigliocca, M., Mella, R., Scaglia, E., & Bartoli, E. (2012). Sex differences in lipid profiles in relation to the progression of glucose abnormalities. *Journal of Diabetes*, 4, 95-101.

Carroll, J.F., Chiapa, A.L., Rodriguez, M., Phelps, D.R., Cardarelli, K.M., Vishwanatha, J.K., ... Cardarelli, R. (2008). Visceral fat, waist circumference, and BMI: Impact of race/ethnicity. *Obesity (Silver Spring)*, 16, 600-607.

Chan, D.C., Watts, G.F., Ng, T.W.K., Yamashita, S., & Barrett, P.H.R. (2008). Effect of weight loss on markers of triglyceride-rich lipoprotein metabolism in the metabolic syndrome. *European Journal of Clinical Investigation*, 38, 743-751.

Chateau-Degat, M-L., Dannenbaum, D.A., Egeland, G.M., Nieboer, E., Laouan Sidi, E.A., Abdous, B., & Dewailly, É (2011). A comparison of the metabolic response to abdominal obesity in two Canadian Inuit and First Nations population. *Obesity*, 19, 2254-2260.

Chateau-Degat, M-L., Dewailly, E., Poirier, P., Gingras, S., & Egeland, G.M. (2008). Comparison of diagnostic criteria of the metabolic syndrome in 3 ethnic groups of Canada. *Metabolism*, 57, 1526-1532.

Chateau-Degat, M-L., Pereg, D., Egeland, G.M., Nieboer, E., Bonnier-Viger, Y., Laouan-Sidi, E.A., ... Dewailly, E. (2009). Diabetes and related metabolic conditions in an Aboriginal Cree community of Quebec, Canada. *Canadian Journal of Diabetes*, 33, 156-162.

Chien, K.L., Hsu, H.C., Su, T.C., Chen, M.F., Lee, Y.T., & Hu, F.B. (2007). Apolipoprotein B and non-high density lipoprotein cholesterol and the risk of coronary heart disease in Chinese. *Journal of Lipid Research*, 48, 2499-2505.

Chou, W-T., Kakizaki, M., Tomata, Y., Nagai, M., Sugawara, Y., Kuriyama, S., Tsuji, I. (2013). Impact of weight change since age 20 and cardiovascular disease mortality risk: The Ohsaki cohort study. *Circulation Journal*, 77, 679-686.

Clarke, R., Daly, L., Robinson, K., Naughten, E., Cahalane, S., Fowler, B., & Graham, I. (1991). Hyperhomocysteinemia: an independent risk factor for vascular disease. *New England Journal of Medicine*, 324, 1149-1155.

Collins, A.C., Vincent, J., Newall, R.G., Mitchell, K.M., & Viberti, G.C. (2001). An aid to the early detection and management of diabetic nephropathy: assessment of a new point of care microalbuminuria system in the diabetic clinic. *Diabetic Medicine*, 18, 928-932.

Connelly, P.W., Hanley, A.J., Harris, S.B., Hegele, R.A., & Zinman, B. (2003). Relation of waist circumference and glycemic status to C-reactive protein in the Sandy Lake Oji-Cree. *International Journal Obesity Related Metabolic Disorders*, 27, 347-354.

Cook, S., & Hess, O.M. (2005). Homocysteine and B vitamins. *Handbook of Experimental Pharmacology*, 170, 325-338.

Curtis, A.B., Strogatz, D.S., James, S.A., & Raghunathan, T.E. (1998). The contribution of baseline weight and weight gain to blood pressure change in African Americans: the Pitt County Study. *Annals of Epidemiology*, 8, 497–503.

Czyzewski, K. (2011). Colonialism as a broader social determinant of health. *International Indigenous Policy Journal*, 2, 5.

D'Agostino Sr., R.B., Grundy, S., Sullivan, L.M., & Wilson, P. (2001). Validation of the Framingham coronary heart disease prediction scores: Results of a multiple ethnic

groups investigation. *The Journal of the American Medical Association*, 286, 180-187.

Daniel, M., & Cargo, M. (2004). Association between smoking, insulin resistance and beta-cell-function in a north-western First Nation. *Diabetic Medicine*, 21, 188-193.

Daniel, M., Rowley, K.G., Mcdermott, R., Mylvaganam, A., & O'Dea, K. (1999). Diabetes incidence in an Australian aboriginal population: An 8-year follow-up study. *Diabetes Care*, 22, 1993-1998.

Daniel, M., Gamble, D., Henderson, J., & Burgess, S. (1995). Diabetes prevalence, behavioral and anthropometric risk factors, and psychosocial constructs in an aboriginal population in British Columbia. *Chronic Diseases in Canada*, 16, 174.

Dannenbaum, D., Torrie, J., Noel, F., Cheezo, J., & Sutherland, L. (2005). Undiagnosed diabetes in 2 Eeyou Istchee (eastern James Bay Cree) communities: A population-based screening project. *Canadian Journal of Diabetes*, 29, 397-402.

Dannenbaum, D., Kuzmina, E., Lejeune, P., Torrie, J., & Gangbe, M. (2008). Prevalence of diabetes and diabetes-related complications in first nations communities in northern Quebec (eeyou istchee), Canada. *Canadian Journal of Diabetes*, 32, 46-52.

Dean, H.J., Young, T.K., Flett, B., & Wood-Steiman, P. (1998). Screening for type-2 diabetes in aboriginal children in northern Canada. *Lancet*, 352, 1523-1524.

Delisle, H.F., & Ekoe, J.M. (1993). Prevalence of non-insulin-dependent diabetes mellitus and impaired glucose tolerance in two Algonquin communities in Quebec. *Canadian Medical Association Journal*, 148, 41-47.

Diabetes Prevention Program Research Group. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*, 346, 393-403.

Dixon, J.B., Dixon, M.E., & O'Brien, P.E. (2001). Elevated homocysteine levels with weight loss after Lap-Band Surgery: higher folate and vitamin B12 levels required to maintain homocysteine level. *International Journal of Obesity*, 25, 219-227.

Doggrell, S.A. (2006) How effective are the lipid modifying medicines at preventing coronary heart disease in patients with type 2 diabetes? *Vascular Disease Prevention*, 3, 335-344.

Dossus, L., Boutron-Ruault, M.C., Kaaks, R., Gram, I.T., Vilier, A., Fervers, B., ... Clavel-Chapelon, F. (2014). Active and passive cigarette smoking and breast cancer risk: results from the EPIC cohort. *International Journal of Cancer*, 134, 1871-1888.

Dwyer-Lindgren, L., Mokdad, A.H., Srebotnjak, T., Flaxman, A.D., Hansen, G.M., & Murray, C.J.L. (2014). Cigarette smoking prevalence in US counties: 1996-2012. *Population Health Metrics*, 12, 5.

Dyck, R., Osgood, N., Lin, T.H., Gao, A., & Stang, M.R. (2010). Epidemiology of diabetes mellitus among First Nations and non-First Nations adults. *Canadian Medical Association Journal*, 182, 249-256.

Elias, B., & LaPlante, J. Assembly of Manitoba Chiefs Health Information Research and Governance Committee (HIRGC). Manitoba First Nations Regional Longitudinal Health Survey (RHS) Report (2002/03). Copyright 2006. Accessed November 18,

2013 at http://amc.manitobachiefs.com/images/pdf/mb_fns_rhs_report_2002_03.pdf

Evers, S., McCracken, E., Antone, I., & Deagle, G. (1987). The prevalence of diabetes in Indians and Caucasians living in southwestern Ontario. *Canadian Journal of Public Health*, 78, 240-243.

Foulds, H.J.A., Bredin, S.S.D., & Warburton, D.E.R. (2011). The prevalence of overweight and obesity in British Columbian aboriginal adults. *Obesity Reviews*, 12, e4-e11.

French S.A., Jeffrey, R.W., Folsom, A.R., McGovern, P., & Williamson, D.F. (1996). Weight loss maintenance in young adulthood: prevalence and correlations with health behavior and disease in a population-based sample of women aged 55-69 years. *International Journal of Obesity*, 20, 303-310.

Friedewald, W.T., Levy, R.I., & Fredrickson, D.S. (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical Chemistry*, 18, 499-502.

Garfagnini, A., Devoto, G., Rosselli, P., Boggiano, P., & Venturini, M. (1995). Relationship between HDL-cholesterol and apolipoprotein A1 and the severity of coronary artery disease. *European Heart Journal*, 16, 465-70.

Garriguet, D. (2008). Obesity and the eating habits of the Aboriginal population. *Health Reports*, 19, 1-15.

Genest Jr. J., McNamara, J.R., Salem, D.N., Wilson, P.W., Schaefer, E.J., & Malinow, M.R. (1990). Plasma homocysteine levels in men with premature coronary artery disease. *Journal of the American College of Cardiology*, 16, 1114–1119.

Genest, J., McPherson, R., Frohlich, J., Anderson,T., Campbell, N., Carpentier, A., … Ur, E. (2009). 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations. *Canadian Journal of Cardiology*, 25, 567-579.

Ghandehari, H., Kamal-Bahl, S., & Wong, N.D. (2008). Prevalence and extent of dyslipidemia and recommended lipid levels in US adults with and without cardiovascular comorbidities: The National Health and Nutrition Examination Survey 2003-2004. *American Heart Journal*, 156, 112-119.

Godel, J. (2006). Use and misuse of tobacco among aboriginal peoples -- update 2006. *Paediatrics and Child Health*, 11, 681-692.

Goldbourt, U., & Medalie, J.H. (1979). High density lipoprotein cholesterol and incidence of coronary heart disease – the Isreali ischemic heart disease study. *American Journal of Epidemiology*, 109, 296-308.

Gotto, A.M., Whitney, E., Stein, E.A., Shapiro, D.R., Clearfield, M., Weis, S., … de Cani, J.S. (2000). Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation*, 101, 477-484.

Graham, I.M., Daly, L.E., Refsum, H.M., Robinson, K., Brattstrom, L.E., Ueland, P.M., ... Andria, G. (1997). Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project. *The Journal of the American Medical Association*, 277, 1775–1781.

Green, C., Blanchard, J.F., Young, T.K., & Griffith, J. (2003). The epidemiology of diabetes in the Manitoba-registered first nation population: Current patterns and comparative trends. *Diabetes Care,* 26, 1993-1998.

Gregg, E.W., Gerzoff, R.B., Thompson, T.J., & Williamson, D.F. (2004). Trying to lose weight, losing weight, and 9-year mortality in overweight U.S. adults with diabetes. *Diabetes Care,* 27, 657-662.

Grubben, M.J., Boers, G.H., Blom, H.J., Broekhuizen, R., de Jong, R., van Rijt, L., ... Katan, M.B. (2000). Unfiltered coffee increases plasma homocysteine concentrations in healthy volunteers: a randomized trial. *American Journal of Clinical Nutrition,* 71, 480–4.

Grunderson, E.P., & Abrams, B. (2000). Epidemiology of gestational weight gain and body weight changes after pregnancy. *Epidemiological Reviews*, 22, 261-274.

Haffner, S.M. (1999). Epidemiology of insulin resistance and its relation to coronary artery disease (review). *American Journal of Cardiology,* 84, 11J-14J.

Hak, A.E., Bak, A.A., Lindemans, J., Planellas, J., Bennink, H.J.T., Hofman, A., ... Witterman, J.C.M. (2001). The effect of hormone replacement therapy on serum homocysteine levels in perimenopausal women: a randomized controlled trial. *Atherosclerosis,* 158, 437-443.

Hamman, R.F., Wing, R.R., Edelstein, S.L., Lachin, J.M., Bray, G.A., Delahanty, L., ... Wylie-Rosett, J., for the Diabetes Prevention Program Research Group. (2006). Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care*, 29, 2102-2107.

Hanley, A.J., Connelly, P.W., Harris, S.B., & Zinman, B. (2003). Adiponectin in a native Canadian population experiencing rapid epidemiological transition. *Diabetes Care*, 26, 3219-3225.

Hanley, A.J., Mckeown-Eyssen, G., Harris, S.B., Regele, R.A., Wolever, T.M.S., Kwan, J., ... Zinman, B. (2001). Cross-sectional and prospective associations between proinsulin and cardiovascular disease risk factors in a population experiencing rapid cultural transition. *Diabetes Care*, 24, 1240-1247.

Hanley, A.J., Harris, S.B., Mamakeesick, M., Goodwin, K., Fiddler, E., Hegele, R.A., ... Zinman, B. (2005). Complications of type 2 diabetes among aboriginal Canadians: Prevalence and associated risk factors. *Diabetes Care*, 28, 2054-2057.

Harjo, T.C., Perez, A., Lopez, V., & Wong, N.D. (2011). Prevalence of diabetes and cardiovascular risk factors among California Native American adults compared to other ethnicities: The 2005 California Health Interview Survey. *Metabolic Syndrome and Related Disorders*, 9, 49-54.

Harris, S.B., Gittelsohn, J., Hanley, A., Barnie, A., Wolever, T.M.S., Gao, J., ... Zinman, B. (1997). The prevalence of NIDDM and associated risk factors in Native Canadians. *Diabetes Care*, 20, 185-187.

Harris, S.B., Zinman, B., Hanley, A., Gittelsohn, J., Hegele, R., Connelly, P.W., ... Hux, J.E. (2002). The impact of diabetes on cardiovascular risk factors and outcomes in a native Canadian population. *Diabetes Research and Clinical Practice*, 55, 165-173.

Harris, S.B., Naqshbandi, M., Bhattacharyya, O., Hanley, A.J.G., Esler, J.G., & Zinman, B. (2011). Major gaps in diabetes clinical care among Canada'a First Nations:

Results of the CIRCLE study. *Diabetes Research and Clinical Practice*, 92, 272-279.

Harris-Hooker, S., & Sanford, G.L. (1994). Lipids, lipoproteins and coronary heart disease in minority populations. *Atherosclerosis,* 108, S83-S104.

Harwell, T.S., Gohdes, D., Moore, K., McDowall, J.M., Smilie, J.G., & Helgerson, S.D. (2001). Cardiovascular disease and risk factors in Montana American Indians and non-Indians. *American Journal of Preventive Medicine* 20, 196-201.

Health Canada. Fact sheet - First Nations and Inuit health branch. Retrieved November 13, 2009, from http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/fnihb-dgspni/fact-fiche-eng.php

Health Canada. First Nations & Inuit health – Tobacco. Date last update, 2011-07-19. Accessed February 4, 2014 from http://www.hc-sc.gc.ca/fniah-spnia/substan/tobac-tabac/index-eng.php

Hediger, M.L., Scholl. T.O., & Schall, J.I. (1997). Implications of the Camden study of adolescent pregnancy: interactions among maternal growth, nutritional status, and body composition. *Annals of the New York Academy Sciences*, 817, 281-91.

Hegele, R.A. (1999). Genetic prediction of atherosclerosis: Lessons from studies in native Canadian populations. Clinica Chimica Acta, 286, 47-61.

Heitmann, B.L., & Garby, L. (2002). Composition (lean and fat tissue) of weight changes in adult Danes. *American Journal of Clinical Nutrition,* 75, 840 – 847.

Henderson, S.O., Haiman, C.A., Wilkens, L.R., Kolonel, L.N., Wan, P., & Pike, M.C. (2007). Established risk factors account for most of the racial differences in cardiovascular disease mortality. *PLoS ONE,* 2, e377.

Holm, J.E., Vogeltanz-Holm, N., Poltavski, D., & McDonald, L. (2010). Assessing health status, behavioral risks, and health disparities in American Indians living on the northern plains of the U.S. *Public Health Reports*, 125, 68-78.

Holme, I., Cater, N.B., Faergeman, O., Kastelein, J.J., Olsson, A.G., Tikkanen, M.J., … Pedersen, T.R. (2008). Lipoprotein predictors of cardiovascular events in statin-treated patients with coronary heart disease: insights from the incremental decrease in end-points through aggressive lipid-lowering trial (IDEAL). *Annals of Medicine*, 40, 456-464.

Horn, O.K., Jacobs-Whyte, H., Ing, A., Bruegl, A., Paradis, G., & Macaulay, A.C. (2007). Incidence and prevalence of type 2 diabetes in the First Nation community of Kahnawake, Quebec, Canada, 1986-2003. *Canadian Journal of Public Health*, 98, 438-443.

Hornstra, J.M., Hoekstra, T., Serné, E.H., Eringa, E.C., Wijnstok, N.J., Blom, H.J., … Smulders, Y.M. (2014). Homocysteine levels are inversely associated with capillary density in men, not in premenopausal women. European Journal of Clinical Investigation, 14, 333-340.

Houston, T.K., Kiefe, C.I., Person, S.D., Pletcher, M.J., Liu, K., & Iribarren, C. (2006). Active and passive smoking and development of glucose intolerance among young adults in a prospective cohort: CARDIA study. *British Medical Journal*, 332, 1064-1069.

Howard, B.V., Cowan, L.D., Go, O., Welty, T.K., Robbins, D.C., & Lee, E.T. (1998). Adverse effects of diabetes on multiple cardiovascular disease risk factors in women: the Strong Heart Study. *Diabetes Care*, 21, 1258-1265.

Hsia, S.H., Pan, D., Berookim, P., & Lee, M.L. (2006). A population-based, cross-sectional comparison of lipid-related indexes for symptoms of atherosclerotic disease. *American Journal of Cardiology*, 98, 1047-1052.

Hubert, H.B., Feinleib, M., McNamara, P.M., & Castelli, W.P. (1983). Obesity as an independent risk factor for cardiovascular disease: A 26-year follow-up of participants in the Framingham Heart Study. *Circulation,* 67, 968-977.

Huxley, R., Barzi, F., & Woodfard, M. (2006). Excess risk of fatal coronary heart disease associated with diabetes in men and women: Meta-analysis of 37 prospective cohort studies. *British Medical Journal,* 332, 73–8.

International Diabetes Federation (IDF). International Diabetes Federation, 2012 Clinical Guidelines Task Force Global Guideline for Type 2 Diabetes. Accessed September 16, 2013 at http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf

Isreal, B.A., Eng, E., Schulz, A.J., Parker, E.A.. (Eds.) (2005). Methods in community-based participatory research for health. San Francisco, CA: John Wiley & Sons.

Jaddoe VWV, de Jonge LL, van Dam RM, Willett WC, Harris H, Stampfer MJ, Hu FB, Michels KB (2014). Fetal exposure to parental smoking and the risk of type 2 diabetes in adult women. *Diabetes Care*, in press.

Janz, T. (2012). Current smoking trends. Health at a Glance. Statistics Canada Catalogue no. 82-624-X. Date modified 2012-06-19. Accessed March 6, 2014 from http://www.statcan.gc.ca/pub/82-624-x/2012001/article/11676-eng.htm

Jernigan, V.B.B., Duran, B., Ahn, D., & Winkleby, M. (2010). Changing patterns in health behaviors and risk factors related to cardiovascular disease among

American Indians and Alaska Natives. American Journal of Public Health, 100, 677-683.

Jin, A., Martin, J.D., & Sarin, C. (2002a). A diabetes mellitus in the First Nations population of British Columbia, Canada. Part 1. Mortality. *International Journal of Circumpolar Health,* 61, 251-253.

Jin, A., Martin, J.D., & Sarin, C. (2002b). Diabetes mellitus in the First Nations population of British Columbia, Canada. Part 2. Hospital morbidity. *International Journal of Circumpolar Health*, 61, 254-259.

Johnson, J.A., Vermeulen, S.U., Toth, E.L., Hemmelgarn, B.R., Ralph-Campbell, K., Hugel, G., ... Crowshoe, L. (2009). Increasing incidence and prevalence of diabetes among the status aboriginal population in urban and rural Alberta, 1995-2006. *Canadian Journal of Public Health,* 100, 231-236.

Joseph, P., Davis, A.D., Miller, R., Hill, K., Banerjee, A., Chow, C., Mente, A., & Anand, S.S. (2012). Contextual determinants of health behaviours in an aboriginal community in Canada: pilot project. *BMC Public Health*, 12, 952.

Jousilahti, P., Tuomilehto, J., Vartianen, E., Pekkanen, J., & Puska, P. (1996). Body weight, cardiovascular risk factors, and coronary mortality: 15 year follow-up of middle-aged men and women in Eastern Finland. *Circulation*, 93, 1372-1379.

Kaler, S.N., Ralph-Campbell, K., Pohar, S., King, M., Laboucan, C.R., & Toth, E.L. (2006). High rates of the metabolic syndrome in a First Nations community in western Canada: Prevalence and determinants in adults and children. *International Journal of Circumpolar Health*, 65, 389-402.

Kaneto, C., Toyokawa, S., Miyoshi, Y., Suyama, Y., & Kobayashi, Y. (2013). Long-term weight change in adulthood and incident diabetes mellitus: MY Health Up Study. *Diabetes Research and Clinical Practice*, 102, 138-146.

Kang, S.S., Wong, P.W.K., & Noruiss, M. (1987). Homocysteinemia due to folate deficiency. *Metabolism*, 36, 458–462.

Kannel, W. B., Castelli, W. P., & McNamara, P. M. (1968). Cigarette smoking and risk of coronary heart disease. epidemiologic clues to pathogenesis. the Framingham study. *National Cancer Institute Monograph, 28*, 9-20.

Kannel, W. B., Dawber, T. R., Thomas Jr, H. E., & McNamara, P. M. (1965). Comparison of serum lipids in the prediction of coronary heart disease. Framingham study indicates that cholesterol level and blood pressure are major factors in coronary heart disease; effect of obesity and cigarette smoking also noted. *Rhode Island Medical Journal, 48*, 243-250.

Kannel, W.B. (1985). Lipids, diabetes, and coronary heart disease: insights from the Framingham Study. *American Heart Journal*, 110, 110-1107.

Kannel, W. B., & McGee, D. L. (1979). Diabetes and glucose tolerance as risk factors for cardiovascular disease: The Framingham Study. *Diabetes Care,* 2, 120-126.

Kannel, W. B., McGee, D. L., & Castelli, W. P. (1984). Latest perspectives on cigarette smoking and cardiovascular disease: The Framingham Study. *Journal of Cardiac Rehabilitation, 4*, 267-277.

Kastelein, J.J.P., van der Steeg, W.A., Holme, I., Gaffney, M., Cater, N.B., Barter, P., … Grundy, S.M. (2008). Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation*, 117, 3002-3009.

Keogh, J.B., Brinkworth, G.D., Noakes, M., Belobrajdic, D.P., Buckley, J.D., & Clifton. P.M. (2008). Effects of weight loss from a very-low-carbohydrate diet on endothelial function and markers of cardiovascular disease risk in subjects with abdominal obesity. *American Journal of Clinical Nutrition*, 87, 567–576.

Khoury, P., Morrison, J.A., Mellies, M.J., & Glueck, C.J. (1983). Weight change since age 18 years in 30- to 55-year old whites and blacks. Associations with lipid values, lipoprotein levels, and blood pressure. *Journal of the American Medical Association*, 250, 3179–3187.

Knowler, W.C., Barrett-Connor, E., Fowler, S.E., Hamman, R.F., Lachin, J.M., Walker, E.A., & Nathan, D.M. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*, 346, 393-403.

Lahiry, P., Cao, H., Ban, MR., Pollex, R.L., Mamakeesick, M., Zinman, B., ... Hegele, R.A. (2010). APOC1 T45S polymorphism is associated with reduced obesity indices and lower plasma concentrations of leptin and apolipoprotein C-I in aboriginal Canadians. *Journal of Lipid Research*, 51, 843-848.

Lakka, H-M., Lakka, T.A., Tuomilehto, J., & Salonen, J.T. (2002). Abdominal obesity is associated with increased acute coronary events in men. *European Heart Journal*, 23, 706-713.

Lavoie, J.G., Forget, E., & Browne, A. (2010a). Caught at the crossroad: First nations, health care and the legacy of the Indian act. *Pimitisiwan: A Journal of Aboriginal and Indigenous Community Health*, 8(1).

Lavoie, J.G., Forget, E.L., Prakash, T., Dahl, M., Martens, P. & O'Neil, J.D. (2010b). Have investments in on-reserve health services and initiatives promoting community control improved First Nations' health in Manitoba? *Social Science & Medicine* 71, 717-724.

Lawes, C. M. M., Vander Hoorn, S., Law, M. R., Elliott, P., MacMahon, S., & Rodgers, A. (2006). Blood pressure and the global burden of disease 2000. part II: Estimates of attributable burden. *Journal of Hypertension, 24*, 423-430.

Lean, M.E., Han, T.S., & Morrison, C.E. (1995). Waist circumference as a measure for indicating need for weight management. *British Medical Journal*, 311, 158-161.

Lear, S.A., Humphries, K.H., Kohli, S., & Birmingham, C.L. (2007). The use of BMI and waist circumference as surrogates of body fat differs by ethnicity. *Obesity (Silver Spring)*, 15, 2817-2824.

Lemstra, M., Rogers, M., Thompson, A., Moraros, J., & Tempier, R. (2011). Prevalence and risk indicators of smoking among on-reserve First Nations youth. *Pediatrics and Child Health*, 16, e71-e77.

Leslie, W.D., Weiler, H.A., & Nyomba, B.L. (2007). Ethnic differences in adiposity and body composition: The First Nations bone health study. *Applied Physiology, Nutrition, and Metabolism*, 32, 1065-1072.

Levey, A.S., Coresh, J., Greene, T., Stevens, L.A., Zhang, Y.L., Hendriksen, S., ...Van Lente, F. (2006). Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Annals of Internal Medicine*, 145, 247-254.

Ley, S.H., Harris, S.B., Connelly, P.W., Mamakeesick, M., Gittelsohn, J., Wolever, T.M., ... Hanley, A.J. (2010). Association of apolipoprotein B with incident type 2 diabetes in an Aboriginal Canadian population. *Clinical Chemistry*, 56, 666-670.

Ley, S.H., Harris, S.B., Mamakeesick, M., Noon, T., Fiddler, E., Gittelsohn, J., ... Hanley, A.J. (2009). Metabolic syndrome and its components as predictors of incident type 2 diabetes mellitus in an Aboriginal community. *Canadian Medical Association Journal*, 180, 617-624.

Ley, S.H., Hegele, R.A., Harris, S.B., Mamakeesick, M., Cao, H., Connelly, P.W., ... Hanley, A.J. (2011). HNF1A G319S variant, active cigarette smoking and incident type 2 diabetes in Aboriginal Canadians: A population-based epidemiological study. *BMC Medical Genetics*, 12(1).

Lindstrom, J., Ilanne-Parikka, P., Peltonen, M., Aunola, S., Eriksson, J.G., Hemio, K., ... Tuomilehto, J., on behalf of the Finnish Diabetes Prevention Study Group. (2006). Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet*, 368, 1673-1679.

Liu, J., Young, T.K., Zinman, B., Harris, S.B., Connelly, P.W., & Hanley, A.J. (2006a). Lifestyle variables, non-traditional cardiovascular risk factors, and the metabolic syndrome in an aboriginal Canadian population. *Obesity (Silver Spring)*, 14, 500-508.

Liu, J., Hanley, A.J., Young, T.K., Harris, S.B., & Zinman, B. (2006b). Characteristics and prevalence of the metabolic syndrome among three ethnic groups in Canada. *International Journal of Obesity*, 30, 669-676.

Lobrano, A., Blanchard, K., Rock, W., Johnson, W., Schmieg, B., …, Abell, T.L. (2006). Assessing thrombosis risk in patients with idiopathic, diabetic, and postsurgical gastroparesis. *Advances in Therapy*, 23, 750-768.

Maberley, D.A.L., King, W., & Cruess, A.F. (2000). The prevalence of diabetes in the Cree of western James Bay. *Chronic Diseases in Canada*, 21, 128-133.

Macaulay, A.C., Montour, L.T., & Adelson, N. (1988). Prevalence of diabetic and atherosclerotic complications among Mohawk Indians of Kahnawake, PQ. *Canadian Medical Association Journal*, 139, 221-224.

Mann, D.M., Bertoni, A.G., Shimbo, D., Carnethon, M.R., Chen, H., Jenny, N.S., Muntner, P. (2010). Comparative validity of 3 diabetes mellitus risk prediction scoring models in a multiethnic US cohort. *American Journal of Epidemiology*, 171, 980-988.

Martens, P.J., Martin, B.D., O'Neil, J.D., & MacKinnon, M. (2007). Diabetes and adverse outcomes in a First Nations population: Associations with healthcare access, and socioeconomic and geographic factors. *Canadian Journal of Diabetes*, 31, 223-232.

Martens, P., Bond, R., Jebamani, L., Burchill, C., Roos, N., Derksen, S., … O'Neil, J. (2002) The Health and Health Care Use of Registered First Nations People Living in Manitoba: A Population-Based Study. March 2002. Manitoba Centre for Health Policy.

Masuda, Y., Kubo, A., Kokaze, A., Yoshida, M., Fukuhara, N., & Takashima, Y. (2008). Factors associated with serum total homocysteine level in type diabetes. *Environmental Health and Preventive Medicine*, 13, 148-155.

Matetzky, S., Freimark, D., Ben-Ami, S., Goldenberg, I., Leor, J., Doolman, R., ... Hod, H. (2003). Association of elevated homocysteine levels with a higher risk of recurrent coronary events and mortality in patients with acute myocardial infarction. *Archives of Internal Medicine*, 163, 1933-1937.

Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., & Turner, R.C. (1985). Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, 28, 412-419.

McQueen, M.J., Hawken, S., Wang, X., Ounpuu, S., Sniderman, A., Probstfield, J.,… Yusuf, S. (2008). Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet*, 372, 224-233.

Meltzer, A.A., & Everhart, J.E. (1995). Unintentional weight loss in the United States. *American Journal of Epidemiology*, 142, 1039-1046.

Menard S. (Ed.). (2008). Handbook of longitudinal research: Design, measurement, and analysis. Burlington, MA: Elseview.

Menard S. (2002). Longitudinal research 2nd edition. Thousand Oaks, California: Sage Publications.

Mijatovic, V., Kenemans, P., Netelenbos, C., Jokobs, C., Popp-Snijders, C., Peters-Muller, E.R., & van der Mooren, M. (1998). Postmenopausal oral 17beta-estradiol continuously combined with dydrogesterone reduces fasting serum homocysteine levels. *Fertility and Sterility*, 69, 876-882.

Milan, A. (2010). Age and sex structure: Canada, provinces and territories, 2010. Statistics Canada. Accessed January 22, 2014 from http://www.statcan.gc.ca/pub/91-209-x/2011001/article/11511/figures/desc/desc01-eng.htm

Minkler, M., & Wallerstein, N. (Eds.). (2008). Community-based participatory research for health: From process to outcomes. (2nd ed.). San Francisco, CA: John Wiley & Sons.

Misra, A., Wasir, J.S., & Vikram, N.K. (2005). Waist circumference criteria for the diagnosis of abdominal obesity are not applicable uniformity to all populations and ethnic groups. *Nutrition*, 21, 969-976.

Moustapha, A., Naso, A., Nahlawi, M., Gupta, A., Arheart, K.L., Jacobsen, D.W., ... Dennis, V.W. (1998). Prospective study of hyperhomocysteinemia as an adverse cardiovascular risk factor in end-stage renal disease. *Circulation*, 97, 138–141.

Monsalve, M.V., Thommasen, H.V., Pachev, G., & Frohlich, J. (2005). Differences in cardiovascular risks in the aboriginal and non-aboriginal people living in Bella Coola, British Columbia. *Medical Science Monitor: International medical journal of Experimental and Clinical Research*, 11, CR21-CR28.

Montour, L.T., & Macaulay, A.C. (1985). High prevalence rates of diabetes mellitus and hypertension on a North American Indian reservation [letter]. *Canadian Medical Association Journal*, 132, 1110-1112.

Montour, L.T., Macaulay, A.C., & Adelson, N. (1989). Diabetes mellitus in Mohawks of Kahnawake, PQ: A clinical and epidemiologic description. *Canadian Medical Association Journal*, 141, 549-552.

McIntyre, L., & Shah, C.P. (1986). Prevalence of hypertension, obesity and smoking in three Indian communities in northwestern Ontario. *Canadian Medical Association Journal*, 134, 345-349.

Natarajan, S., Liao, Y., Cao, G., Lipsitz, S.R., & McGee, D.L. (2003). Sex differences in risk for coronary heart disease mortality associated with diabetes and established coronary heart disease. *Archives of Internal Medicine*, 163, 1735-1740.

Norman, J.E., Bild, D., Lewis, C.E., Liu, K., Smith West, D. (2003). The impact of weight change on cardiovascular disease risk factors in young black and white adults: the CARDIA study. *International Journal of Obesity*, 27, 369-376.

Nsiah-Kumi, P.A., Lasley, S., Whiting, M., Brushbreaker, C., Erickson, J.M., Qiu, F., ... Larson, J.L. (2013). Diabetes, pre-diabetes and insulin resistance screening in Native American children and youth. *International Journal of Obesity*, 37, 540-545.

Nygård, O., Vollset, S.E., Refsum, H., Stensvold, I., Tverdal, A., Nordrehaug, J.E., ..., Kvåle, G. (1995). Total plasma homocysteine and cardiovascular risk profile: The Hordaland Homocysteine Study. *Journal of the American Medical Association*, 274, 1526-1533.

O'Connell, J.M., Wilson, C., Manson, S.M., & Acton, K.J. (2012). The costs of treating American Indian adults with diabetes within the Indian Health Service. *American Journal of Public Health*, 102, 301-308.

Oster, R.T., Hemmelgarn, B.R., Toth, E.L., King, M., Crowshoe, L., & Ralph-Campbell, K. (2009a). Chapter 10: Diabetes and the status Aboriginal Population in Alberta. *Alberta Diabetes Atlas*, 189-212.

Oster, R.T., & Toth, E.L. (2009b). Differences in the prevalence of diabetes risk-factors among First Nation, Metis and non-aboriginal adults attending screening clinics in rural Alberta, Canada. *Rural Remote Health*, 9, 1170.

Oster, R.T., Virani, S., Strong, D., Shade, S., & Toth, E.L. (2009). Diabetes care and health status of First Nations individuals with type 2 diabetes in Alberta. *Canadian Family Physician*, 55, 386-393.

Oster, R.T., Johnson, J.A., Balko, S.U., Svenson, L.W., & Toth, E.L. (2012). Increasing rates of diabetes amongst aboriginal youth in Alberta, Canada. *International Journal of Circumpolar Health*, 71, 1-7.

Oster, R.T., Johnson, J.A., Hemmelgarn, B.R., King, M., Balko, S.U., Svenson, L.W., ... Toth, E.L. (2011). Recent epidemiological trends of diabetes mellitus among status Aboriginal adults. *Canadian Medical Association Journal*, 2011, 183, E803-E808.

Parsons, M., Newman, D.J., Pugia, M., Newall, R.G., & Price, C.P. (1999). Performance of a reagent strip device for quantification of the urine albumin: creatinine ratio in a point of care setting. *Clinical Nephrology*, 51, 220-227.

Patenaude, J., Tildesley, H., MacArthur, A., Voaklander, D.C., & Thommasen, H.V. (2005). Prevalence of diabetes mellitus in aboriginal and nonaboriginal people living in the Bella Coola Valley. *British Columbia Medical Journal*, 47, 429-437.

Peng, M., Wu, S., Jiang, X., Jin, C., & Zhang, W. on behalf of Kailuan Cardiovascular Survey Group. (2013). Long-term alcohol consumption is an independent risk factor of hypertension development in northern China: evidence from Kailuan study. *Journal of Hypertension*, 31, 2342-2347.

Pérez-López, F.R., Larrad-Mur, L., Kallen, A., Chedraui, P., & Taylor, H.S. (2010). Gender differences in cardiovascular disease: hormonal and biochemical influences. *Reproductive Sciences*, 17, 511-531.

Perreault, L., Kahn, S.E., Christoph, C.A., Knowler, W.C., & Hamman, R.F., the Diabetes Prevention Program Research Group. (2009). Regression from pre-diabetes to normal glucose regulation in the Diabetes Prevention Program. *Diabetes Care*, 32, 1583-1588.

Perreault, L., Ma, Y., Dagogo-Jack, S., Horton, E., Marrero, D., Crandall, J., & Barrett-Connor, E. for the Diabetes Prevention Program. (2008). Sex differences in diabetes risk and the effect of intensive lifestyle modification in the Diabetes Prevention Program. *Diabetes Care*, 31, 1416-1421.

Peters, S.A.E., Huxley, R.R., & Woodward, M. (2014). Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775385 individuals and 12539 strokes. *Lancet*, 383, 1973-1980.

Piatti PM, Setola E, Galluccio E, Costa S, Fontana B, Stuccillo M, …Monti LD (2014). Smoking is associated with impaired glucose regulation and a decrease in insulin sensitivity and the disposition index in first-degree relatives of type 2 diabetes subjects independently of the presence of metabolic syndrome. *Acta Diabetologica*, 51, 793-799.

Pierce JP. (1989). International comparisons of trends in cigarette smoking prevalence. *American Journal of Public Health*, 79, 152-157.

Pioro, M.P., Dyck, R.F., & Gillis, D.C. (1996). Diabetes prevalence rates among First Nations adults on Saskatchewan reserves in 1990: comparison by tribal grouping, geography and with non-First Nations people. *Canadian Journal of Public Health*, 87, 325-328.

Pischon, T., Girman, C.J., Sacks, F.M., Rifai, N., Stampfer, M.J., & Rimm, E.B. (2005). Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. *Circulation*, 112, 3375-3383.

Pollex, R.L., Hanley, A.J., Zinman, B., Harris, S.B., Khan, H.M., & Hegele, R.A. (2006). Metabolic syndrome in aboriginal Canadians: Prevalence and genetic associations. *Atherosclerosis*, 184, 121-129.

Razak, F., Anand, S., Vuksan, V., Davis, B., Jacobs, R., Teo, K.K., & Yusuf, S. (2005). Ethnic differences in the relationships between obesity and glucose-metabolic abnormalities: A cross-sectional population-based study. *International Journal of Obesity*, 29, 656-667.

Razak, F., Anand, S.S., Shannon, H., Vuksan, V., Davis, B., Jacobs, R., ... Yusuf, S. (2007). Defining obesity cut points in a multiethnic population. *Circulation*, 115, 2111-2118.

Retnakaran, R., Hanley, A.J.G., Connelly, P.W., Harris, S.B., & Zinman, B. (2006a). Elevated C-reactive protein in Native Canadian children: An ominous early complication of childhood obesity. *Diabetes, Obesity & Metabolism*, 8, 483-491.

Retnakaran, R., Hanley, A.J., Connelly, P.W., Harris, S.B., & Zinman, B. (2005). Cigarette smoking and cardiovascular risk factors risk factors among Aboriginal Canadian youths. *Canadian Medical Association Journal*, 173, 885-889.

Retnakaran, R., Zinman, B., Connelly, P.W., Harris, S.B., & Hanley, A.J.G. (2006b). Nontraditional cardiovascular risk factors in pediatric metabolic syndrome. *The Journal of Pediatrics*, 148, 176-182.

Retterstol, L., Paus, B., Bohn, M., Bakken, A., Erikssen, J., Malinow, M.R., & Berg, K. (2003). Plasma total homocysteine levels and prognosis in patients with previous premature myocardial infarction: a 10-year follow-up study. *Journal of Internal Medicine*, 253, 284–292.

Richmond, C.A.M., & Ross, N.A. (2008). Social support, material circumstance and health behaviour: influences on health in First Nation and Inuit communities of Canada. *Social Science & Medicine*, 67, 1423-1433.

Riediger, N.D., & Bruce, S.G. (2010). Homocysteine and its relationship with individual, family, and community-level stressors in a Manitoba First Nation community. Oral presentation at the Network Environments for Aboriginal Health Research National Gathering of Graduate Students, Vancouver, BC, June 24-26, 2010.

Riediger, N.D., & Clara, I (2011). Prevalence of metabolic syndrome in the Canadian adult population. *Canadian Medical Association Journal*, 183, E1127-E1134.

Riediger, N.D., Bruce, S.G., & Young, T.K. (2011). Cardiovascular risk according to plasma apolipoprotein and lipid profile in a Canadian First Nation. *Preventing Chronic Disease*, 9, A05.

Riediger, N.D., Lix, L.M., Lukianchuk, V., Bruce, S. (2014). Trends in diabetes and cardiometabolic conditions in a Canadian First Nation community. *Preventing Chronic Disease*, 11(E198), 1-8.

Roberts, H., Jiles, R., Mokdad, A., Beckles, G., & Rios-Burrows, N. (2009). Trend analysis of diagnosed diabetes prevalence among American Indian/Alaska Native young adults – United States, 1994-2007. *Ethnicity & Disease*, 19, 276-279.

Rodionov, R.N., & Lentz, S.R. (2008). The homocysteine paradox. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 28, 1031-1033.

Romanow, R. J. (2002). Commission on the future of health care in Canada. Building on values: The future of health care in Canada.

Ruan, L., Chen, W., Srinivasan, S.R., Xu, J., Toprak, A., Berenson, G.S. (2009). Plasma homocysteine is adversely associated with glomerular filtration rate in asymptomatic black and white young adults: the Bogalusa heart study. *European Journal of Epidemiology*, 24, 315-319.

Samji, H., & Wardman, D. (2009). First Nations communities and tobacco taxation: A commentary. *American Indian and Alaska Native Mental Health Research*, 16, 1-10.

Self, R.B., Birmingham, C.L., Elliott, R., Zhang, W., & Thommasen, H.V. (2005). The prevalence of overweight adults living in a rural and remote community. The Bella Coola Valley. *Eating and Weight Disorders*, 10, 133-138.

Selhub, J., Jacques, P.F., Wilson, P.W., Rush, D., & Rosenberg, I.H. (1993). Vitamin status and intake as primary determinants of homocyst(e)inemia in an elderly population. *Journal of the American Medical Association*, 270, 2693–2698.

Sellers, E.A., Blydt-Hansen, T.D., Dean, H.J., Gibson, I.W., Birk, P.E., & Ogborn, M. (2009). Macroalbuminuria and renal pathology in First Nation youth with type 2 diabetes mellitus. *Diabetes Care*, 32, 786-790.

Sellers, E.A.C., Wicklow, B.A., & Dean, H.J. (2012). Clinical and demographic characteristics of type 2 diabetes in youth at diagnosis in Manitoba and northwestern Ontario (2006-2011). *Canadian Journal of Diabetes*, 36, 114-118.

Sellers, E.A.C., Yung, G., & Dean, H.J. (2007). Dyslipidemia and other cardiovascular risk factors in a Canadian First Nation pediatric population with type 2 diabetes mellitus. *Pediatric Diabetes,* 8, 384-390.

Shepherd, L. (2005). Does statin monotherapy address the multiple lipid abnormalities in type 2 diabetes? *Atherosclerosis Supplements*, 6, 15-19.

Sheu, W.H., Wu, H.S., Wang, C.W., Wan, C.J., & Lee, W.J. (2001) Elevated plasma homocysteine concentrations six months after gastroplasty in morbidly obese subjects. *Internal Medicine,* 40, 584–*588.*

Shubair, M.M., & Tobin, P.K. (2010). Type 2 diabetes in the First Nations population: a case example of clinical practice guidelines. *Rural & Remote Health*, 10, 1505.

Silha, J.V., Nyomba, B.L.G., Leslie, W.D., & Murphy, L.J. (2007). Ethnicity, insulin resistance, and inflammatory adipokines in women at high and low risk for vascular disease. *Diabetes Care,* 30, 286-291.

Simes, R.J., Marschner, I.C., Hunt, D., Colquhoun, D., Sullivan, D., Stewart, R.A., … Tonkin, A. (2002). Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels?. *Circulation,* 105, 1162-1169.

Sinclair, K.A., Bogart, A., Buchwald, D., & Henderson, J.A. (2011). The prevalence of metabolic syndrome and associated risk factors in northern Plains and Southwest American Indians. *Diabetes Care*, 34, 118-120.

Smith, P., Frank, J., Mustard, C. (2009). Trends in educational inequalities in smoking and physical activity in Canada: 1974-2005. *Journal of Epidemiology and Community Health*, 63, 317-323.

Smith, W.G., Gowanlock, W., Babcock, K., Collings, A., & McCarthy, A. (2005). Prevalence of acanthosis nigricans in First Nations children in central Ontario, Canada. *Canadian Journal of Diabetes*, 29, 410-414.

Smolders, R.G., Sipkema, P., Kenemans, P., Stehouwer, C.D., & Van Der Mooren, M.J. (2004). Homocysteine impairs estrogen-induced vasodilation in isolated rat arterioles. *Menopause*, 11, 98–103.

Sniderman, A.D., Scantlebury, T., & Cianflone, K. (2001). Hypertriglyceridemic hyperapoB: The unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. *Annals of Internal Medicine*, 135, 447-459.

Spencer, T.A., Chai, H., Fu, W., Ramaswami, G., Cox, M.W., Conklin, B.S., ..., Chen, C. (2004). Estrogen blocks homocysteine-induced endothelial dysfunction in porcine coronary arteries. *Journal of Surgical Research*, 118, 83–90.

Stamler, J., Stamler, R., & Neaton, J.D. (1993). Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Archives of Internal Medicine*, 153, 598-615.

Stevens, J., Erber, E., Truesdale, K.P., Wang, C-H., & Cai, J. (2013). Long- and short-term weight change and incident coronary heart disease and ischemic stroke. *American Journal of Epidemiology*, 178, 239-248.

Stringer, D.M., Sellers, E.A.C., Burr, L.L., & Taylor, C.G. (2009). Altered plasma adipokines and markers of oxidative stress suggest increased risk of cardiovascular disease in First Nation youth with obesity or type 2 diabetes mellitus. *Pediatric Diabetes*, 10, 269-277.

Suk, S-H., Sacco, R-L., Boden-Albala, B., Cheun, J.F., Pittman, J.G., Elkind, M.S., & Palik, M.C. (2003). Abdominal obesity and risk of ischemic stroke: The Northern Manhattan Stroke Study. *Stroke*, 34, 1586-1592.

Sumner, A.E. (2008). The relationship of body fat to metabolic disease: Influence of sex and ethnicity. *Gender Medicine*, 5, 361-371.

Sun, K., Liu, D., Wang, C., Ren, M., Yang, C., & Yan, L. (2014). Passive smoke exposure and risk of diabetes: a meta-analysis of prospective studies. *Endocrine*, in press.

Szapary, P.O., & Rader, D.J. (2004). The triglyceride-high-density lipoprotein axis: An important target of therapy? *American Heart Journal*, 148, 211-221.

Thommasen, H.V., Patenaude, J., Anderson, N., McArthur, A., & Tildesley, H. (2004). Differences in diabetic co-morbidity between aboriginal and non-aboriginal people living in Bella Coola, Canada. *Rural & Remote Health*, 4, 319.

Tjepkema, M., Wilkens, R., Goedhuis, N., & Pennock, J. (2012). Cardiovascular disease mortality among First Nations people in Canada, 1991-2001. *Chronic Diseases and Injuries in Canada*, 32.

Tjepkema, M., Wilkins, R., & Long, A. (2013a). Cause-specific mortality by income adequacy in Canada: A 16-year follow-up study. *Health Reports*, 24, 14-22.

Tjepkema, M., Wilkins, R., & Long, A. (2013b). Socio-economic inequalities in cause-specific mortality: A 16-year follow-up study. *Canadian Journal of Public Health*, 104, e472-478.

Tohidi, M., Hatami, M., Hadaegh, F., Safarkhani, M., Harati, H., & Azizi, F. (2010). Lipid measures for prediction of incident cardiovascular disease in diabetic and non-diabetic adults: Results of the 8.6 years follow-up of a population based cohort study. *Lipids in Health and Disease*, 9, 6.

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, Tri-council policy statement: ethical conduct for research involving humans (TCPS) (2010). Chapter 9: Research involving the First Nations, Inuit and Métis peoples of Canada. Accessed September 8, 2014 from http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf

Tuomilehto, J., Lindstrom, J., Eriksson, J.G., Valle, T.T., Hamalainen, H., Ilanne-Parikka, P., ... Uusitupa, M. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine*, 344, 1343-1350.

Tybor, D.J., Lichtenstein, A.H., Dallal, G.E., Daniels, S.R., & Must, A. (2011). Independent effects of age-related changes in waist circumference and BMI z scores in predicting cardiovascular disease risk factors in a prospective cohort of adolescent females. *American Journal of Clinical Nutrition*, 93, 392-401.

Urgert, R., van Vliet, T., Zock, P.L., & Katan, M.B. (2000). Heavy coffee consumption and plasma homocysteine: a randomized controlled trial in healthy volunteers. *American Journal of Clinical Nutrition,* 72, 1107–10.

Van Baal, W.M., Smolders, R.G.V., van der Mooren, M.J., Teerlink, T., & Kenemans, P. (1999). Hormone replacement therapy and plasma homocysteine levels. *Obstetrics and Gynecology,* 94, 485-491.

Van Guelpen, B., Hultdin, J., Johansson, I., Witthoft, C., Weinehall, L., Eliasson, M., …, Winkvist, A. (2009). Plasma folate and total homocysteine levels are associated with the risk of myocardial infarction, independently of each other and of renal function. *Journal of Internal Medicine* 266, 182-195.

Van Guldener, C. (2006). Why is homocysteine elevated in renal failure and what can be expected from homocysteine-lowering? *Nephrology Dialysis Transplantation* 21, 1161-1166.

Van Lennep, J.E., Westerveld, H.T., van Lennep, H.W., Zwinderman, A.H., Erkelens, D.W., & van der Wall, E.E. (2000). Apolipoprotein concentrations during treatment and recurrent coronary artery disease events. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 20, 2408-2413.

Verhoef, P., Kok, F., Kruyssen, A.C., Schouten, E.G., Witterman, J.C.M., … Refsum, H. (1997). Plasma total homocysteine, B vitamins and risk of coronary atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 17, 989 – 995.

Verhoef, P., Pasman, W.J., Van Vliet, T., Urgert, R., & Katan, M.B. (2002). Contribution of caffeine to the homocysteine-raising effect of coffee: a randomized controlled trial in humans. *American Journal of Clinical Nutrition*, 76, 1244-1248.

Wahi, G., Zorzi, A., Macnab, A., & Panagiotopoulos, C. (2009). Prevalence of type 2 diabetes, obesity and the metabolic syndrome among Canadian First Nations children in a remote pacific coast community. *Paediatrics & Child Health*, 14, 79-83.

Wald, N.J., Watt, H.C., Law, M.R., Weir, D.G., McPartlin, J., & Scott, J.M. (1998). Homocysteine and ischemic heart disease: results of a prospective study with implications regarding prevention. *Archives of Internal Medicine*, 158, 862–867.

Waldram, J.B., Herring, D.A., & Young, T.K. (2006). Aboriginal health in Canada: Historical, cultural, and epidemiological perspectives. (Second edition ed.). Toronto, Canada: University of Toronto Press.

Walldius, G., Jungner, I., Aastveit, A.H., Holme, I., Furberg, C.D., & Sniderman, A.D. (2004). The apoB/apoA-I ratio is better than the cholesterol ratios to estimate the balance between plasma proatherogenic and antiatherogenic lipoproteins and to predict coronary risk. *Clinical Chemistry and Laboratory Medicine*, 42, 1355-1363.

Walldius, G., & Jungner, I. (2006). The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy — a review of the evidence. *Journal of Internal Medicine*, 259, 493-519.

Walldius, G., Jungner, I., Holme, I., Aastveit, A.H., Kolar, W., & Steiner, E. (2001). High apolipoprotein B, low apolipoprotein A-I, and improvement in the

prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet*, 358, 2026-33.

Wang, Z., & Hoy, W.E. (2005). Is the Framingham coronary heart disease absolute risk function applicable to aboriginal people? *Medical Journal of Australia*, 182, 66-69.

Wikstrom, K., Peltonen, M., Eriksson, J.G., Aunola, S., Ilanne-Parikka, P., Keinanen-Kiukaanniemi, S., ... Lindstrom, J. (2009). Educational attainment and effectiveness of lifestyle intervention in the Finnish Diabetes Prevention Study. *Diabetes Research and Clinical Practice*, 86, e1-e5.

Will, J.C., Strauss, K.F., Mendlein, J.M., Ballew, C., White, L.L., & Peter, D.G. (1997). Diabetes Mellitus among Navajo Indians: Findings from the Navajo Health and Nutrition Survey. *Journal of Nutrition*, 127, 2106S-2113S.

Williams, J.W., Zimmet, P.Z., Shaw, J.E., de Courten, M.P., Cameron, A.J., Chitson, P., ... Alberti, K.G. (2003). Gender differences in the prevalence of impaired fasting glycaemia and impaired glucose tolerance in Mauritius. Does sex matter? *Diabetic Medicine*, 20, 915-920.

Williamson, D.F., Pamuk, E., Thun, M., Flanders, D., Byers, T., & Health, C. (1999). Prospective study of intentional weight loss and mortality in overweight white men aged 40-64 years. *American Journal of Epidemiology*, 149, 491-503.

Wilson, K., & Rosenberg, M.W. (2002). Exploring the determinants of health for first nations peoples in Canada: Can existing frameworks accommodate traditional activities? *Social Science & Medicine*, 55, 2017-2031.

Wilson, D., & Macdonald, D. The income gap between aboriginal peoples and the rest of Canada. Canadian Centre for Policy Alternatives, 2010.

Wilson, P.W., D'Agostino, R.B., Levy, D., Belanger, A.M., Silbershatz, A., & Kannel, W.B. (1998). Prediction of coronary heart disease using risk factor categories. *Circulation*, 97, 1837-1847.

World Health Organization, & International Diabetes Federation. (2006). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. report of a WHO/IDF consultation. World Health Organization.

World Health Organization. Obesity and overweight. Fact sheet Number 311. September 2006. Accessed October 4, 2013.

Yamashita, K., Kondo, T., Osugi, S., Shimokata, K., Maeda, K., Okumura, N., & Murohara, T. (2012). The significance of measuring body fat percentage determined by bioelectrical impedance analysis for detecting subjects with cardiovascular disease risk factors. *Circulation Journal*, 76, 2435-2442.

Young, T.K., & Mustard, C. (2001). Undiagnosed diabetes: does it matter? *Canadian Medical Association Journal*, 164, 24-28.

Young, T.K., McIntyre, L.L., Dooley, J., & Rodriguez, J. (1985). Epidemiologic features of diabetes mellitus among Indians in northwestern Ontario and northeastern Manitoba. *Canadian Medical Association Journal*, 132, 793-797.

Young, T.K., Szathmary, E.J.E., Evers, S., & Wheatley, B. (1990). Geographical distribution of diabetes among the native population of Canada: A national survey. *Social Science and Medicine*, 31, 129-139.

Young, T.K. (1996a). Obesity, central fat patterning and their metabolic correlates among the Inuit of the central Canadian arctic. *Human Biology*, 68, 245-263.

Young, T.K. (1996b). Sociocultural and behavioural determinants of obesity among inuit in the central Canadian arctic. *Social Science and Medicine*, 43, 1665-1671.

Young, T.K. (1994). The health of Native Americans. New York, NY: Oxford University Press.

Young, T.K., Dean, H.J., Flett, B., & Wood-Steinman, P. (2000). Childhood obesity in a population at high risk for type 2 diabetes. *The Journal of Pediatrics*, 136, 365-369.

Young, T.K., Chateau, D., & Zhang, M. (2002). Factor analysis of ethnic variation in the multiple metabolic (insulin resistance) syndrome in three Canadian populations. *American Journal of Human Biology*, 14, 649-658.

Young, T.K. (2005). Chapter 2: Measuring health and disease in populations. In Population Health: concepts and methods 2nd edition. Editor: TK Young. New York (NY): Oxford University Press.

Zorzi, A., Wahi, G., Macnab, A.J., & Panagiotopoulos, C. (2009). Prevalence of impaired glucose tolerance and the components of metabolic syndrome in Canadian Tsimshian Nation youth. *Canadian Journal of Rural Medicine*, 14, 61-67.

8.0 APPENDIXES

Appendix 8.1. Direct sex- and age-standardization of diabetes prevalence in Sandy Bay First Nation in 2002/2003 and 2011/2012.

			Sandy Bay 2003/2003				Sandy Bay 2011/2012			
	Canadian population, 2010 (1000's)		Rate (%)		Expected cases (1000's)		Rate (%)		Expected cases (1000's)	
Age group	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
18-29	85.2	81.7	8.2	15.9	6.99	12.99	5.2	9.8	4.43	8.01
30-39	67.6	67.4	23.1	20.3	15.62	13.68	25.4	23.9	17.17	16.11
40-49	77.0	75.9	36.7	33.9	28.26	25.73	33.8	31.8	26.03	24.14
50+	162.3	180.9	53.5	68.9	86.83	124.64	65.3	61.2	105.98	110.71
Total	392.1	405.9			137.69	177.04			153.61	158.96
			Sex- and age-standardized prevalence: 39.44% (95% CI: 35.08, 43.80)				Sex- and age-standardized prevalence: 39.17% (95% CI: 35.25, 43.09)			

Appendix 8.2. Direct age-standardization of hypertension prevalence in Sandy Bay First Nation in 2002/2003 and 2011/2012.

			Sandy Bay 2003/2003				Sandy Bay 2011/2012			
	Canadian population, 2010 (1000's)		Rate		Expected cases (1000's)		Rate		Expected cases (1000's)	
Age group	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
18-29	85.2	81.7	9.6	26.1	8.17	21.31	22.4	14.9	19.08	12.13
30-39	67.6	67.4	38.5	32.1	26.00	21.60	50.0	31.3	33.80	21.13
40-49	77.0	75.9	47.9	52.6	36.90	39.95	50.0	40.9	38.50	31.05
50+	162.3	180.9	72.1	81.4	117.01	147.24	85.7	71.4	139.11	129.22
Total	392.1	405.9			188.07	230.11			230.49	193.52
				Sex- and age-standardized prevalence: 52.40% (95% CI: 47.89, 56.91)				Sex- and age-standardized prevalence: 53.13% (95% CI: 49.09, 57.19)		

Appendix 8.3. Direct age-standardization of obesity prevalence in Sandy Bay First Nation in 2002/2003 and 2011/2012.

			Sandy Bay 2003/2003				Sandy Bay 2011/2012			
	Canadian population, 2010 (1000's)		Rate		Expected cases (1000's)		Rate		Expected cases (1000's)	
Age group	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
18-29	85.2	81.7	35.6	61.8	30.3448	50.4620	37.3	50.00	31.79	40.85
30-39	67.6	67.4	43.1	61.5	29.1201	41.4766	41.7	67.16	28.17	45.27
40-49	77.0	75.9	62.5	64.8	48.1250	49.1946	25.8	68.18	19.83	51.75
50+	162.3	180.9	58.5	78.0	95.0056	141.1906	36.7	61.22	59.62	110.75
Total	392.1	405.9			202.5955	282.3238			139.41	248.62
				Sex- and age-standardized prevalence: 60.77% (95% CI: 56.35, 65.19)				Sex- and age-standardized prevalence: 48.63% (95% CI: 44.63, 52.67)		

Appendix 8.4. Direct age-standardization of abdominal obesity prevalence in Sandy Bay First Nation in 2002/2003 and 2011/2012.

			Sandy Bay 2003/2003				Sandy Bay 2011/2012			
	Canadian population, 2010 (1000's)		Rate		Expected cases (1000's)		Rate		Expected cases (1000's)	
Age group	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
18-29	85.2	81.7	38.4	75.8	32.68	61.89	40.9	74.3	34.85	60.67
30-39	67.6	67.4	41.5	79.5	28.08	53.57	48.3	86.6	32.67	58.35
40-49	77.0	75.9	70.2	79.2	54.06	60.15	50.0	89.4	38.50	67.85
50+	162.3	180.9	78.0	95.0	126.67	171.86	61.2	87.8	99.37	158.75
Total	392.1	405.9			241.50	347.47			205.3941	345.61
			Sex- and age-standardized prevalence: 73.81% (95% CI: 69.81, 77.81)				Sex- and age-standardized prevalence: 69.05% (95% CI: 65.34, 72.80)			

Appendix 8.5. Direct age-standardization of dyslipidemia prevalence in Sandy Bay First Nation in 2002/2003 and 2011/2012.

			Sandy Bay 2003/2003				Sandy Bay 2011/2012			
	Canadian population, 2010 (1000's)		Rate		Expected cases (1000's)		Rate		Expected cases (1000's)	
Age group	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
18-29	85.2	81.7	16.4	27.5	14.01	22.50	15.6	18.6	13.25	15.22
30-39	67.6	67.4	29.2	35.4	19.76	23.89	33.9	34.3	22.92	23.14
40-49	77.0	75.9	36.7	39.0	28.29	29.59	17.6	28.8	13.59	21.85
50+	162.3	180.9	20.9	48.9	33.97	88.44	20.4	55.1	33.12	99.68
Total	392.1	405.9			96.02	164.41			82.88	159.89
				Sex- and age-standardized prevalence: 32.64% (95% CI: 28.45, 36.83)				Sex- and age-standardized prevalence: 30.42% (95% CI: 26.78, 34.06)		

Appendix 8.6. Direct age-standardization of metabolic syndrome prevalence in Sandy Bay First Nation in 2002/2003 and 2011/2012.

			Sandy Bay 2003/2003				Sandy Bay 2011/2012			
	Canadian population, 2010 (1000's)		Rate		Expected cases (1000's)		Rate		Expected cases (1000's)	
Age group	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
18-29	85.2	81.7	28.8	45.5	24.51	37.14	29.5	33.0	25.17	26.96
30-39	67.6	67.4	40.0	55.1	27.04	37.16	54.2	58.2	36.66	39.23
40-49	77.0	75.9	68.1	67.9	52.43	51.56	42.4	65.2	32.67	49.45
50+	162.3	180.9	68.3	87.5	110.84	158.29	67.3	87.8	109.30	158.75
Total	392.1	405.9			214.81	284.14			203.81	274.39
				Sex- and age-standardized prevalence: 62.53% (95% CI: 58.12, 66.94)				Sex- and age-standardized prevalence: 59.92% (95% CI: 55.96, 63.88)		

Appendix 8.7. Correlations of baseline cardiometabolic variables and change in[a] cardiometabolic variables over time with change in BMI[a].

	Men		Women	
	Spearman correlation	p-value	Spearman correlation	p-value
Baseline				
SBP	-0.376	0.001	-0.291	0.007
DBP	-0.341	0.002	-0.211	0.052
BMI	-0.531	<0.001	-0.163	0.132
Waist circumference	-0.450	<0.001	-0.155	0.158
Waist-to-hip ratio	-0.420	<0.001	-0.262	0.016
Glucose	-0.464	<0.001	-0.465	<0.001
HbA1c	-0.489	<0.001	-0.489	<0.001
HDL-cholesterol	0.327	0.003	0.201	0.062
LDL-cholesterol	-0.342	0.003	-0.024	0.829
TG	-0.446	<0.001	-0.074	0.496
ApoA	0.084	0.460	0.169	0.119
ApoB	-0.460	<0.001	-0.125	0.250
Homocysteine	0.221	0.051	0.079	0.465
HOMA-IR	-0.537	<0.001	-0.221	0.041
HOMA β-cell function	-0.001	0.990	0.208	0.036
ACR	-0.242	0.041	-0.118	0.292
Change in[a]:				
Waist-to-hip ratio	0.505	<0.001	0.176	0.110
Glucose	-0.199	0.079	0.172	0.111
HbA1c	-0.204	0.072	0.079	0.469
Total cholesterol	0.368	0.001	-0.072	0.505
LDL cholesterol	0.513	<0.001	0.021	0.857
TG	0.441	<0.001	0.113	0.298
ApoB	0.438	<0.001	0.091	0.407
Insulin	0.568	<0.001	0.366	0.001
Hcy	-0.287	0.010	-0.387	<0.001
HOMA-IR	0.221	0.051	0.353	0.001
HOMA- β-cell function	0.513	<0.001	0.047	0.668
HDL cholesterol	-0.413	<0.001	-0.480	<0.001
ApoA	-0.248	0.027	-0.194	0.073
At follow-up				
eGFR	-0.139	0.220	-0.073	0.501

[a] Change was measured as the value at time 2 minus the value at time 1.

Appendix 8.8. Correlations of baseline cardiometabolic variables and change in[a] cardiometabolic variables over time with change in apoB[a].

	Men		Women	
	Spearman correlation	p-value	Spearman correlation	p-value
Baseline				
SBP	-0.322	0.004	0.148	0.171
DBP	-0.330	0.003	-0.017	0.875
BMI	-0.357	<0.001	-0.041	0.710
Waist circumference	-0.304	0.006	-0.083	0.453
Waist-to-hip ratio	-0.339	0.002	-0.217	0.048
Glucose	-0.281	0.011	-0.176	0.096
HbA1c	-0.322	0.004	-0.114	0.288
HDL-cholesterol	0.234	0.037	0.060	0.576
LDL-cholesterol	-0.566	<0.001	-0.381	<0.001
TG	-0.420	<0.001	-0.385	<0.001
ApoB	-0.600	<0.001	-0.510	<0.001
Homocysteine	0.041	0.721	-0.075	0.482
HOMA-IR	-0.368	0.001	-0.116	0.278
ACR	-0.284	0.015	0.100	0.376
Change in[a]				
DBP	0.287	0.010	0.060	0.581
BMI	0.438	<0.001	0.091	0.407
waist	0.429	<0.001	0.074	0.506
glucose	-0.231	0.039	0.231	0.028
TG	0.478	<0.001	0.460	<0.001
apoA	0.238	0.033	0.109	0.308
HOMA β-cell function	0.241	0.031	-0.238	0.025
At follow-up				
eGFR	-0.194	0.084	0.197	0.063

[a] Change is defined as value at follow-up minus value at baseline.

Appendix 8.9. Correlations of baseline cardiometabolic variables and change in[a] cardiometabolic variables over time with change in homocysteine[a].

	Men		Women	
	Spearman correlation	p-value	Spearman correlation	p-value
Baseline				
Waist-to-hip ratio	-0.003	0.977	0.234	0.031
Glucose	0.323	0.003	0.310	0.003
HbA1c	0.283	0.011	0.213	0.044
TG	0.178	0.115	0.155	0.143
ApoB	0.203	0.072	0.159	0.134
Homocysteine	-0.331	0.003	-0.172	0.103
HOMA-IR	0.202	0.072	0.069	0.516
HOMA β-cell function	-0.299	0.007	-0.215	0.043
ACR	0.195	0.098	0.165	0.138
Pack-years	0.086	0.468	0.202	0.066
# cigarettes/day	0.054	0.640	0.215	0.041
Change in:				
BMI	-0.287	0.010	-0.387	<0.001
Waist circumference	-0.213	0.059	-0.180	0.100
Glucose	-0.259	0.020	-0.122	0.248
HDL	0.322	0.004	0.037	0.729
TG	-0.246	0.028	-0.074	0.486
HOMA-IR	-0.309	0.005	-0.085	0.427
At follow-up				
eGFR	-0.260	0.020	-0.104	0.328

[a]Change is defined as value at follow-up minus value at baseline.