

Beyond Blood Sugar Control: A Review of Metformin's Therapeutic Potential in Age-Related Disease

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Abstract

Evidence has suggested that the pharmacokinetic mechanisms of metformin may show benefit in the etiology of chronic disease beyond that of diabetes control. This review investigates various clinical trials and analyses the efficacy of metformin in non-diabetic individuals focusing on cardiovascular disease, neurodegenerative disease, and lung neoplasm. Findings suggest an overall neutrality in the effects of metformin across the three analyzed aspects of chronic disease. Specifically, 38% of participants in the cardiovascular disease studies exhibited a favorable response to metformin. These benefits were observed in blood pressure control, left ventricular mass and NT-pro-BNP, with some evidence indicating an improved lipid profile. Additionally, 39% of participants in the neurodegenerative disease trials demonstrated positive outcomes. Significant enhancements were observed in cerebral blood flow within the orbitofrontal region, as well as executive function in Alzheimer's disease patients. Mechanical power and duration in gait analysis in those with Myotonic dystrophy demonstrated beneficial outcomes. However, among participants with lung neoplasm, only 12% displayed overall benefit with metformin as an adjunct therapy. Findings suggested of six-month progression-free survival; however, conflicting data suggested a negative trend to the same parameter as well as overall survival. These findings may underscore the nuanced effects of metformin across different stages of disease and highlight the importance of considering various factors when evaluating therapeutic potential. In conclusion, while metformin shows promise in certain aspects of chronic disease, further research is needed to provide further insight into metformin's role in chronic disease and prolonging health span.

Beyond Blood Sugar Control: A Review of Metformin's Therapeutic Potential in Age-Related Disease

Mortality, as described by Attia (2023), can largely be attributed to “the four horsemen of chronic disease”, a claim in which: cardiovascular disease (CVD), neoplasms, neurodegenerative disease (NDD), and metabolic disease contribute to chronic disease (CD)-related mortality (1). This description of mortality is widely applicable in Canada, as these four pillars are responsible for six out of the ten leading causes of death in 2022 (2). The understanding that these four pillars alone contribute to the majority of CD-related mortality depicts the importance of

addressing these contributing factors to prevent the onset of CD and further extend one's health span.

The medical model adheres to a dual care methodology, prioritizing primary prevention and subsequent treatment interventions (3). In preventing CD, these measures remain inadequate as its incidence prevails (2). Relying solely on therapeutic intervention post-establishment of CD limits the effectiveness of interventions and does not allow for mitigation of disease(4). Further investment must focus on pre-emptive strategies appropriately addressing this limitation to delay the onset of CD.

Recent studies have suggested a broader scope for metformin, a commonly used anti-glycemic agent (5,6). These studies imply that metformin may play a role in preventative medicine by decreasing morbidity and delaying mortality in individuals without diabetes (7). Metformin's potential expanding scope in preventative healthcare may uncover new avenues for use in CD mitigation (4), thus decreasing the burden of disease.

Metformin, subjected to thorough investigation and recognized for its cost-effectiveness and strong safety profile (8), has emerged as a promising modality in CD and longevity. Findings have suggested that metformin targets various factors contributing to CD's intricate etiology and progression (9–13)

The etiology underlying CD and aging is linked to a combination of mechanisms, which commonly include: inflammation (12); cellular damage (9,10); mitochondrial dysfunction (10);

altered cell signalling; genetic and epigenetic factors; lifestyle factors; and immunological integrity (11). These factors have a dynamic interplay in which they mutually interact and impact the complexity of CD and aging (11). Metformin has been investigated with potential influence in multiple mechanisms of action that contribute to the intricate etiology and progression of CD and aging (9–13).

Beyond its anti-glycemic effects in diabetes, metformin has garnered attention for its potential impact on inflammation (7). Regarding chronic inflammation, cytokines, TNF- α , IL-6, IL-1, and CRP have been implicated in frailty, malnutrition, vascular dysfunction, and cognitive decline (11,12). Furthermore, excess glucose uptake is associated with the activation of IL-1 (10,14,15) and increased production of TNF- α (10), IL6 (16,17), and CRP (15,16). The anti-glycemic mechanism of metformin may decrease the proinflammatory effect, providing a dual-faceted regulation of both glucose and inflammation (15). Tertiary effects of metformin include increased immunological integrity, as inflammation is primarily associated with immunosenescence (11). Metformin also targets AMP-activated protein kinase (AMP-K), a cardinal metabolic energy regulator affecting cellular, lipid, and glucose metabolism (13). In CD, AMP-K is inactivated, thus disrupting cellular signalling, increasing proinflammatory cytokines, and elevating rates of CD (13). An anti-aging factor determined in metformin is its inactivation of insulin secretion and IGF-1, a growth factor associated with all-cause mortality and aging (18,19). Lastly, metformin decreases the signalling pathways prominent in neoplastic development, NDD, and metabolic disease through the inhibition of the mammalian target of rapamycin (mTOR) (20). By leveraging these mechanisms that deter the manifestation of age-related pathologies, metformin may extend health span, postpone the onset of morbidity, and

potentially reduce premature mortality. See *Figure 1* for further depiction of metformin's anti-senescence mechanism.

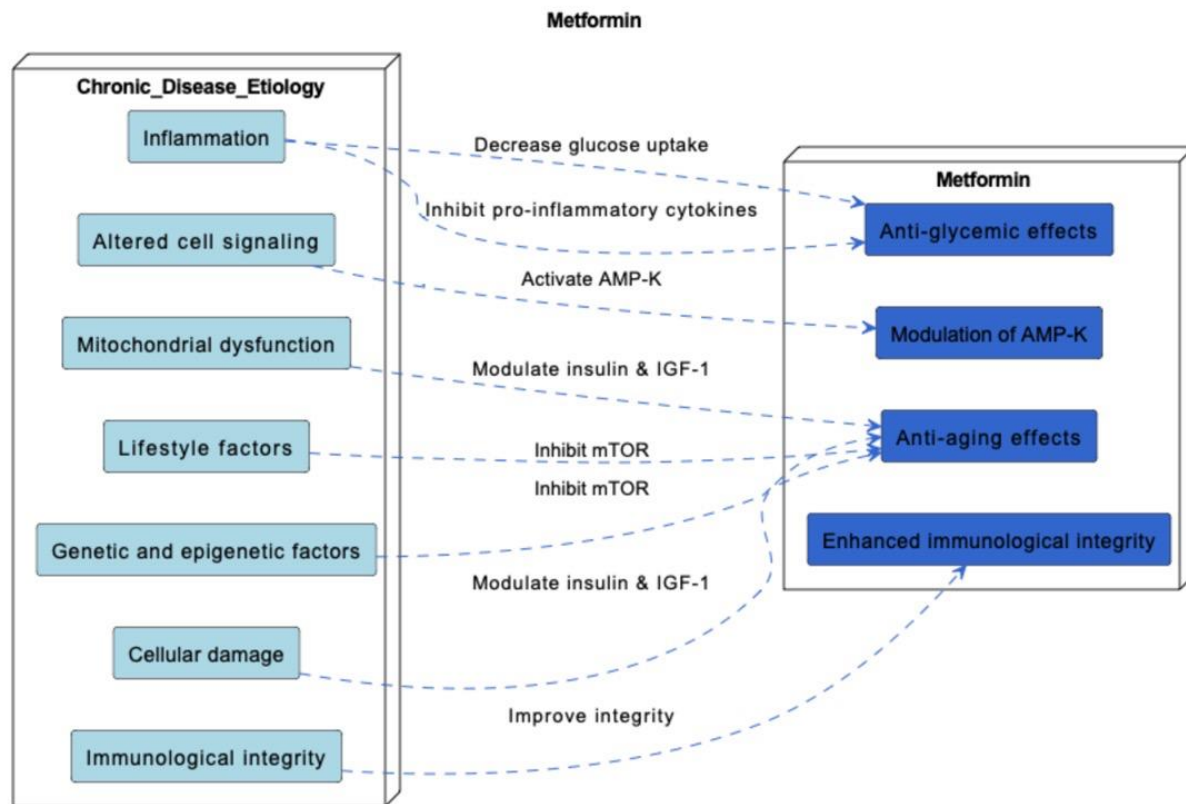


Figure 1: Image depicts the common etiologies of chronic disease and their connection to metformin via various mechanisms as previously sourced above. The acronyms used throughout the figure: AMP-K (activated protein kinase), IGF-1 (insulin growth factor-1), mTOR (mammalian target of rapamycin).

The purpose of this study is to review the existing literature with a focus on metformin's impact on CVD, NDD, and neoplasms. Unlike prior research, which has explored metformin's relations to morbidity, this study will explicitly focus on the four pillars of CD primarily associated with mortality (6,21–23). This literature will not focus on the fourth pillar of CD, metabolic disease, as metformin is currently prescribed for diabetes, a large component of metabolic disease. This review aims to analyze further existing research concentrating on the impacts of metformin on individuals without diabetes or metabolic disease, specifically focusing on the capacity to reduce morbidity and prolong mortality. Metformin will be assessed to

determine if it has the potential to reduce the burden of CD and improve the quantity and quality of life towards a broader target of individuals. Multiple studies have explored the extended benefit of metformin (5,6,21,23,24); however, the problem lies in determining when sufficient understanding should translate to actionable measures. This project intends to contribute valuable insights into metformin's potential uses and broadened scope.

Methods

Objective

This literature review aims to identify and analyze all research that investigates the impact of metformin on the four pillars of CD beyond diabetes or metabolic disease. This research will identify potential benefits and risks associated with metformin use outside of diabetes management. Additionally, the mechanisms by which metformin affects longevity of all disease and non-disease states and the quality and reliability of the studies available will be examined.

Search Strategy

The search was restricted to clinical trials, observational studies, randomized control trials and multicenter studies. The primary literature search was conducted in the PubMed database. The keywords in *Appendix A* were adopted for primary search.

After entering search terms and keywords into the database, a comprehensive search was performed. A preliminary review was then conducted, and research titles and abstracts were assessed to determine if the articles were relevant to the topic. In addition, relevant citations were also retrieved, reviewed, and selected.

Inclusion and Exclusion criteria

The following inclusion criteria were used for this literature review: [1] human-focused studies to avoid skewed/extrapolated population findings; [2] non-diabetic populations to assess the extended use of metformin. [3] adults were the focus of all studies analyzed. The data reviewed focused on the primary outcomes with the addition of specific secondary outcomes including body weight/BMI, cholesterol, CRP, and NT-proBNP, and systolic blood pressure.

The exclusion criteria were: [1] patients with diabetes; [2] articles published before 2003; [3] abstracts, case reports, meta-analysis, and reviews. [4] single-arm clinical trials. All listed were excluded from the results and discussion.

Results

This comprehensive overview analyzes metformin's impact on CVD, NDD, and neoplasms.

Cardiovascular Disease

One hundred and one articles were retrieved upon a primary search with PubMed. Following an initial review, seven articles qualified for comparative analysis. The reviewed articles examined metformin's effect on various CVD aspects, including the pathology of atherosclerosis, major adverse cardiovascular events (MACE), stroke, cardiomyopathy, weight loss, Apolipoprotein B (ApoB), blood pressure (BP), and lipid profile. Findings can be visualized in *Table 1*.

In 2014, Priess et al. performed the CAMERA study, where participants received 850 mg of metformin twice daily for 18 months (25). This double-blinded, randomized, placebo-controlled study included 173 individuals on statins, with a mean age of 63. The study revealed a statistically non-significant impact on lipid profile with an increase in HDL of 0.04 mmol/L ($p=0.095$); triglyceride decrease of 0.08 mmol/L ($p=0.054$); non-HDL-cholesterol decrease of 0.07 mmol/L ($p=0.53$) and a decrease in total cholesterol of 0.03 mmol/L ($p=0.78$). In addition, the study explored the inflammatory marker C-reactive protein (CRP), which demonstrated a non-significant decrease of 0.19 log;mg/L ($p=0.054$). Furthermore, this study examined the thickness of patients' carotid intima-media (cIMT) revealing the metformin group to have a non-significantly increased cIMT of 0.007mm ($p=0.29$). Despite the non-significance values shared above, metformin exhibits a notable and significant reduction in total body weight of -3.2kg ($p<0.0001$) and tissue plasminogen activator of -0.077 ng/mL ($p=0.029$). The most common adverse effects associated with metformin were diarrhea, nausea, and vomiting (25).

The MET-REMODEL trial (2019) examined the effect of metformin on left ventricular hypertrophy (26). Mohan and colleagues randomly assigned 68 patients without diabetes who had coronary artery disease with insulin resistance and prediabetes to receive either metformin XL (2000 mg daily dose) or placebo for 12 months. The author's primary endpoint was to assess change in the patient's left ventricular mass indexed to height (LVMI). Using magnetic resonance imaging, data showed a significantly reduced LVMI compared to placebo (absolute mean difference -1.37; $p=0.033$). The left ventricle mass (LVM) was statistically significant, with a change of -3.3 g ($p=0.032$). Other significant findings included a decreased body weight

of -3.6 kg ($p = 0.001$) and a decreased systolic blood pressure of -9.21 mmHg ($p = 0.022$). Metformin was reported to be well tolerated by the participants (26).

Junior et al (2019), examined participants of overweight body habitus, with a mean age of 57(27). Participants of the metformin cohort were subject to eight weeks of 1700 mg twice daily post-dose titration. BP remained unaltered from baseline and nonsignificant from placebo ($p=0.52$, 0.28 respectively). Additionally, analysis of lipid profile showed a nonsignificant change from baseline compared to placebo in all categories including, cholesterol ($p=0.77$), LDL ($p=0.70$), HDL ($p=0.34$), triglycerides ($p=0.53$), glucose ($p=0.92$), BMI ($p=0.17$), CRP ($p=0.34$). Despite a nonsignificant BMI change of 0.07kg/m^2 ($p=0.17$), metformin treatment reduced waist circumference by 5.8 cm ($p=0.02$) (27).

The longitudinal trials by Goldberg et al. (2022) included a sizeable cohort of 3234 individuals with a mean age of 51 (28). Over 21 years, randomized participants taking metformin at 850 mg twice daily showed no significant impact on the incidence of MACE ($p=0.81$), myocardial infarction ($p=0.73$), LDL-C (-0.02 mmol/l, $p=0.24$), or triglycerides (-0.05 mmol/l, $p = 0.052$), when compared to the placebo group. However, there was a statistical trend in stroke incidence with a decrease of 0.57 hazard ratio ($p=0.07$) in addition to a significant increase in high-density lipoprotein (HDL) (0.05 mmol/l, $p = 0.003$), and BMI decrease (-0.08kg/m^2 , $p=0.017$) compared to placebo cohort (28).

The GIPS-III trial (2014), was comprised of 380 individuals with a mean age of 59, and with a history of ST elevation myocardial infarction (STEMI) (29). Participants received 500 mg

of metformin twice daily for four months post-percutaneous coronary intervention. Left ventricular ejection fraction (LVEF) analyzed with cardiac MRI showed no difference compared to the placebo ($p=0.1$). NT-proBNP and MACE were unchanged between placebo and the metformin cohorts (29). Further analyses by Eppinga et al. in 2016 analyzed cholesterol profiles of the same subset of participants (30). Measurements in total cholesterol showed no statistical significance to the difference between the placebo and metformin ($p^*=0.06$); however, the metformin cohort had a decrease in LDL ($p^*=0.01$). High density lipoprotein (HDL), triglycerides and ApoB between groups showed no significant difference ($p^*=0.09, 0.31, 0.48$ respectively) (30).

Hussain et al. (2016) compared the effects of metformin, sitagliptin, and placebo in a cohort of 100 individuals newly diagnosed with dyslipidemia and hypertension over three months (31). Individuals in the metformin arm received 850 mg twice daily, which revealed distinctive outcomes. Metformin increased HDL by 0.23 mmol/L ($p<0.01$) and surpassed sitagliptin by an additional 0.05 mmol/L. Additionally, metformin exhibited a greater reduction in LDL from baseline by -2.07 mmol/L ($p<0.01$) and triglycerides (-1.40 mmol/L ($p<0.01$)) compared to the sitagliptin cohort, where reductions were -0.85 mmol/L ($p < 0.05$) for both LDL and triglycerides from baseline.

Furthermore, metformin also produced a reduction in several metabolic parameters, reducing body weight by -10kg ($p<0.05$), decreasing BMI by -4.4kg/m² ($p<0.05$), lowering SBP of -15mmHg ($p<0.05$), decreasing DBP of -4.2 mmHg ($p<0.05$), and reducing triglyceride levels by -1.63 mmol/L ($p<0.05$). However, compared to sitagliptin, metformin did not yield as significant for reducing blood pressure ($p<0.01$) (31).

Study	N	Dose	Statistical Relevance	Target	Findings (Q)	p-value
Cardiovascular Disease						
CAMERA study Preiss et al. (2014)	173		Benefit	Body weight	-3.2kg	<0.0001
			Neutral	tPA	-0.077 ng/mL	<0.029
				cIMT	0.007 mm	0.29
	CRP	-0.19 log:mg/L		0.054		
	HDL	0.04 mmol/L		0.095		
	Non-HDL	0.07mmol/L		0.53		
	850mg BID	Total cholesterol	-0.03 mmol/L	0.78		
Triglyceride	-0.08mmol/L	0.054				
MET-REMODEL Mohan et al. (2019)	68		Benefit	Body weight	-3.6 kg	0.001
			LVMi	-1.37 g/m (1.7)	0.033	
			LVM	-3.3 g	0.032	
	1000 mg BID	Systolic BP	-9.21 mmHg	0.022		
Junior et al. (2019)	97		Neutral	NTproBNP	210.62 pg/mL	0.435
			BMI	0.7 kg/m ²	0.17	
			CRP	0 log:mg/L	0.34	
			Cholesterol	-0.54 mmol/L	0.77	
			HDL-C	-0.80 mmol/L	0.34	
			LDL-C	-0.51 mmol/L	0.7	
	1700 mg BID	Triglycerides	0.12 mmol/L	0.53		
Goldberg et al. (2022)	3234		Benefit	SBP office	3.9 mmHg	0.52
			DBP office	0.1 mmHg	0.28	
			BMI	-0.08 kg/m ²	0.017	
			HDL	0.05	0.003	
			Neutral	MACE incidence ^	1.03	0.81
			Cardiovascular death ^	1.46	0.13	
	MI incidence ^	1.07	0.73			
850 mg BID	LDL	-0.02 mmol/L	0.24			
GIPS-III trial Lexis et al. (2014)	380		Trend	Stroke incidence	-0.57 events	0.07
			Triglycerides	-0.05mmol/L	0.052	
			Neutral	LVEF	-1.7%	0.1
GIPS-III Eppinga et al. (2016)	380		Neutral	NT-proBNP	0 ng/L	0.66
			MACE incidence	4 events	0.16	
			Benefit	LDL reduction	-0.1 mmol/L	0.01*
			NT-proBNP	-4 ng/L	0.008*	
			Neutral	ApoB	-0.02 g/L	0.48*
Hussain et al. (2016)	100		Benefit	HDL	-0.1	0.09*
			Triglycerides	0.06 mmol/L	0.31*	
			Trend	Total cholesterol	-0.1 mmol/L	0.06*
			Body weight	-10 kg	<0.05	
			BMI	-4.4 kg/m ²	<0.05	
			HDL	0.23 mmol/L	<0.01	
850 mg BID	LDL	-2.07 mmol/L	<0.01			
	Triglycerides	-1.40 mmol/L	<0.01			
	SBP	-15 mmHg	<0.05			
DBP	-4.2 mmHg	<0.05				

Table 1: Synthesis of research findings evaluating the efficacy of Metformin across various studies, categorized by levels of benefit, neutrality, and emerging trends in relation to Metformin. Significance levels are denoted by bold p-values. (*) indicates p-values adjusted for randomization, BMI, sex, baseline laboratory values, and statin use. (^) represents hazard ratio. (Q) indicates treatment difference (Metformin-Placebo). Acronyms used within the table include: tPA (tissue plasminogen activator), cIMT (carotid intima media thickness), CRP (C-Reactive Protein), HDL-C (High-Density Lipoprotein Cholesterol), LDL-C (Low-Density Lipoprotein Cholesterol), LVM (Left Ventricular Mass), LVMi (Left Ventricular Mass Index), SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), BMI (Body Mass Index), MACE (Major Adverse Cardiovascular Events), MI (Myocardial Infarction), NT-proBNP (N-Terminal Pro B-Type Natriuretic Peptide), and ApoB (Apolipoprotein B).

Neurodegenerative Disease

Three articles were retrieved from PubMed upon primary search. Further analysis narrowed down two articles that fit the inclusion criteria. The reviewed articles examine metformin's effects on non-diabetic individuals with NDD. See *Table 2*.

Study	N	Dose	Statistical Relevance	Findings Δ	p-value
Neurodegenerative Disease					
Koenig et al. (2017)	20	1000mg BID	Benefit	Cognitive function: Significant improvement in executive function	0.0337
				MRI cerebral blood flow: Significant increase in middle orbitofrontal region	<0.05
			Neutral	CSF glucose: No significant change	0.0913
				CSF protein: No significant change	0.2059
				CSF AB1-42: No significant change	0.4008
				CSF total tau: No significant change	0.6744
				CSF phosphorylated tau: No significant change	0.1614
				MRI cerebral blood flow: Non significant increase to other* brain regions	0.9754
Bassez et al. (2018)	23	1000mg TID	Trend	Cognitive function: Statistical trend favoring enhanced learning and memory	0.0633
				Cognitive function: Statistical trend favoring enhanced attention	0.0708
			Benefit	6-meter walk test: Gain from baseline	29.2 meters 0.048
				Gait analysis - mechanical power: craniocaudal direction	1.8 meters 0.011
	Gait analysis - mechanical power: anteroposterior direction	1 meter 0.028			
	Gait analysis - mechanical power: mediolateral direction	0.2 meters 0.735			

Table 2: Compilation of Research Results on Metformin and Neurodegenerative Diseases. Classified by Benefit, Neutrality, and Emerging Trends. Classification based on P-Value analysis. Bold P-values signify statistical significance. (Δ) indicates treatment difference (Metformin-Placebo). Acronyms used include MRI (Magnetic resonance imaging), CSF (cerebral spinal fluid).

Koenig et al conducted a study in 2017 focusing on metformin's impact on the early stages of Alzheimer's disease (AD) (32). The study included 20 individuals with mild cognitive impairment or early dementia secondary to AD, with a mean age of 71, randomized with a dose of 1000 mg twice daily of metformin or placebo over eight weeks. The findings revealed no significant changes to cerebral spinal fluid (CSF) parameters: CSF glucose (p=0.0913); CSF protein (p=0.2059); CSF AB1-42 (p=0.4008); CSF total tau (p=0.6744); CSF phosphorylated tau (p=0.1614). However, MRI assessment of cerebral blood flow (CBF) showed a significant increase in specific regions, particularly in the middle orbitofrontal region (p<0.05). Other regions observed showed no statistical impact. Assessment tools ADAS-Cog, and CANTAB (PAL, TMT-B and DMS) evaluated cognitive and functional scores and showed post-metformin

treatment had a significant improvement in executive function ($p=0.0337$). Koenig et al proposed statistical trends favouring enhanced learning and memory ($p=0.0633$) and attention ($p=0.0708$) (32).

In the MYOMET study (2018), 23 participants, all diagnosed with myotonic dystrophy (MD), received 1000mg of metformin three times daily for 52 weeks (33) Findings indicated significant enhancement in a 6-meter walk test showing improvements of 29.2m gain from baseline ($p=0.048$) compared to an improvement of 3.71m in the placebo cohort. Gait analysis revealed increased mechanical power in craniocaudal movements ($p=0.011$), and anteroposterior movements ($p=0.028$) compared to the placebo, despite other gait variables showing no change in either group. These findings suggest metformin's positive impact on mobility and gait parameters. Note that 5% of initial participants could not tolerate the gastrointestinal side effects of metformin (33)

Neoplasms

Neoplastic research was reviewed, specifically focusing on non-small cell lung cancer (NSCLC) as it is the leading contributor to lung-related neoplastic-related deaths in Canada (34). The primary search yielded 338 results. After initial investigation, four articles were considered suitable. See *Table 3*.

In the OCOG-AMERA study conducted by Tsakiridis et al, in 2021, 54 patients with diagnosed non-small cell lung cancer (NSCLC), stage IIIA/B were treated with

chemoradiotherapy +/- 1000mg of metformin twice daily over 12 months (35). The study concluded that the addition of metformin to chemoradiotherapy was associated with worse treatment efficacy and increased adverse effects compared to combined modality therapy alone. The 1-year progression-free survival (PFS) rate was reduced by 28.2% compared with the control. Furthermore, the overall survival rate was reduced by 37.5% as compared to control (35).

Skinner et al. produced a phase II trial (2021) investigating the effects of 2000mg daily of metformin as an adjunct to first-line chemoradiotherapy in NSCLC stage IIIA/B patients (36). The study observed metformin to have a non-significant 1-year PFS rate compared to the control group (-9.1%; $p=0.24$). Overall survival outcomes showed no significant difference in treatment management ($p=0.89$). There was no significant difference in adverse effects among the two cohorts (36).

Marrone et al. 2019, conducted a randomized phase II trial assessing 1000mg twice daily of metformin concurrently administered with first-line chemotherapy (carboplatin, paclitaxel, and bevacizumab) in individuals with NSCLC (37). This study included 24 chemotherapy-naïve patients with stage IIIB or IV NSCLC. It is pertinent to highlight that direct comparison with the alternative cohort was precluded as all participants had progressive disease or withdrew before 1-year follow-up and therefore previous historical results were used as a comparative. The study reported metformin significantly improved PFS by 32% in contrast to historical values ($p=0.024$). Furthermore, this study reported increased overall survival of 2 months compared

with historical values ($p=0.186$). There were no significant differences in adverse effects amongst cohorts (37).

Sayed et al conducted a randomized controlled trial targeting stage IV NCSLC individuals in 2015 (38). This study enrolled 30 individuals who underwent first-line chemotherapy (gemcitabine/cisplatin) with or without the addition of 500mg of metformin once daily. The median PFS rate for the metformin group 0.5 months greater in those participants treated with adjunct metformin ($p=0.062$). Metformin did exhibit significant promise in ameliorating chemotherapy-induced nausea (26.7% metformin arm vs 66.7% control, $p=0.028$) (38).

Study	N	Dose	Statistical Relevance	Target	Findings		p-value
					Neoplasms		
					Metformin	Control	
Tsakiridis et al. (2021)	54	2000mg daily	Negative Trend	1-year progression-free survival	34.80%	63%	0.051
				Overall survival	47.70%	85.20%	N/A
Skinner et al. (2021)	200	1000 mg BID	Neutral	1-year progression-free survival	51.30%	60.40%	0.24
				Overall survival	80.80%	80.20%	N/A
Marrone et al. (2019)	24	1000 mg BID	Benefit	6 month -Progression-free survival	47%	15% **	0.024
			Neutral	Overall survival	15.9 months	13.9 months**	0.186
Sayed et al. (2015)	30	500mg daily	Neutral	Progression-free survival	5.5 months	5 months	0.062
				Objective response rate	46.70%	13.30%	0.109

Table 3: Summary of Research Findings on Metformin and Neurodegenerative Diseases, Classified by Benefit, Neutrality, and Emerging Trends. Classification based on P-Value analysis. Bold P-values indicate statistical significance. (**) Denotes historical value as control findings not presented.

Overall Comparison

Comparative analysis based upon categorical benefit across all studies reviewed suggests overall neutrality. However, it is noteworthy that studies focusing on CVD and NDD indicated benefits associated with metformin use. It is important to note that neoplasm studies were the only source showing potential negative outcomes with metformin use. See *Figure 2*.

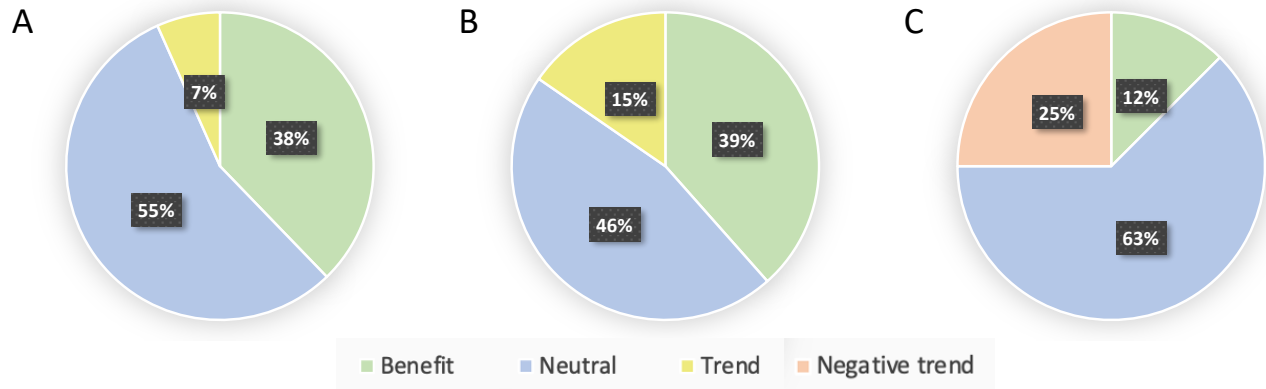


Figure 2: Categorical Comparative Analysis. A: Effects on Cardiovascular disease (CVD), B: Effects on neurodegenerative disease, C: Effects on pulmonary neoplasms. Data demonstrating general neutrality across the three investigated aspects (CVD, Neurodegenerative Diseases, and Neoplasms). Graphs illustrate minimal negative findings, with emerging negative trends observed specifically in relation to neoplasms.

Discussion

Metformin, as a therapy for prolonging health span, has been thoroughly assessed with a focus on CVD, NDD, and neoplasms. Unfortunately, this review incompletely addresses the spectrum of leading CD causes in Canada. This is due to the necessity for additional investigation and the sheer volume of existing research pertaining specifically to neoplasms, surpassing the scope of this paper. Overall, metformin is shown to have a modest impact on various factors related to health and longevity.

The available evidence suggests that metformin may confer certain CVD benefits, particularly in weight reduction and BP control. However, the impact of metformin on BP remains uncertain, partly in due to the correlation between weight loss and BP decrease (39). It is important to be critical of the Junior et al study, which found minimal changes to BP over an eight-week period. This null result may be attributed to the relevantly short duration for metformin to exert its therapeutic effect.

Furthermore, trends observed in triglycerides, LDL, and HDL were largely inconsistent among the studies. These inconsistencies may be a result of varying dose, therapy length, and baseline demographics. See *Appendix B*.

Long-term studies indicated a potential reduction in the incidence of strokes in metformin users, while findings regarding MACE did not consistently show rate reduction. The assessment of atherosclerosis, a crucial factor in CVD, yielded mixed results. Observed cIMT indicated no benefit from the use of metformin. This could be influenced by pre-existing statin therapy in the study population. Additionally, while metformin appears to reduce LVMI, there was no evidence of a concurrent change in ejection fraction or volume. This discrepancy in cardiac parameters may be due to the course of therapy, which was restricted to 12 months, warranting further investigation into the long-term effects of metformin and cardiac remodelling. Overall, metformin showed benefit in weight reduction, BP modulation, stroke incidence, and LVMI. Although MACE, atherosclerosis and other cardiac parameters remained unchanged, there was no evidence of increased harm. A prospective trial, VA IMPACT, may further elucidate metformin's therapeutic benefit on CVD (<https://classic.clinicaltrials.gov/ct2/show/NCT02915198#studydesign>) (26,40).

The limited scope of metformin in NDD research, mainly rodent-focused models, poses translational challenges in understanding its potential impact at a human level. AD and MD were the focus in this review due to the scarcity of human studies. Among participants with AD, metformin users had increased CBF within specific brain regions, which accompanied improvements in executive function with trends towards enhanced learning and memory. It is

essential to note that this study specifically focused on patients with mild cognitive impairment; therefore, it remains unclear if metformin prevents future cognitive decline.

Similarly, participants with MD using metformin showed significant gains in mobility and gait parameters, indicating a role in enhancing motor function. These findings have warranted phase III clinical trials (33). Nevertheless, the confined analysis of NDD disease limits the utility of metformin for all NDDs, as it excludes considerations of many NDDs, indicating the need for broader investigations.

Due to the overwhelming research in metformin-neoplasm-focused studies, this review focused on lung-related neoplasms, specifically NSCLC, the largest contributor to cancer-related death in Canada (34). Metformin as an adjunct to chemotherapy regimens showed some benefit, particularly in overall survival. The evidence of improved PFS was inconclusive with only a few studies showing metformin's potential. The assessed studies primarily showed that metformin displayed no risk or benefit compared to control. Therefore, the efficacy of metformin as an adjunct to lung cancer treatment continues to warrant the need for further investigation. It is crucial to note that all patients assessed were in late-stage disease, limiting the extrapolation of metformin's therapeutic benefit in cancer prevention.

Demographic

The demographic composition reviewed exhibited a wide diversity, encompassing variations in age, gender, and race. Comorbidities such as dyslipidemia, hypertension and insulin resistance were pervasive among many participants, highlighting the complex interplay between metabolic disorders and age-related disease. See *Appendix B*. It is imperative to recognize that all

participants reviewed harboured underlying comorbidities, necessitating a nuanced evaluation of the stage of illness and overall health status of participants. Thus, extrapolating benefits in the prevention of CD and prolonging health span in healthy individuals is inappropriate as there was limited medical history. Furthermore, it is crucial to account for variation in sex and age, particularly in studies with predominantly male participants. These variables pose challenges in interpretation and subsequent actionable measures. Consideration of these demographic factors is essential when navigating the data and translating these findings into meaningful action.

Therapy Consistency

The trials reviewed exhibited considerable variability in dosing regimens, with minimal consensus on the lowest therapeutic dose of metformin. The dose range predominantly ranged between 850mg and 1000mg twice daily, with a few outliers. The time frame of analysis also varied between studies, with therapeutic effects analyzed from eight weeks through to 21 years. These variations impede interpretation and comparison as efficacy is largely correlated with dosing (41) Thus, clinical implementation is limited as no consensus has been reached.

Adverse Effects

Common adverse effects primarily comprised of gastrointestinal (GI) effects including nausea, diarrhea, and abdominal discomfort. Few participants reported precarious adversities, including a decline in vitamin B12, lactatemia, and hypoglycemia. See *Appendix B*. Adherence was inconsequential, with only a small subset of participants reporting early discontinuation of

treatment due to GI intolerance; while others managed adverse effects with loperamide.

Interestingly, metformin showed promise in reducing chemotherapy-induced nausea, suggesting synergistic potential in cancer treatment. Notably, no cases of lactic acidosis or serious harm were identified throughout the analysis of all studies.

Limitations and Conflict of Interest

No conflicts of interest are to be disclosed. However, it is important to acknowledge and reflect on limitations and potential biases that may have influenced the findings. Although the search strategy aimed to encompass all relevant studies, this research may have been limited by focusing to a singular search engine with specific keywords in the English language. This review, however, did focus on high quality and reliable studies at the discretion of the author. Additionally, this review relied on ethical conduct from previous publishers regarding conflict of interests and funding sources. Despite these limitations and potential biases, the intent of this review was to present information in an unbiased manner.

Conclusion and Future Direction

In conclusion, metformin displays overall neutrality among CVD, NDD and respiratory neoplasm. Despite this neutrality, metformin demonstrated many benefits in mitigating CD, specifically in CVD and NDD. Analysis of neoplasm data displayed the most negative resistance; however, it is challenging to extrapolate this due to the severity of illness being assessed. In general, neoplasms and prevention of neoplasm should be further investigated to aid

in applying findings to healthy individuals. Subsequent research should explore its potential in other NDDs and optimize its use in diverse populations to maximize its therapeutic potential in prolonging health span and limiting the onset of CD. Despite the uncertainty of metformin for targeting longevity, it has been shown to have a favorable safety profile, characterized by mild adverse effects that are largely manageable. This review does not provide definitive actionable insight; however, it contributes to the accumulating evidence suggesting metformin may play a role in mitigating aspects associated with CD and aging.

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Appendix

"aging/physiology"[MeSH Terms] Longevity"[MeSH Terms]	"Metformin"[MeSH Terms] "Metformin"[Title/Abstract] "dimethyl biguanide"[Title/Abstract]	"Cardiovascular Diseases"[Mesh] "Atherosclerosis"[Mesh] "Coronary Artery Disease"[Mesh]	"Neurodegenerative Diseases"[Mesh] "Parkinson Disease"[Mesh] "Lewy Body Disease"[Mesh] "Dementia"[Mesh] "Huntington Disease"[Mesh] "Myotonic Dystrophy"[Mesh] "Motor Neuron Disease"[Mesh] "Multiple System Atrophy"[Mesh] Alzheimer Disease"[Mesh] "Neurodegenerative Diseases"[Mesh] Amyotrophic Lateral Sclerosis"[Mesh]	"Lung Neoplasms"[Mesh] "Small Cell Lung Carcinoma"[Mesh] "Carcinoma, Non-Small-Cell Lung"[Mesh] Adenocarcinoma of Lung"[Mesh]
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Appendix A: Search Map: the top horizontal words were AND searches and the vertical words are OR searches.

	Study	Duration	Dosage	Demographics				Adverse Effects
				Mean Age	Sex	Comorbidities	Polypharmacy	
CVD	Preiss et al (2014) - CAMERA study	18m	850 mg bid	63	81% male	ACS, Angiograph porven chornic heart disease	Statin therapy	diarrhea (21%) nausea/vomiting (12%), B12 decline (p<0.0001)
	Goldberg et al (2022) - Cardiovascular Events LT study	21y	850 mg bid	51	68%female, 55%caucasian	Not specified	antihypertension, statin therapy (0.54%)	Not specified
	Hussain (2016) - Sitagliptin vs Metformin	3m	850 mg bid	27	57% male	Dyslipidemia, HTN	no medications	No adverse effects noted
	Mohan et al (2019) - MET-REMODEL trial	12m	1000 mg bid	65	47% male	Smoker (13%), ETOH use (65%)	not specified	diarrhea (47%), flatulence (26%) abdominal discomfort (25%)
	Lexis (2014) - GIPS-iii trial	4m	500 mg bid	59	75% male, 96% caucasian	previous STEMI with PCI tx, HTN (30%), dislipidemia (63%), smoker (55%)	antiplatelet therapy (100%), ACEI/ARB (79%), BB (96%), CCB (3.2%), Statin (99.5%)	no findings of lactic acidosis
	Junior et al 2019	8 w	1700 mg bid	57	79% female	overweight	antihypertensive (25%) diuertics (72%), ACEI/ARB (72%), CCB (24%), statin (17%),	diarrhea (17%), abdominal pain, 1 premature termination due to adverse effects
	Eppingina et al 2016	4m	500mg bid	59	75% male	STEMI with PCI tx	statin (7%), BB (94%), ACEI/ARB (83%), CCB (5%)	Not reported
NDD	Koenig et al. (2017)	8w	1000mg bid	71	55% male, 100% caucasian	previous diagnosis MCI/Early dementia due to AD	Not specified	lactatemia (p value = 0.47 compared to control) Gastrointestinal symptoms(anorexia/common diarrhea, nausea), hypoglycemia
	Bassez et al. (2018)	52w	1000mg tid	42	58% female	myotonic dystrophy type 1	Not specified	GI disorders (diarrhea, abdominal pain, dyspepsia). 4 patients withdrew due to adverse effects.
Neoplasms	Tsakiridis et al. (2021)	12m	200mg daily	66	56% female	100% Stage 3 A/B diagnosis of unresectacted locally advanced NSCLC	100% cisplatin or carboplatin chemotherapy	No adverse effects associated with metformin
	Skinner et al. (2021)	1y	1000mg bid	64	58% male,82% caucasian	100% Unresectible stage 3 NSCLC	100% carboplatin or paclitaxle,	Gastrointestinal problems (17.7% low severity, 54.4% mild severity, 13.9% moderate severity, no severe or extreme severity)
	Marrone et al. (2019)	1y	1000mg bid	61	63% female, 84% caucasian	100% naive stage 3B/4 advanced or medistatic nonsquamas NSCLC with life expectancy greater than 12 weeks. Smokers (68%)	100%carboplatin, paclitaxle and bevacicumab,	No adverse effects recorded due to metformin
	Sayed et al. (2015)	1y	500mg od	54	80% male	100% Chemo-naive stage 4 NSCLC, previous smoker (73%)	100% Gemcitabine or cysplatin	No associated adverse effects

Appendix B: Comprehensive table summarizing the reviewed papers on metformin’s duration, dose, demographics and adverse effects.