The association between metabolic risk factors, depression and cognitive function: a cross-sectional and longitudinal investigation

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Abstract

Background Depression and dementia are the most common causes of disability worldwide and are leading causes of global disease burden. Both conditions are associated with poor psychosocial functioning and impaired capacity to manage other illnesses. There is potential to delay the onset/progression of dementia and depression through targeting their modifiable risk factors, several of which have an onset in mid-life. Understanding how these three commonly occurring factors (metabolic dysregulation, depression and poor cognitive function) could interact with one another to potentially increase the risk of conditions such as depression or dementia, can contribute towards the prevention of these conditions in old age.

Objectives The first objective was to examine the cross-sectional association between comorbid depressive symptoms and metabolic dysregulation and poor cognitive function. The second objective was to examine the temporal association between comorbid metabolic risk factors, history of depression, and low cognitive function and risk of a major depressive episode five years later.

Methods In the first study, the outcome variable was poor cognitive function, which was composed of the combined score of three cognitive function measures: fluid intelligence, reaction time and pairs associates learning. The three cognitive domains assessed in both studies were: executive function, processing speed and episodic memory. Poor cognitive function was defined as the lower quartile of the overall cognitive function (g-score) distribution. The independent variables were depressive symptoms, defined as having a score of 6 and above out of a maximum score of 27 in the PHQ-9 and metabolic dysregulation, defined as having three or more of the five metabolic risk factors. The five metabolic factors included obesity,

hypertension, high triglyceride levels, low HDL cholesterol, and high fasting blood glucose. In the second study, the outcome variable was having reported experiencing an episode of major depression in the previous year during the CIDI interview. The first independent variable was having reported a history of depression during the CIDI interview with an onset prior to the year of baseline CaG assessment. The second independent variable was having low cognitive function, defined as being on the upper quartile of the distribution of the g-score and the last independent variable was having one of the five metabolic risk factors, which were measured during baseline CaG. A subsample of the CARTaGENE (CaG) cohort, who agreed to participate in a follow-up study five years later, made up the study sample. For the first study, n=1991 participants had information on depressive symptoms and cognitive function. These participants were divided into four groups based on the presence of depressive symptoms and metabolic dysregulation. An overall age and education standardized cognitive function score was computed. Linear and logistic regression analyses were conducted. For the second study, n=1788 participants had information available on metabolic conditions, cognitive function, and depression. These participants were divided into five groups based on whether they had one of the three conditions: a metabolic risk factor, low cognitive function, a history of depression; if they had none of these conditions, or if they had all three conditions. Logistic regression analyses were conducted and repeated for each metabolic condition, to compare the odds ratios between the five groups.

Analyses in both studies were adjusted for education, age, sex and additional risk factors for dementia and depression.

Results First study: the comorbid group (depressive symptoms and metabolic dysregulation) had the poorest cognitive function compared to the depressive symptoms only group and the metabolic dysregulation only group. Linear regression analyses suggested a linear increase in cognitive function across groups. In the second study, the comorbid group (metabolic risk factors, history of depression, and low cognitive function) had the highest risk of future episodes of depression compared to the groups with one condition only. In both studies, the associations were synergistic.

Conclusion A cross-sectional association between comorbid depressive symptoms and metabolic dysregulation and poor cognitive function was observed. The combined association of depressive symptoms and metabolic dysregulation with poor cognitive function was stronger than additive. In the second study, history of depression was independently associated with greater risk of a depression episode after five years, while individual metabolic risk factors and low cognitive function were not independently associated with risk of depression. When combined, however, depressive history, metabolic risk factors and low cognitive function were associated with an increased risk of depression that was stronger than additive.

Résumé

Contexte La dépression et la démence représentent la première cause de maladie et la principale charge médicale à travers le monde. Ces deux conditions sont associées à un mauvais fonctionnement psychosocial ainsi qu'à une défaillance dans le système de prise en charge d'autres maladies. Il est possible de retarder l'apparition ainsi que la progression de la démence et de la dépression en ciblant les facteurs de risque modifiables, dont plusieurs se déclarent en milieu de vie. Afin de prévenir l'apparition de telles maladies pendant le vieillissement, il est essentiel de chercher à comprendre s'il existe, en milieu de vie, des comorbidités courantes dans la population qui augmentent le risque de dépression et ont un impact négatif sur la fonction cognitive.

Objectifs Le premier objectif était d'examiner l'association transversale entre la comorbidité entre les symptômes dépressifs et la dérégulation métabolique, et le risque d'une fonction cognitive diminuée. Le deuxième objectif était d'examiner l'association temporelle entre les facteurs de risque métaboliques, les antécédents de dépression, la fonction cognitive et le risque d'épisode dépressif cinq ans plus tard.

Méthodes Un sous-échantillon de la cohorte CARTaGENE (CaG), qui a accepté de participer à l'étude de suivi EMHS cinq ans plus tard, a constitué l'échantillon de l'étude. Pour la première étude, n = 1991 avait des informations sur les symptômes dépressifs et la fonction cognitive. Ces participants ont été divisés en quatre groupes en fonction de la présence de symptômes dépressifs et d'une dérégulation métabolique. Un score global de fonction cognitive normalisé selon l'âge et l'éducation a été calculé. Des analyses de régression linéaire et logistique ont été réalisées. Pour la deuxième étude, n = 1788 disposait de données sur les conditions métaboliques, la fonction cognitive et la dépression. Ces participants ont été divisés en cinq groupes selon l'une des trois

conditions: un facteur de risque métabolique, une fonction cognitive faible, et des antécédents dépressif. Une analyse de régression logistique, répétée pour chaque condition métabolique, a été réalisée afin de comparer les rapports de cotes entre les cinq groupes. Les trois domaines cognitifs qui ont été évalués dans les deux études : l'intelligence fluide (IF), le temps de réaction (TR) et la mémoire visuelle (MV). Une fonction cognitive défaillante était définie comme le quartile inférieur de la distribution globale de la fonction cognitive. Les cinq facteurs métaboliques comprenaient l'obésité, l'hypertension, des taux élevés de triglycérides, un faible cholestérol HDL et une glycémie élevée à jeun. Les analyses dans les deux études ont été ajustées en fonction de l'éducation, de l'âge, du sexe et des facteurs de risque supplémentaires de démence et de dépression.

Résultats Le groupe comorbide avec des symptômes dépressifs et un dérèglement métabolique avait la fonction cognitive la plus faible en comparaison du groupe ne possédant que des symptômes dépressifs, ainsi que de celui qui ne présentait qu'une dérégulation métabolique. Les analyses de régression linéaire semblent suggérer une augmentation linéaire de la fonction cognitive entre les groupes. De même, le groupe (facteurs de risque métaboliques, antécédents de dépression et faible fonction cognitive) présentait le risque le plus élevé vis-à-vis de futurs épisodes de dépression en comparaison des deux autres groupes. Dans les deux études, les associations étaient synergiques.

Conclusion Une association transversale entre les symptômes dépressifs , la dérégulation métabolique et le risque d'une fonction cognitive diminuée a été observée. L'association combinée des symptômes dépressifs avec une dérégulation métabolique et une fonction cognitive diminuée était plus forte que la somme des effets individuelle de chacun. De même, les antécédents de dépression étaient associés indépendamment avec le risque accru d'épisodes de

dépression après cinq ans, tandis que les facteurs de risque métaboliques individuels et la faible fonction cognitive ne sont pas directement associés au risque de dépression. Cependant, lorsqu'ils étaient combinés, les antécédents dépressifs, les facteurs de risque métaboliques et la faible fonction cognitive étaient associés à un risque accru de dépression plus fort que l'additif.

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I would like to first acknowledge and thank my supervisor, Dr. Norbert Schmitz, who has truly portrayed qualities of a true leader, an educator and a researcher. When I began working with Dr. Schmitz, I was excited to learn, to be challenged and to be under the mentorship of a renowned researcher. I was not expecting, however, to work with a professor who is truly empathetic, who is always thinking of helping his students grow, and who is someone that makes an effort on, a weekly basis, to keep his students feel encouraged and motivated. I feel eternally grateful to have been able to observe what it means to be a true researcher and have experienced what it means to have an esteemed mentor.

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Preface and contribution of authors

This thesis is composed of seven chapters. Chapter one outlines the rationale and objectives of the thesis. Chapter two is composed of the literature review on depression, metabolic risk factors, and cognitive function. Chapter three is composed of the cross-sectional study (study one), and it includes tables from the manuscript. Chapter four bridges study 1 and 2. Chapter five is composed of the longitudinal study (study two), and it also includes the tables from the manuscript. Chapter six contains the principal findings, the strengths and limitations, the implications of the findings, directions for future research, and concluding remarks. Chapter seven includes the references used throughout the text. This thesis conforms to the guidelines and requirements of a manuscript-based thesis at McGill University.

As the first author of both studies, I (Floriana Ferri) have worked on the development of a hypothesis together with Dr. Norbert Schmitz, my thesis supervisor. We have also worked together on the research design, statistical analysis, data interpretation as well as the drafting and revising of manuscripts for study 1 and 2. Dr. Norbert Schmitz has also helped in terms of interpreting the results, providing critical revisions to both manuscripts, and providing the data from the CARTaGENE study to be used for the analyses. He is a co-author of both manuscripts. Dr. Sonya Deschênes, who is also a co-author of both manuscripts, has provided substantial contributions regarding manuscript preparation and provided critical revisions to both manuscripts. Lastly, Niamh Power (M.Sc.), as co-author of both manuscripts, has contributed to the interpretation of results and provided critical revisions.

List of abbreviations and acronyms

AD	Alzheimer's disease
CaG	CARTaGENE
CIDI	Composite International Diagnostic Interview
EMHS	Emotional Health and Well-being Study
MetD	Metabolic Dysregulation
LDL	Low-Density Lipoprotein
PHQ-9	Patient Health Questionnaire nine-item depression scale
95% CI	95 % Confidence Interval

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Manuscript 1: Association between depressive symptoms, metabolic risk factors, and cognitive function: cross-sectional results from a community study in Quebec, Canada

Manuscript 2: The Association between cognitive function, metabolic risk factors and depression: a prospective community study in Quebec, Canada

Chapter 1: Introduction

1.1 Rationale

According to the latest World Health Organization report on disability, dementia is one of the main causes of disability worldwide[1] and among the most common chronic diseases in older adults [2]. It is estimated that roughly 50 million people are currently living with dementia, and this number is expected to rise with the growth of the aging population around the globe[3]. As there is no cure for dementia, the research focus has shifted towards understanding the modifiable lifestyle factors that are associated with dementia [4]. While dementia is understood as a disease of the elderly, an increasing amount of studies are taking early signs and markers of dementia throughout the lifespan into consideration[5]. Middle-aged individuals of ages 40-69 years old are of particular interest as understanding whether risk factors for dementia start to impact cognitive function earlier in adulthood will have important implications for preventing and treating dementia.

Chronic conditions such as depression and metabolic risk factors such as obesity and hypertension are among the modifiable risk factors that have been associated with an increased risk of dementia [4]. Metabolic risk factors and depression are highly co-occurrent [6] and share inflammatory, endocrine, and neurobiological pathways through which they impact cognitive function [7]. The co-occurrence of two or more chronic conditions has been associated with poorer disease outcomes, reduced health-related quality of life [8], and increased risk of mortality in the elderly [2]. Individuals with comorbid health conditions have complex healthcare needs that are often unmet by current health interventions [2]. It is, therefore,

necessary to examine the associations between depression, metabolic risk factors, and cognitive function in order to better understand how they might impact the onset of dementia.

Depression is the second greatest cause of disability worldwide [9], and metabolic risk factors, especially obesity and hyperglycemia, are also risk factors for depression. Likewise, multiple medical morbidity burden has been previously found to be a risk factor for depression [10].

It has been reported that as many as two-thirds of individuals with depression have some type of cognitive deficit [11-13]. Recent evidence suggests that cognitive impairment is more than a by-product of depression but rather represents a core feature of depression [11]. This hypothesis was supported by two meta-analyses, which concluded that the deficits in cognitive function persist even after remission from depression [11, 14]. Moreover, impaired cognitive functioning has been linked with a poor response to antidepressant treatment [15, 16], which has important clinical implications.

Hence, understanding the association between concurrent metabolic risk factors, depression, and poor cognitive function on depression and dementia is critical.

The data from the Emotional Health and Well-being Study (EMHS) was used to explore the potential cross-sectional and longitudinal associations between metabolic risk factors, depression, and cognitive function. The EMHS study is a follow-up of the CARTaGENE (CaG) study, which was conducted in the period 2009-2010 in Quebec, Canada[17]. CaG had recruited 20 004 middle-aged (40 to 69 years old) participants to provide health, lifestyle and sociodemographic information, physiological measures, and biological samples from four

metropolitan areas of Quebec [18]. Five years after the baseline assessment of the CaG, 2524 participants from baseline CaG were recruited and agreed to participate in the EMHS study during which they provided additional health information and completed a structured diagnostic interview for depression.

1.2 Thesis objectives

The purpose of this thesis was to identify individuals who are at an increased risk for poor cognitive function and depression. The first objective (manuscript 1) was to gain a better understanding of the general association between depressive symptoms, metabolic risk factors, and poor cognitive function in middle-aged individuals, thus we examined the cross-sectional association between these three factors. More specifically, we wanted to determine whether individuals with comorbid metabolic risk factors and depressive symptoms have a poorer cognitive function than those who have either metabolic risk factors or depressive symptoms.

In manuscript two, we wanted to gain a better understanding of the temporal relationship between the three factors. Thus, the objective was to examine whether middle-aged individuals with impaired cognitive function, history of depression, and metabolic risk factors are more likely to experience an episode of major depression after five years in comparison to individuals with only one of the three conditions.

Chapter 2: Review of the literature

2.1 Depression

2.1.1 Definition of depression

Depression is characterized by persistent sadness and a lack of interest in activities/things that were previously found enjoyable[19]. Additional symptoms include irregular sleep or eating habits, fatigue, and poor concentration[19]. Depression tends to have an episodic course; the majority of individuals fully recover from the first episode [20], however, some individuals, begin to experience recurrent episodes and develop chronic depression[20]. Depressive disorders are a major public health concern and are a leading cause of disability worldwide. There is a range of depressive disorder categories, however, major depression, as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) [21], remains the most prevalent type in the general population [22]. According to the stress-vulnerability model, the likelihood of depression is dependent on the interaction between intrinsic vulnerability (heritability) and extrinsic risk factors (live events, chronic conditions, and unhealthy lifestyle) [23]. Thus, the experience of depression can differ in individuals depending on their lifestyle, age, sex, and other risk factors. Late-onset depression (> 55 years), for example, can be less noticeable and more likely to be accompanied by chronic conditions such as cardiovascular disease [24]. Known risk factors for depression include unfavorable lifestyle (smoking, drinking, lack of physical activity), poor physical health (multiple comorbidity burden, chronic diseases, and higher BMI), less education, and loneliness [10, 23].

Depression is associated with a reduced quality of life, impaired functioning and contributes to the development of somatic diseases, such as diabetes, stroke, hypertension, obesity, and dementia [25].

2.1.2 Measuring depression in epidemiology

The gold standard of diagnosing clinical depression in clinical and epidemiological studies is via a structured clinical interview[26]. In population studies, however, it is difficult to conduct clinical interviews as surveys often do not focus exclusively on depression or psychiatric conditions. Moreover, structural clinical interviews are time-consuming and are expensive[26]. Brief measures are often used to reduce costs and respondent burden. A common alternative is the use of depressive symptom rating scales, which can be completed by the respondent and have the advantage of being less time consuming and less expensive [26]. Various instruments have been developed to appraise depression at a population level. One of the most established measures is the Patient Health Questionnaire nine-item depression scale (PHQ-9) [27]. The PHQ-9 is based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [27] and was developed as a screening tool for major depression. It measures depressive symptoms in the last two weeks through nine questions. Response scores are divided into the following categories of increasing severity: 0–4, 5–9, 10–14, 15–19, and 20 or greater, with a maximum score of 27 [28]. A score of 6 is indicative of mild to severe depressive symptoms [28]. The PHQ-9 has excellent internal reliability; two studies have reported Cronbach's α of 0.86-0.89. Similarly, it also has an excellent test-retest reliability; the correlation of the PHQ-9 completed by the patient in the clinic and that completed by a mental health

professional through the telephone was 0.84. Thus, despite its brevity, the PHQ-9 has been shown to be a valid and reliable measure of depression severity [28].

The most widely used instrument in psychiatric epidemiology for depression is the World Mental Health—Composite International Diagnostic Interview (CIDI) 2.1. [29]. CIDI is a structured diagnostic interview designed for use by lay trained interviewers who are not clinicians and its purpose is to generate accurate clinical psychiatric diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [27] criteria [30]. The CIDI has been developed and validated for diagnosing major depressive disorder in the past 12 months and over the lifetime, and also major depressive syndrome (MDS) [31].

The CIDI includes three screening questions (known as STEM) about sadness/depressed mood, feelings of discouragement, and loss of interest lasting several days or longer. Participants who endorse any of the three questions are then given the depression module. The screening questions are there to reduce respondent fatigue and they have been shown to dramatically increase the accuracy of diagnostic assessments.

A moderate concordance has been reported for PHQ-9 and CIDI [31]. This could be explained by the fact that the PHQ-9 focuses on general symptoms of depression and not every question is indicative of depression. While, the CIDI identifies depression and each item is indicative of depression. These differences may explain the disagreement in the outcomes of these two measures [31].

2.1.3 Depression as a risk factor for cognitive decline/dementia

Depression has been associated with cognitive impairment and increased risk of dementia. Most studies have examined late-life (e.g., that occur in those age 60 or older) depression or depressive symptoms and these studies overall support an association between late-life depression and risk of dementia, but there are inconsistencies across these individual studies [32]. Roughly half of the prospective studies have found evidence supporting that late-life depression is associated with a 2 to 5-fold increased risk of dementia. The longest prospective study of 17 years even reported the strongest association, where depression was reported to increase the risk of dementia by 70% [32]. However, these studies were not able to distinguish if depression or depressive symptoms are a prodromal phase of dementia, a consequence of the onset of Alzheimer's disease (AD) or risk factors [32].

Many studies have focused on earlier-life depression as a risk factor for dementia, given the high occurrence of depression in young adulthood and middle age, and the long preclinical period of dementia. Longitudinal studies have reported that earlier-life depression is associated with a 2 to 4-fold increased risk of developing dementia [32]. One prospective study of 24 years reported that depression has a dose-related effect on cognitive impairment where recurrent depressive episodes in middle-age are associated with an increased risk of dementia [33].

Factors such as inflammation, low physical activity, hypertension and smoking have been found to mediate the relationship between depression and cognitive decline in adults over the age of 50 [34]. Another mechanism through which depression might influence cognitive impairment is through beta-amyloid burden [35]. It's unknown how depression leads to the accumulation of

beta-amyloid plaques found in dementia, but studies have found that plasma β-amyloid concentrations in patients with depression are related to cognitive impairment [36]. Other mechanisms include decrease of the brain growth factors that are necessary to maintain synaptic plasticity and overall cognitive function, ischemic damage that causes cognitive deficits, and hippocampal atrophy which may result from increased cortisol levels [32].

2.1.4. Cognitive impairment and risk for depression

The symptomatology and course of depression differ in young versus middle/old aged individuals. Depression in middle/old age is more likely to be related to cerebrovascular changes and be accompanied by cognitive dysfunction (Casey, 2012; Sneed and Culang-Reinlieb, 2011). Cognitive impairment has also been demonstrated to play a role in the prognosis of depression.

Whereas previously cognitive impairment was perceived as a symptom of depression, more recent evidence suggests that cognitive impairment might represent a core feature of depression [33]. This idea that cognitive impairment is more than a symptom of depression was introduced by two meta-analyses, which found that the deficits in cognitive function persist even after remission from depression [14, 33]. Persisting cognitive deficits are thought to contribute to poor quality of life and psychosocial functioning in patients who have recovered from depressive symptoms; this might place these individuals at a higher risk for recurrence or chronicity of depression [33]. Impaired cognitive functioning has also been linked with poor response to antidepressant treatment [15, 16]. Thus, cognitive impairment is clinically relevant and a valuable target for interventions when trying to improve functional outcomes for patients with depression [11].

There are inconsistencies across reported results regarding specific domains of cognitive function affected by depression. A meta-analysis concluded that depression severity was related to cognitive performance in specific domains of cognitive function, including executive function, processing speed, and episodic memory, but not semantic memory, speed, or visuospatial memory [38]. It is necessary to further examine which cognitive domains are involved.

2.2 Metabolic risk factors

2.2.1 Definition of metabolic risk factors and metabolic dysregulation

Metabolic risk factors are a group of conditions that often co-occur and are known to increase the risk of major chronic conditions such as diabetes and cardiovascular disease. These factors are known to share underlying causes, mechanisms, and pathways[34] and are each affected by lifestyle modifications, such as physical activity and smoking [35]. The World Health Organization was the first to tie together the key components of insulin resistance, obesity, dyslipidemia, and hypertension and to define a cluster of metabolic risk factors as metabolic syndrome. There has been some controversy regarding the exact definition of metabolic syndrome [35]. There are five major definitions, but two are most commonly used. The most widely used definition was created in 2001 by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) and defines metabolic syndrome as the presence of *any* three or more of the following five criteria: waist circumference over 40 inches (men) or 35 inches (women), blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl

(men) or 50 mg/dl (women) and fasting blood sugar over 100 mg/dl [36]. In 2005, the International Diabetes Foundation (IDF) published a new definition that requires obesity to be present and two out of the four other factors [37], and this criterion is the second most commonly used.

For this thesis, the term metabolic dysregulation was used to define a cluster of three or more metabolic risk factors, as we had excluded participants with diabetes at baseline in the EMHS study, and the metabolic syndrome tends to be common in individuals with diabetes.

Moreover, impaired glycemic control was measured through hemoglobin A1c (HbA1c) levels, which captures chronic glucose exposure in a period of 2-3 months rather than acute glucose levels [38]. Information on fasting blood glucose levels for the CARTaGENE sample was not available for the full sample. Instead, Hemoglobin A1c levels were used to determine whether participants had elevated blood glucose levels; participants with HbA1c in the range of 5.7-6.5% were considered to have elevated blood glucose levels.

2.2.2 Metabolic risk factors and risk of depression

Chronic somatic diseases such as diabetes and cardiovascular disease (CVD) are associated with the onset of depression and depressive symptoms [39, 40]. Individual metabolic risk factors and metabolic syndrome are known risk factors for diabetes and CVD [41-44], but they are also associated with depression. Metabolic syndrome and depression are highly co-occurrent; the prevalence of metabolic dysregulation among individuals with depression is as high as 48% [6]. In middle-age populations, there is an increased risk of depressive symptom

onset for persons with metabolic syndrome [45, 46]. Metabolic syndrome and depression share inflammatory, endocrine, and neurobiological pathways through which they impact cognitive function [7]. Pathophysiological mechanisms have been linked with both metabolic depression and cognitive impairment, some of which include disturbances in the hypothalamic-pituitary adrenal axis, abnormalities in brain-derived neurotrophic signaling, adipose-derived hormones, insulin signaling, inflammatory cytokines, and oxidative and nitrosative stress pathways [47].

Despite the evidence suggesting that metabolic syndrome is associated with an increased risk of depression, the association between individual metabolic risk factors and depression has not been uniformly robust [46, 48]. For example, large waist circumference was found to predict the *onset* of depression while metabolic syndrome and the rest of the metabolic risk factors were not. Meanwhile, metabolic syndrome was found to predict *chronicity* of depression (unadjusted OR = 3.29; 95% CI, 1.36–7.98), while individual metabolic risk factor components were not [49].

A more recent study found that only low levels of HDL cholesterol and high levels of triglycerides were associated with an 18% to 19% lower probability of having no depression symptoms after five years in participants with depressive symptoms at baseline[50]. There was no association found with elevated glucose levels, abdominal obesity, or hypertension[50]. Meanwhile, obesity is known to be highly co-occurrent with depression, and a bidirectional association between obesity and depression has been confirmed by previous studies [51]. Moreover, obesity in middle-age has been associated with an increased risk of depression after five years in individuals without depression at baseline [52]. Similarly, the relationship between hypertension and depression has been vastly examined, but it is unclear whether hypertension

increases the risk of depression. Two meta-analyses have recently concluded that hypertension is not a risk factor for depression [53, 54]. Lastly, elevated blood glucose levels have been moderately associated with the risk of depression, and the risk seems to gradually increase with the deterioration of glucose metabolism among the non-elderly [55]. Thus, there are still many inconsistencies regarding the role of individual risk factors on depression that should be further examined.

2.2.3 Metabolic risk factors and cognitive function

Metabolic syndrome is one of the main risk factors for dementia [56] and has been associated with reduced cognitive functioning. Of the individual metabolic risk factors, high triglycerides, abdominal obesity, and hypertension were found to be significant risk factors for the progression of cognitive impairment to dementia. While the opposite effect was observed for low HDL cholesterol and elevated blood glucose levels, which were associated with lower rates of dementia [57]. Fewer studies have examined the effect of metabolic risk factors on the cognitive functioning of middle-aged adults, but one study found that in middle-aged adults, hypertension and diabetes mellitus were associated with an increased risk of cognitive decline after six years but not low HDL cholesterol [58].

Individual metabolic risk factors have also been associated with cognitive impairment. Longitudinal studies have consistently found a strong association between hypertension in middle age, cognitive impairment, and dementia, while cross-sectional studies have found mixed results[59]. The Whitehall study was the first to find an association between hypertension and cognitive decline [60]. More recent longitudinal studies have found that individuals with

prolonged hypertension starting in middle-age are at exceptionally high risk for cognitive impairment later in life [61]. A mechanism through which chronic hypertension is thought to reduce cognitive function is by causing vascular restructuring and thereby inducing brain hypoperfusion (reducing blood flow to the brain) [62]. Chronic hypertension can cause vessel stiffness, increased vascular resistance, and disturbed hemodynamic flow patterns, which can cause damage to brain endothelial cells and smooth muscle cells, causing pulsatile pressure changes on the cerebral microvasculature [62].

Obesity has also been associated with cognitive impairment. Obesity in middle-age has been associated with an increased risk of later-life dementia and reduced cognitive performance in middle-age [63]. A review concluded that obese adults show cognitive impairment across almost all cognitive domains; however, it remains unclear through what mechanism obesity reduces cognitive function. One hypothesis is that obesity causes neuroinflammation by causing low-grade inflammation in peripheral tissues and circulation, which spreads from peripheral tissue to the brain and leads to cognitive dysfunction [64]. Moreover, emerging research has implicated the gut-brain axis as playing a critical role in this association. Dysbiosis of the microbiota, which can be a result of a poor diet, is thought to impair cognitive function by either direct inflammatory stimulation, the production of pro-inflammatory metabolites, or the loss of immune-regulatory function [64]. Despite these findings, obesity is known to be highly comorbid with depression, which is strongly associated with cognitive impairment. Thus, it possible that the association between obesity and low cognitive function might be mediated by obesity-related comorbidities such as depression [64, 65].

2.3 Cognitive function

2.3.1. Assessment of cognitive function

Various tools for assessing cognitive function are available. Cognitive assessment tools aim to measure the functioning of different cognitive domains, such as memory/recall, visuospatial awareness, verbal fluency/expressive language, and executive function [66]. However, one of the main limitations in measuring cognitive function/impairment is the lack of robust evidence to support the reliability and validity of the many screening tools available. In population studies, only a few instruments have been validated in the populations for which they are intended to be used in [66]. Moreover, brief cognitive assessments are necessary for population studies, which imposes another impediment in the proper measurement of cognitive function. Computerized cognitive batteries are commonly used to measure cognitive function in population studies. These cognitive batteries often share similarities in that they aim to measure the most common components of cognitive function, including attention, memory, spatial processing, reasoning, and reaction time [67]. Many of these cognitive tests such as the Mini-Mental State Examination, the Dementia Questionnaire, the Minnesota Cognitive Acuity Screen, however, are designed to measure cognitive impairment in the elderly populations and have low accuracy for mild levels of impairment [68]. In the UK Biobank, a large population study following close to 500,000 participants [69, 70], healthy and pathological age-related cognitive changes were measured using a cognitive battery with five domains. It briefly measured baseline visual memory through the Pairs Memory test, processing speed through the Reaction Time test, reasoning through the Fluid Intelligence test, working memory through Numeric Memory Test

and prospective memory through the Prospective Memory Test [71] [72]. The Numeric Memory Test was removed from the baseline testing due to time constraints [69]. Three of the five tests used in the Biobank, the Pairs Memory, the Reaction Time and the Fluid Intelligence were also used in the CARTaGENE study, which is a population study conducted in Quebec, Canada [18]. The Pairs Memory test asked participants to memorize the positions of the seven symbols presented and after removing the symbols, asks them to identify the location of individuals symbols [73]. A higher number of guesses needed to correctly identify all seven locations indicated poorer cognitive function. The Reaction Time test asked participants to press one of two buttons as quickly as possible each time a symbol was presented on the screen. Longer reaction times were indicative of poorer cognitive function. Lastly, the Fluid Intelligence Test is a quiz that participants had to complete in two minutes. It was composed of twelve logic and reasoning questions, such as identifying the largest number in a list or selecting the correct synonym for a given word. A higher score was indicative of better cognitive function. Despite the brief, non-standard nature of the UK Biobank cognitive tests, these tests have shown substantial concurrent validity and test-retest reliability [71].

2.3.2.Cognitive impairment/poor cognitive function

Mild cognitive impairment or simply cognitive impairment is the best term to describe individuals without dementia and impairment in daily living but showing signs of reduced cognitive functioning [74]. Cognitive impairment is more common than dementia and is present in roughly 4% to 19% of people aged 65 years or older, depending on the definition used and how it is interpreted [74]. Around 39% of those diagnosed with mild cognitive impairment in

specialist settings and 22% in population studies, develop dementia over the next 3 to 10 years [75]. While, of the population without mild cognitive impairment at the same age, only 3% develop dementia [76]. It remains unclear, however, when signs of cognitive impairment first begin and whether middle-age adults (ages 40-69 years old) show signs of cognitive impairment that could be targeted to prevent dementia. Targeting cognitive impairment earlier on in adulthood through addressing modifiable risk factors might lead to better outcomes for preventing the progression of cognitive impairment to dementia.

2.3.3. Modifiable risk factors for cognitive impairment and dementia

According to the latest report by the Lancet Commission, smoking, obesity, depression, dyslipidemia, lack of physical activity, hypertension, diabetes mellitus, hearing loss, social isolation, and alcohol use are the key modifiable risk factors for dementia [56]. Moreover, according to the life-course model of risk proposed by the report, targeting or eliminating particular risk factors at specific life stages could reduce future incidences of dementia; for example, increasing education in childhood and eliminating hypertension and obesity in middle-age [56]. In late life, reducing social isolation and depression, while increasing physical activity reduces the risk of dementia [56]. Another model for preventing dementia encompasses increasing cognitive reserve and reducing brain damage and inflammation[56]. Evidence shows that by engaging in cognitively stimulating activities in late life, individuals without dementia, lower their risk of dementia [56]; one mechanism through which cognitive activities delay dementia is by increasing cognitive reserve. Cognitive reserve has been shown to be the mediating factor between higher education levels and reduced risk against dementia[77].

According to the brain reserve hypothesis[78], individuals with higher education levels have greater reserve capacity, and therefore need more pathologic changes to manifest dementia[77].

Chapter 3: Manuscript 1

Association between depressive symptoms, metabolic risk factors, and cognitive function: cross-sectional results from a community study in Quebec, Canada

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Conflict of Interest
The authors have no conflicts of interest to declare.

3.1 Abstract

Objective: To investigate the cross-sectional association between depressive symptoms and metabolic risk factors with cognitive function in a middle-aged population.

Methods: A stratified subsample of the CARTaGENE (CaG) cohort (n=1991) was used to compare cognitive function outcomes between groups. The stratification was based on the presence of depressive symptoms and metabolic dysregulation (MetD): the presence of a) neither condition (reference group); b) MetD only; c) depressive symptoms only; and d) both depressive symptoms and MetD. Individuals with type 2 diabetes were excluded. Three cognitive domains were assessed: processing speed, episodic memory, and executive function. An overall cognitive function score standardized for age and education was computed. Poor cognitive function was defined as the lower quartile of the overall cognitive function distribution. Linear and logistic regression analyses were conducted.

Results: The poorest cognitive performance was observed in the group with both depressive symptoms and MetD, followed by the group with only depressive symptoms, then the group with only MetD and finally, the reference group. Mean (SD) overall cognition scores for the four groups were -0.25 (1.13), -0.13 (1.05), 0.11 (0.90), and 0.15 (0.93), respectively. Linear regression analyses suggested a linear increase in cognitive function across groups.
In the logistic regression analyses, the highest risk of poor cognitive function was observed in the comorbid (depressive symptoms and MetD) group (adjusted OR=1.99, 95% CI 1.46, 2.71).

Conclusion: Comorbidity of depressive symptoms and MetD was associated with reduced cognitive performance in middle-aged adults without diabetes.

Keywords

Depressive symptoms • Metabolic risk factors • Metabolic dysregulation • Cognitive function • Cohort study

Key Points

- Poor cognitive function is a major public health concern and can be potentially prevented by targeting its modifiable risk factors.
- Metabolic dysregulation and depression have both been independently associated with cognitive impairment.
- Comorbidity of metabolic dysregulation and depressive symptoms is associated with an increased risk of poor cognitive function in middle-aged individuals.
- Future health interventions might benefit by screening for comorbidity in patients with poor cognitive function and by targeting depression and metabolic dysregulation together.

3.2 Introduction

Impaired cognitive functioning adversely affects quality of life [79] and is linked to poorer disease outcomes and quality of life [80]. Cognitive deterioration is present in 3% to 19% of adults over the age of 65 years, and more than half of these cases progress to dementia within five years [81]. Dementia is the leading cause of dependence and disability worldwide [82] with an increasing social and economic burden [83]. Studies have reported a decline/stabilization in the incidence of dementia in the past 20 years in both Western and non-Western countries [84, 85]; the decline was observed particularly in individuals born in later birth years compared to earlier birth cohorts [85]. Although it remains unclear what factors account for the decline, prevention and management of vascular risk factors such as stroke, hypertension, hypercholesterolemia, smoking, diabetes, and obesity have been consistently discussed across studies [86]. It has been suggested that up to 35% of the dementia cases are accounted for by modifiable risk factors, several of which have an onset in midlife [56]. This implies the potential to delay the onset/progression of dementia by targeting its modifiable risk factors.

Metabolic dysregulation and depression are two risk factors that have individually been associated with poor cognitive function in the elderly. Depression has been long recognized as a risk factor for cognitive decline in older age [87], with late-onset of depression and recurrent depression being a prodrome for dementia [88]. A recent meta-analysis reported that the pooled relative risk of dementia was 28% higher in individuals with depressive symptoms than in those without [89]. Moreover, depression has been associated with impairment in executive function, memory, and attention [11].

Metabolic risk factors, which in clusters of three or more form metabolic dysregulation (MetD) [90], include high triglycerides, low high-density lipoprotein cholesterol, high blood pressure, abdominal obesity, and impaired glucose regulation (according to the IDF criterion) [35]. MetD has also been associated with cognitive decline and risk for dementia [91, 92]; a recent meta-analysis reported pooled odds ratios of 2.95 for progression from cognitive impairment to dementia in people with MetD [57]. Of the metabolic factors, hyperglycemia is the main contributor to the association between MetD and cognition [92]. However, the complex interaction of MetD and poor cognitive function is still not well understood.

MetD often co-occurs with depression, the prevalence of MetD among individuals with depression can be as high as 48% [6]. This has led to the identification of a subtype of depression, commonly referred to as "metabolic depression" [93]. MetD and depression are thought to share inflammatory, endocrine, and neurobiological pathways through which they might impact cognitive function [7]. Pathophysiological mechanisms have been linked with both metabolic depression and poor cognitive function, some of which include disturbances in the hypothalamic-pituitary-adrenal-axis, abnormalities in brain-derived neurotrophic signalling, adipose-derived hormones, insulin signalling, inflammatory cytokines, and oxidative and nitrosative stress pathways [94].

Previous population studies have found an additive effect of comorbid risk factors on poor cognitive function [69]. Despite frequent comorbidity between MetD and depression, it remains unclear whether this specific comorbidity is associated with poorer cognitive function. To our knowledge, only one study has examined the association between comorbid depressive symptoms and MetD on cognitive impairment [95]. The study, however, did not control for risk

factors associated with poor cognitive function such as smoking and physical activity and had a small sample size (*N*=300). Moreover, cognitive function was measured using the Short Portable Mental Status Questionnaire (SPMSQ), which is a very brief questionnaire that has been shown to have low sensitivity and specificity [96]. Lastly, this study examined cognitive function in an elderly population only.

Although studies examining cognitive function have focused mainly on the elderly population (> 65 years old), some evidence suggests that signs of cognitive decline may be apparent in middle age. For example, the accumulation of cardiometabolic conditions in middle age has been shown to have an additive effect on poor cognitive function [69]. Similarly, the accumulation of multiple vascular risk factors, such as smoking and hypertension, in middle age (40–59 years of age), has shown to substantially increase the risk of dementia [97]. As a result, the aim of present study was to examine the association between comorbid metabolic dysregulation and depressive symptoms and cognitive function in a middle-aged population (40-69 years old) of Quebec, Canada.

3.3 Methods

3.3.1 Design and Participants

The sample was comprised of 1991 participants of the 2009-2010 CARTaGENE (CaG) study (www.cartagene.qc.ca). CaG is a population study that collected detailed health, lifestyle and sociodemographic information, physiological measures and biological samples from 20,004 participants in four metropolitan areas of Quebec, Canada (Montreal, Quebec City, Saguenay, Sherbrooke, Gatineau, and Trois-Rivieres) [18]. Full details on the CaG study have been

published elsewhere [18]. The subsample in this study was composed of participants who were stratified into four groups for another study known as the Emotional Health and Well-being Study (EMHS). The EMHS study has been explained elsewhere [98]. The inclusion criteria for the current study were age between 40-69 years, and availability of information on depressive symptoms, metabolic conditions and cognitive function. A diagnosis of type 2 diabetes was an exclusion criterium. A two-way stratification approach was used to recruit participants into four groups: no depressive symptoms & no MetD, no depressive symptoms & MetD, depressive symptoms & no MetD; and depressive symptoms & MetD (comorbid group).

3.3.2 Measures

Cognitive function

Cognitive function was measured on-site using a computerized touch screen interface. Three tests were administered to measure the following cognitive domains: processing speed, episodic memory, and executive function. The respective tests for each domain were the reaction time test, the paired associates learning test, and the verbal and numerical reasoning test, also known as the fluid intelligence test. All three tests were previously used to assess cognitive function with reasonable reliability in the UK Biobank, a large population study following close to 500,000 participants [69, 70].

For the reaction time (two-choice) test, participants were tasked to press one of two buttons as quickly as possible each time a symbol was presented on either the left or right side of the screen. Sixty presentations were divided into eight response-stimulus-interval groups. The

mean time to correctly identify the left or right location of the symbol was calculated. This test measured reaction speed in milliseconds [73], and longer reaction times were indicative of poorer cognitive functioning. Times over 2000ms were considered an error and removed.

For the paired associates learning task, seven squares were presented on-screen, with each square displaying a different symbol for two seconds. Participants were asked to memorize the positions of the seven symbols to the best of their abilities. The symbols were then removed, and participants were shown one symbol and asked to identify its location in one of the seven squares [73]. The number of guesses needed to correctly identify all seven locations was recorded. The guesses ranged from 7 to 30; guesses over 30 were assigned a value of 30. A higher score suggested more errors made and, therefore, was indicative of poorer cognitive functioning.

The fluid intelligence test was composed of twelve logic and reasoning questions. Each question presented a unique verbal or arithmetic problem, such as identifying the largest number in a list or selecting the correct synonym for a given word. The time limit to complete the test was two minutes. The score was calculated by adding the number of correct answers, with a maximum score of 13. A higher score was indicative of better cognitive functioning. The Cronbach alpha coefficient for these items was previously reported to be 0.62, and the measure previously showed reasonable reliability [69, 70].

Depressive symptoms

Depressive symptoms were measured using the Patient Health Questionnaire (PHQ-9). The questionnaire was made up of nine questions regarding depressive symptoms, each rated from "0" (not at all) to "3" (nearly every day) based on the experience of the last two weeks. Participants were categorized into the depressive symptoms group if their cumulative score on the PHQ-9 was six or higher [98]. A score of six and above out of a maximum score of 27 was indicative of mild to severe depressive symptoms [28]. The PHQ-9 has been previously validated against lifetime mood disorder diagnoses established by the Structured Clinical Interview for DSM-IV [99]; it has also been shown to have good validity and reliability [100].

Metabolic dysregulation

To be classified in the MetD group, participants had to have three or more of the following metabolic risk factors: blood pressure of more than 130/95 Hg/use of anti-hypertensive medication, impaired glycemic control (HbA1c 5.7-6.5%), triglycerides higher than 1.7 mmol l^{-1}, high-density lipoprotein cholesterol of less than 1.03 mmol l^{-1} in men/1.30 mmol l^{-1} in women, and waist circumference of more than 102 cm for men and more than 88 cm for women [98]. This classification was based on the 2005 International Diabetes Foundation definition of metabolic syndrome [35]. The term metabolic dysregulation was used in lieu of metabolic syndrome as participants with diabetes were excluded from the sample, and metabolic syndrome is common in individuals with diabetes. Thus, the term metabolic dysregulation was used as it more clearly defines the clustered metabolic risk factors for this sample.

Covariates

Education was classified into three categories: less than high school, high school, college and above. Ethnicity was classified into white/non-white. Smoking status was assessed by asking participants, “Do you currently smoke?” with a yes/no option. Physical activity was assessed using the International Physical Activity Questionnaire, which has shown to have good test-retest reliability and moderate convergent validity with accelerometers [101]. Participants were asked to report the number of days and the time in hours that they were physically active in the last seven days; physical activities included completing household chores, walking, being active at work, and engaging in exercise and sport. The language was classified into English/French/other.

3.3.3 Statistical Analysis

Linear and logistic regression models were used to assess the associations between the four groups and cognitive function. Scores for reaction time and paired associates learning task were both positively skewed; thus, reaction time scores were transformed using the natural log function and the pairs associates learning scores were transformed using the LN + 1 function. After these adjustments, all outcome variables were normally distributed. All analyses were conducted using SPSS.

A principal component analysis was conducted to combine the scores of the three cognitive measures into one overall cognitive function score (g-score). To do this, the scores for the three measures were standardized (Mean=0 and Std=1) so that lower scores would represent poorer cognitive function and higher scores better cognitive function. A one-factor solution was

obtained (45% explained variance) with similar factor loading (0.69, 0.66 and 0.64 for the Fluid intelligence test, reaction time test, and pairs associates learning test, respectively). The g-score function score was standardized for age and education.

The g-score was used as outcome variable in the linear regression models. To examine whether cognitive function scores for the four groups followed a negative linear trend (from the reference group to the comorbid group), a linear trend analysis was conducted.

Logistic regression models were conducted to compare the odds of poor cognitive function in the four participant groups. The group with no depressive symptoms and no MetD was used as the reference group. Poor cognitive function was categorized as being on the lower quartile of the g-factor distribution.

The fully adjusted models were adjusted for sex, physical activity, smoking status, language and ethnicity and compared to the unadjusted (base) models.

To examine if the association between depressive symptoms and MetD with cognitive function was more than additive, the interaction contrast ratio (ICR) was calculated [102]. ICR was defined using the following equation: ICR =OR (depressive symptoms & MetD) – OR (depressive symptoms & no MetD) - OR (no depressive symptoms & MetD) +1. An ICR greater than zero indicates a synergistic association, such that the interaction effect is greater than the additive effect [103].

In the sensitivity analyses, the regression analyses was repeated with the individual cognitive dimensions as separate outcome variables.

3.4 Results

Of the Of the 2525 EMHS participants, 1991 individuals had complete scores for all three cognitive function tests and formed the analytic sample. The sociodemographic and clinical characteristics of the participants are presented in Table 1. The mean age of the sample was 53.9 (SD= 7.5) years, 56.7% of the participants were female, and 93.5% were of white origin. There were 592 participants in the no depressive symptoms & no MetD (reference) group; 565 participants in the no depressive symptoms & MetD group; 498 participants in the depressive symptoms & no MetD group; and 336 participants in the depressive symptoms & MetD group.

Mean (SD) overall cognition scores for the four groups were 0.15 (0.93), 0.11 (0.90), -0.13 (1.05), and -0.25 (1.13), respectively. Effect sizes for comparing the depressive symptoms & MetD group to the reference group were 0.40 for the g-score, 0.27 for the reaction time test, 0.09 for the pairs associates learning test, and 0.46 for the fluid intelligence test.

Table 2 shows the results from the linear regression analyses in the base and fully adjusted models. The reference group for the study was defined as the group with no depressive symptoms & no MetD, which was hypothesized to be the healthiest group. In both, the base and fully adjusted models, the cognitive scores incrementally declined moving from the healthy group to the comorbid group. The cognitive scores declined significantly for the depressive symptoms & no MetD group and the comorbid group; however, the decrease was not significant for the no depressive symptoms & MetD group.

In the fully adjusted model, in which we controlled for additional risk factors for poor cognitive function, including sex, smoking status, physical activity, language and ethnicity, the association was marginally enhanced. The results of the linear trend analysis were significant, suggesting that there might be a steady decrease of cognitive function scores from the reference group (no depressive symptoms & no MetD) to the comorbid group (depressive symptoms & MetD).

Our sensitivity analyses showed similar results when using the individual cognitive dimensions as separate outcome measures: individuals in the depressive symptoms & MetD group had the lowest cognitive scores. There was a significant linear trend for the fluid intelligence test and the reaction time test.

Table 3 shows the results obtained from the base and fully adjusted logistic regression analyses. The fully adjusted model controlled for age, education, sex, smoking status, physical activity, language and ethnicity. The results indicate that depressive symptoms without MetD (OR=1.57, 95% CI 1.18-2.09) and depressive symptoms with MetD (OR=1.99, 95% CI 1.46-2.71) are both associated with an increased risk of poor cognitive function. Only MetD without depressive symptoms did not show an increased risk of poor cognitive function compared to the reference group (OR=0.78, 95 % CI 0.58-1.05). The odds ratios were marginally enhanced in the fully adjusted model. In both models, the comorbid group (depressive symptoms & MetD) had the highest risk of poor cognitive function.

The relative excess risk due to interaction in the adjusted model was 0.64 (95% CI 0.05-1.22) (ICR = 1.99 – 1.57 – 0.78 + 1 = 0.64). The ICR was greater than zero, suggesting a synergistic effect; this means that the combined effect of depressive symptoms and MetD might be greater than the sum of the individual effects.

3.5 Discussion.

In this study of middle-aged individuals of Quebec, Canada, we evaluated the association of metabolic dysregulation and depressive symptoms on cognitive function. Linear regression analyses suggested that individuals with comorbid depressive symptoms and MetD had the lowest cognitive function score when combining all three cognitive outcomes. According to the logistic regression analyses, individuals with both depressive symptoms and MetD were also at most risk for poor cognitive function. The risk was double that of healthy individuals with neither condition. Moreover, the association might be synergistic, which indicates that comorbid depressive symptoms and MetD might interact with each other in such a way that when in combination, they pose a higher risk of poor cognitive function in middle-aged individuals.

To our knowledge, this is the first study examining the association between MetD and depressive symptoms on cognitive function in a middle-aged population.

A major strength of this study is that our sample was composed of healthier and younger individuals. Studies examining cognitive function tend to focus on the elderly populations, however, examining cognitive function in middle-age is key for understanding dementia. Additionally, we only measured depressive symptoms, and did not specifically select for participants with chronic or severe depression, although chronic depression is more strongly

associated with cognitive impairment [104-106]. Thus, our results suggest that even younger individuals without chronic diseases such as diabetes, who have comorbid metabolic conditions and depressive symptoms are at an increased risk of poor cognitive function. Another strength of the study is that individuals with diabetes at baseline were excluded. Diabetes is one of the main risk factors for dementia [56] and is associated with an increased risk of cognitive disorders [107]. The presence of diabetes might therefore confound the association between metabolic dysregulation and poor cognitive function. Other strengths include the large sample size and the use of reliable measures for depression, metabolic risk factors and cognitive function that have been previously used in large studies [66].

Our study has several limitations. The cross-sectional design of the study does not allow for an examination of a cause-effect relationship between metabolic depression and poor cognitive function. Moreover, our sample consisted of primarily white participants (93.5 %) and MetD varies in prevalence among different ethnicities [108-110], which is why future studies should try to sample from a more ethnically diverse population. Depression was measured using the PHQ-9, which is a self-report scale that measures depressive symptoms in the last two weeks and doesn't take into account the previous history of depression. Although it is a good screening tool for depression, it cannot be substituted for a comprehensive diagnostic instrument for diagnosing clinical depression. Moreover, findings from a review suggest that cross-sectional studies where depression is measured using a self-reported symptom scale report a stronger association between depression and MetD, which could be potentially explained by the inclusion of participants with subsyndromal depression [111]. However, cohort studies suggest otherwise; that participants with MetD are more likely to develop clinically diagnosed depression than self-

reported symptoms [111]. Lifestyle-related behaviors, including smoking and physical activity, were also assessed by self-reported measures, which introduces the risk of reporting bias. Another limitation is that only three cognitive function domains were assessed in the original CaG study and metabolic syndrome have been found to negatively affect additional domains such as verbal memory, learning and language [112, 113], which were not assessed during CaG. Lastly, our hypothesis was unidirectional. Due to the cross-sectional design, our study did not examine the potential role of reverse causality. It is plausible that comorbid poor cognitive function and MetD increase the risk of experiencing a depressive episode.

Analogous conclusions have been reached by previous studies, such as a Taiwanese study, which examined the association between MetD and depression on cognitive impairment in middle-aged individuals and concluded that both conditions are independently associated with cognitive impairment [95]. Depressive symptoms have also been found to mediate the association between metabolic risk factors and poor cognitive function [114]. Other similar studies, which have examined the comorbidity of depression and diabetes on cognitive function, have found that individuals with diabetes and comorbid depression have a more reduced cognitive performance [115]. A recent systematic review reported that the presence of depressive symptoms in people with diabetes is associated with poorer cognitive outcomes [116].

The mechanism through which depressive symptoms and metabolic factors interact to increase the risk of poor cognitive function remains unknown. However, depression is associated with poorer self-care behaviors (such as not following a healthy diet, smoking, lack of physical exercise), which could impede the management of metabolic conditions and increase the risk of cognitive decline [114]. Metabolic dysregulation might also increase the risk of chronic

depression [117], which in turn increases allostatic load, resulting in a potential cognitive decline [118].

Future studies should assess additional cognitive domains, such as attention, language, and verbal memory and report the impact of comorbidity on each cognitive domain independently. Similarly, examining individual metabolic risk factor comorbid with depression might provide us with additional information on which metabolic conditions are more likely to interact with depression to impair cognitive function. Lastly, future studies might examine how the effect of this comorbidity on cognitive function varies across different genders and age groups, in order to understand whether specific age groups are at a higher risk or whether we see differences in cognitive function in males versus females.

Recent findings of population-based studies have shown that up to 44% of patients with mild cognitive impairment return to normal cognitive function a year later [119]. This indicates that there is a potential to target poor cognitive function as a method of preventing dementia. A preliminary study has reported promising results of improving cognitive function through targeting hyperglycemia in patients with comorbidity of depression and diabetes [120]. According to the latest report on dementia by the World Health Organization, lifestyle modifications such as increasing physical activity, cessation of smoking, cognitive interventions, engaging in social activities, management of weight, diabetes mellitus, hypertension, dyslipidemia, and depression are among the main recommendations for preventing cognitive decline associated with dementia [121]. Dementia, in particular, Alzheimer's disease often has a long pre-clinical phase that can last a few years to a decade [122]. By providing evidence that the comorbidity of metabolic dysregulation and depressive symptoms increases the risk of poor

cognitive function much earlier in adulthood, this paper can contribute to the understanding of pathways of the pre-clinical phases of dementia. Future longitudinal studies should examine whether poor cognitive function in middle-aged individuals with metabolic depression is responsive to cognitive interventions in order to better understand the nature of poor cognitive function observed in our study.

Our study provides evidence of an interaction between metabolic depression and poor cognitive function in middle-aged adults. According to our findings and previous research, comorbid depressive symptoms and metabolic dysregulation increase the risk of poor cognitive function. Screening for comorbidity and targeting comorbid conditions together could further mitigate the risk of poor cognitive function. The findings from this study could be applied when promoting and designing dementia-prevention programs. They could also be of use towards the management of treatment-responsive young-onset dementias [123].

3.6 Tables

Table 1 Sociodemographic and clinical characteristics of the cohort stratified by group status

Group	**No depressive symptoms & no MetD** N= 592	**No depressive symptoms & MetD** N= 565	**Depressive symptoms & no MetD** N= 498	**Depressive symptoms & MetD** N= 336
Age, Mean (SD)	53.2 (7.6)	55.5 (7.6)	51.6 (6.7)	54.3 (6.9)
Sex, % Women	 59.8	 47.3	 63.7	 56.5
Education, % Less than high school High school College/Graduate Studies/University	 0.3 12.8 86.9	 0.4 16.3 83.3	 1.0 22.2 76.8	 3.9 30.1 66.0
Metabolic risk factors, % Hypertension Impaired glycaemic control Low high-density lipoprotein cholesterol Elevated triglycerides Central obesity	 13.6 18.7 13.5 12.4 10.5	 41.5 41.4 45.0 45.8 45.4	 13.8 14.9 14.2 12.7 13.4	 31.0 25.0 27.3 29.1 30.7
Depressive symptoms(PHQ-9), Mean (SD)	 1.7 (0.6)	 1.7 (0.6)	 3.4 (0.7)	 3.5 (0.8)
Cognitive function (standardized scores), Mean (SD) Reaction time (ms) Pairs matching Fluid intelligence G score	 507.0 (165.0) 15.8 (5.8) 4.7 (1.7) 0.15 (0.93)	 510.9 (117.5) 15.3 (5.5) 4.5 (1.7) 0.11 (0.90)	 543.9 (199.0) 15.9 (5.9) 4.1 (1.7) -0.13 (1.05)	 552.6 (173.3) 16.3 (6.3) 3.9 (1.8) -0.25 (1.13)

Table 2 Results from linear regression model with overall cognitive score as the dependent variable and the four groups as the independent variables

	Base model			***Fully adjusted*** ‡			***Linear trend***
Group	Beta coefficient†	95% CI	P value	Beta coefficient†	95% CI	P value	Sig.
No depressive symptoms & MetD	0.05	(-0.06, 0.16)	0.37	0.03	(-0.08, 0.15)	<0.63	<0.001
Depressive symptoms & no MetD	-0.29	(-0.41, -0.17)	<0.001	-0.30	(-0.42, -0.18)	<0.001	
Depressive symptoms & MetD	-0.33	(-0.46, -0.19)	<0.001	-0.36	(-0.50, -0.23)	<0.001	

† Beta values reflect the difference vs. healthy controls.

‡: Adjusted for sex, smoking status, physical activity, language, and ethnicity.

Abbreviation: CI, confidence interval.

Table 3 Results from the logistic regression model with overall cognitive score as the dependent variable and the four groups as the independent variables

	Base model			*Fully adjusted*†		
Group	OR	95% CI	P value	OR	95% CI	P value
No depressive symptoms & no MetD	Reference			Reference		
No depressive symptoms & MetD	0.77	(0.58, 1.03)	0.08	0.78	(0.58, 1.05)	0.10
Depressive symptoms & no MetD	1.55	(1.12, 2.03)	<0.001	1.57	(1.18, 2.09)	<0.001
Depressive symptoms & MetD	1.87	(1.39, 2.52)	<0.001	1.99	(1.46, 2.71)	<0.001

† Adjusted for sex, smoking status, physical activity, language and ethnicity

Abbreviation: CI, confidence interval and OR, odds ratio.

Chapter 4: Bridge Connecting Manuscript 1 And 2

The first manuscript cross-sectionally examined the association between comorbid metabolic dysregulation and depressive symptoms on poor cognitive function in middle-aged adults. Thus, the aim was to understand whether individuals with depressive symptoms and metabolic dysregulation comorbidity were more likely to be cognitively impaired in middle-age, which has not been previously examined. The results indicated that this particular comorbidity was associated with poor cognitive function, which was expected as both metabolic dysregulation and depression are independently associated with an increased risk of cognitive impairment. However, this study also found a synergetic association meaning that when metabolic dysregulation and depressive symptoms occur together, they interact with each other to further increase the risk of poor cognitive function.

There were some substantial limitations in the first study that were addressed by the second study. For example, the cross-sectional design, which makes it difficult to infer any type of causality between the comorbid conditions and poor cognitive function. To address that limitation, the association examined in Manuscript 2 used a longitudinal approach to study the temporal relationship between metabolic factors, cognitive function, and depression. Additionally, in study one, only information on depressive symptoms in the last two weeks was available, meaning that the findings might not be generalizable to those with clinical depression. While in study two, depression was assessed using the CIDI interview, which is a fully structured diagnostic interview capable of diagnosing depression according to DSM criteria. Moreover, considering that cognitive impairment usually accompanies depression, it remains unclear what the temporal relationship between depression and poor cognitive function is. The

aim of Manuscript 2 was to address the temporal relationship between depression and cognitive function by examining whether low cognitive function increases the risk of experiencing a depressive episode after five years. Like in study one, low cognitive function was examined in comorbidity with metabolic risk factors and also depression history, to determine whether these three factors have a synergistic effect on the risk of depression. However, metabolic risk factors were individually examined in their association with depression in study two. Lastly, the data used for Manuscript 1 was composed of a stratified sample of the baseline CARTaGENE participants who provided information on depressive symptoms, metabolic conditions and completed cognitive functioning tests. In Manuscript 2, the data from a subsample of the CARTaGENE participants who provided baseline information and then also completed additional assessments by participating in the EMHS follow-up study five years later were used for the analysis.

Chapter 5: Manuscript 2

The Association between Cognitive Function, Metabolic Risk Factors and Depression: a prospective community study in Quebec, Canada

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5.1 Abstract

Background: Metabolic conditions, low cognitive function and history of depression are known risk factors for future depressive episodes. This paper aims to evaluate the potential interactions between these factors on the risk of major depressive episodes in the past-year in middle-aged individuals.

Methods: Baseline and follow-up data from a population-based study of Quebec, Canada were used. The sample consisted of 1788 adults between 40 and 69 years of age without diabetes. Cognitive function and metabolic risk factors were assessed at baseline. Three cognitive domains were assessed: processing speed, episodic memory and executive function. Depression was assessed five years later by a clinical interview. Logistic regression analysis was conducted to evaluate potential interactions between individual metabolic risk factors, low cognitive function, and depression history.

Results: Participants with comorbidity of at least one metabolic factor, history of depression and low cognitive function had the highest risk of experiencing a depressive episode. The highest risk was observed in individuals with abdominal obesity, low cognitive function and a history of depression (OR= 8.66, 95% CI 3.83-19.59). The risks for those with abdominal obesity only, depression history only, and low cognitive function were 1.20 (95% CI 0.71-2.02), 3.10 (95% CI 1.81-5.24), and 1.39 (95% CI 0.72-2.67).

Limitations: Depression was only assessed at follow-up.

Conclusion: Comorbid metabolic conditions and low cognitive function in middle-aged individuals with a history of depression are associated with an increased risk of a future depressive episode. This study highlights the importance of screening for metabolic and cognitive comorbidities in patients with a history of depression.

Key Words: - depression - metabolic risk factors - low cognitive function – comorbidity - middle-age

Highlights

- Metabolic risk factors, cognitive impairment, and depression history are all known risk factors for late-life depression.
- Comorbidity is also a known risk factor for late-life depression.
- The role of comorbidity as a risk factor for mid-life depression has not been widely examined.
- Comorbidity of metabolic factors, low cognitive function, and depression history is associated with an increased risk of depression that is greater than the sum of the individual effects of each of the conditions.

5.2 Introduction

Depression is a chronic disease that is currently the second leading cause of disability worldwide [9]. Individuals with depression are more likely to have a reduced quality of life and to be at an increased risk of developing chronic illnesses such as cardiovascular disease, stroke, and diabetes [25].

Depression is a highly recurrent disorder, where at least 50% of individuals who experience a first episode and recover will experience one or more additional episodes in their lifetime [124]. It has been suggested that depression beginning earlier in life is likely to be recurrent [125, 126], while depression in mid or old age is more likely to be related to cerebrovascular changes and accompanied by cognitive dysfunction [125, 127].

Metabolic risk factors, such as high triglycerides, low high-density lipoprotein cholesterol, high blood pressure, abdominal obesity, and impaired glucose regulation [90] are well-established risk factors for chronic diseases [41-44] and depression. A systematic review by Pan et al. [111] suggested a bidirectional association between depression and the metabolic syndrome.

Studies that have investigated individual metabolic risk factors have reported associations between depression and high blood pressure [128], abdominal obesity [129] low HDL cholesterol level [50, 129], and high triglycerides [50]. Although, it is evident that metabolic syndrome is associated with an increased risk of depression, findings that have examined the association between individual metabolic risk factors and depression have not been uniformly robust [46, 48]. Associations have reported between depression and high blood pressure [128],

depression and abdominal obesity [129], depression and low HDL cholesterol levels [50, 129], and depression and high triglycerides levels [50]. It remains necessary to examine how each individual risk factor interact comorbid with other conditions (such as cognitive impairment and a history of depression) may or may not increase the risk of future episodes of depression.

Cognitive impairment has also been associated with depression. A meta-analysis [11] found moderate cognitive deficits in executive function, memory, and attention in patients with depression relative to controls. Lower cognitive function was associated with an increased risk of major depression in a cohort of 666,804 Danish men [130]. A recent meta-analysis concluded that the association between cognitive impairment and later onset of depression might be confounded by the presence of concurrent depression symptoms at the time of cognitive assessment [131]. Whether cognitive impairment is a risk factor for future depression episodes independently of previous depression history is unclear.

Cognitive function is also associated with metabolic factors. A recent study in middle-aged women found that those with the metabolic syndrome, compared with those without, had a larger 10-year decline in cognitive function after adjustment for sociodemographic characteristics, lifestyle, mood, and menopause factors [132].

Most studies examining cognitive impairment/decline in association with depression or metabolic risk factors have focused on the elderly population (> 65 years old)[133, 134]. More recent evidence suggests that risk factors such as cognitive impairment may be apparent in middle age. For example, the accumulation of cardiometabolic conditions in middle age has been shown to have an additive effect on cognitive impairment [69].

When measuring depression, most previous population studies have used questionnaires and have focused on depressive symptoms in the last weeks rather than depressive episodes assessed by a clinical interview. Therefore, information on depression history is often lacking.

While metabolic factors and poor cognitive function are risk factors for depression, no previous studies have examined those factors simultaneously in middle-aged population-based cohorts.

It is possible that metabolic risk factors and cognitive function share pathways through which they increase the risk of depression in middle-aged individuals, but it is not clear if this is independent of previous depressive episodes.

Hence, the aim of the current study was to examine whether comorbidity of each metabolic risk factor with low cognitive function and depression history is associated with a risk of a major depressive episode in the past year in a community sample of middle-aged adults (40 to 69 years old) and whether this comorbidity poses a synergistic risk for depression.

5.3 Methods

5.3.1 Design and Participants

Data were from the Emotional Well-Being, Metabolic Factors and Health Status (EMHS) study and included 1788 adults between 40 and 69 years without diabetes at baseline. A detailed description of the EMHS study is available elsewhere [17]. In short, the aim of the EMHS study was to examine the role of metabolic abnormalities and depressive symptoms in the onset of

diabetes. Participants in EMHS were recruited from the CARTaGENE (CaG) study (www.cartagene.qc.ca), a community-based cohort in Quebec, Canada (2009-2010; Awadalla et al., 2013). Individuals with and without depressive symptoms and metabolic risk factors were reassessed approximately five years after CaG baseline. Individuals with depressive symptoms and metabolic factors were oversampled[17].

3.3.2 Measures

Cognitive function

Cognitive function was measured on-site during the CARTaGENE baseline assessments using a computerized touch screen interface. Participants completed three tests on the following cognitive domains: processing speed, episodic memory, and executive function. The respective measures for each domain were the Reaction Time test, the Paired Associates Learning Test, and the Verbal and Numerical Reasoning Test, also known as the Fluid Intelligence test. This cognitive battery was previously used to assess cognitive function for the UK Biobank, a large population study following close to 500,000 participants; the individual tests showed reasonable reliability in the UK Biobank studies [69, 70].

The reaction time test measures reaction speed in milliseconds [73]. Participants are shown a symbol on either the left or the right side of the screen and are asked to press the respective buttons (left or right) as soon as possible. Sixty presentations were divided into eight response-stimulus-interval groups. The mean time to correctly identify the location of the symbol

was calculated. Times over 2000ms were considered an error [73] and were removed. Longer reaction times were indicative of poorer cognitive functioning.

For the Paired Associates Learning Test, participants were asked to memorize the positions of seven symbols presented on the screen. The symbols were then removed. Then one symbol at a time was shown, and participants had to identify the location of it in one of the seven squares [73]. The number of guesses required to correctly identify all seven locations was recorded. The guesses ranged from 7 to 30; guesses over 30 were assigned a value of 30. A higher score was indicative of more errors made and, therefore, poorer cognitive functioning.

The Fluid Intelligence test was composed of twelve logic and reasoning questions. Each question presented a unique verbal or arithmetic problem, such as identifying the largest number in a list or selecting the correct synonym for a given word. Participants had two minutes to complete the test. The number of correct answers was used to calculate the score, with the maximum score being 13. A higher score was indicative of better cognitive functioning.

A principal component analysis was conducted in order to combine the scores of the three cognitive measures into one overall cognitive function score (G-Score). The scores for the three measures were standardized (Mean=0 and Std=1) so that lower scores would represent poorer cognitive function and higher scores better cognitive function. The overall cognitive function score was standardized for age and education. Low cognitive function categorized as being on the upper quartile of the g-factor distribution.

Metabolic risk factors

Measures of blood pressure, high-density lipoprotein (HDL) cholesterol, triglycerides, waist circumference, and hemoglobin A1c levels were measured on-site during the baseline CARTaGENE assessment. Patients with a blood pressure of more than 130/95 Hg/use or of anti-hypertensive medication were categorized as having high blood pressure. Male participants with HDL cholesterol levels of less than 1.03 mmol l^{-1} and female participants with HDL cholesterol levels of less than 1.30 mmol l^{-1} were considered to have low HDL cholesterol. Participants with HbA1c levels of 5.7- 6.5% were categorized as having high blood glucose levels. Those with triglyceride levels higher than 1.7 mmol l^{-1} were categorized as having high triglyceride levels. Lastly, males with a waist circumference of more than 102 cm and females with a circumference of more than 88 cm were categorized as having high central obesity [135].

Depression History

Diagnostic assessments of recent (previous 12 months) and lifetime major depression disorder (MDD) were conducted at follow-up using the computerized World Mental Health—Composite International Diagnostic Interview (CIDI) 2.1 [30], a standardized instrument for the assessment of mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [27] criteria. The CIDI is a fully structured diagnostic interview that can be administered by lay-interviewers. The lifetime version of the CIDI collects information on age at the most recent depressive episode and age at the first onset. Participants with an onset of depression before the CAG baseline assessment were categorized as having a

history of depression. A recent depressive episode in the previous 12 months before the follow-assessment was considered as the main outcome variable.

Covariates

We considered several covariates that might affect the association between cognitive function, metabolic risk factors, and depression, including age [136], education, physical activity, living alone, and smoking status are also risk factors for depression and cognitive impairment [137, 138]. Education was classified into two categories: less than high school/more than high school. Similarly, living alone was classified into the two following categories: living alone versus living with somebody. Physical activity was assessed using the International Physical Activity Questionnaire, which has shown to have good test-retest reliability and moderate convergent validity with accelerometers [101]. Participants were asked to report the number of days and the time in hours that they were physically active in the last seven days; physical activities included completing household chores, walking, being active at work, and engaging in exercise and sport. Participants were divided into three levels of physical activity. High: vigorous activity for 3 days/ at least 1500 MET-minutes per week or 7 days of combination activities including walking and vigorous activity/ at least 3000 MET-minutes per week. Moderate: 3 days of vigorous activity for 20 minutes/day or 5 days of moderate activity for 30 minutes/day or 5 days of combination activities for at least 1500 MET-minutes per week. Low: participants that did not meet the criteria for high or moderate activity levels [139].

Smoking status was assessed by asking participants, ‘Do you currently smoke?’ with a yes/no option.

5.3.3 Statistical Analysis

Logistic regression models were used to assess the interaction between cognitive function, depression history, and each individual metabolic risk factor at baseline and risk of a major depressive episode in the past year. Separate models were considered for the five metabolic risk factors. The models were adjusted for age, education, sex, physical activity, smoking status, and living status. Dummy variables were created to evaluate potential interactions between low cognitive function, depression history and individual metabolic factors. Individuals with normal to high cognitive function, no depression history, and no metabolic risk factor were considered as the reference group for each metabolic risk factor.

To examine if the associations between depression history, low cognitive function and each metabolic risk factor with risk of a major depressive episode in the last year were more than additive, the RERI (relative excess rate due to interaction) index was computed was for each metabolic condition [140]. RERI is an index for interaction on the additive scale and was calculated using the following equation: RERI =OR(depressive history, low cognitive function, metabolic factor) - OR(depressive history) – OR (low cognitive function) – OR(metabolic factor) +2. The 95% confidence intervals were obtained by a bootstrap approach in which odds ratios were calculated from each of 2000 bootstrap samples. A RERI greater than zero indicates a more than additive (i.e., synergistic) interaction [103]. All analyses were conducted using SPSS.

5.4 Results

Table 1 provides characteristics of the individuals stratified by each of the five metabolic factors. Individuals with all three conditions (low cognitive function, depression history, and metabolic factor) were slightly older than those without any of the three conditions. The proportion of women was also higher for those with all three conditions compared to those without any condition.

Table 2 shows the results of the adjusted logistic regression analysis. Individuals with a metabolic risk factor but without depression history were not at higher risk for a depression episode in the past year than those in the reference group (none of the three risk factors). This was true for all five metabolic conditions. A similar association was observed for cognitive function: individuals with low cognitive function but without depression history were not at a higher risk for a depressive episode in the past year than those in the reference group.

A potential interaction between the three risk factors was observed for three metabolic conditions (obesity, hypertension, and high triglyceride levels): individuals with all three risk factors (metabolic condition, low cognitive function, and depression history) had a higher risk for a depressive episode in the past year than individuals with only one or two conditions. For example, the odds ratio for a depressive episode for individuals who were obese had low cognitive function, and had a depression history was 8.66 (95% CI 3.83, 19.59) while the odds ratio for obesity only, low cognitive function only, and depression history only were 1.20 (95% CI 0.71, 2.02), 1.39 (95% CI 0.72, 2.67), and 3.10 (95% CI 1.81, 5.24), respectively. RERI coefficients for obesity, hypertension, and high triglyceride levels were 3.92 (95% CI 0.05, 9.80),

2.35 (95% CI 0.35, 5.03), and 2.20 (95% CI 0.02, 5.02), respectively, suggesting a potential synergistic effect.

The association was less clear for HDL cholesterol and elevated HbA1c levels. Individuals with all three conditions were at high risk for a major depressive episode, but the odds ratios were slightly smaller than those for individuals without the metabolic factor but low cognitive function and depression history. RERI coefficients for HDL cholesterol and elevated HbA1c levels were 1.77 (95% CI -0.02, 4.33) and 1.14 (95% CI -0.60, 3.66), respectively.

5.5 Discussion

In this longitudinal study, we evaluated the impact of metabolic risk factors, depression history and low cognitive function on the risk of a major depressive episode in the past year in middle-aged adults of Quebec, Canada. Our findings suggest that individuals with any of the five metabolic conditions and poor cognitive function are only at risk for a major depressive episode if they have a history of depression. For those with a depression history, we found a synergistic interaction between metabolic risk factors, low cognitive function, and depression history, suggesting that the combined risk of these factors is greater than the addition of their individual risks. To our knowledge, this is the first study examining the association between these three factors in a middle-aged population. Our findings are in line with the evidence that an increased number of comorbidities is one of the main predictors of depressive mood in the elderly [141].

There might be several explanations why the co-existence of several risk factors increases the risk of depression: metabolic risk factors, depression, and cognitive impairment are known to

share pathophysiological mechanisms, some of which include disturbances in the hypothalamic-pituitary adrenal axis, abnormalities in brain-derived neurotrophic signaling, adipose-derived hormones, insulin signaling, inflammatory cytokines, and oxidative and nitrosative stress pathways [47]. Depression history, low cognitive function, and metabolic risk factors might stimulate each other's occurrence, which can in turn result in an increased risk of future depressive episodes.

There might also be behavioral pathways that could potentially explain the increased risk of depression in individuals with metabolic risk factors and low cognitive function. For example, the management of metabolic conditions like obesity includes increasing physical activity and changing one's diet. Depression has been shown to adversely impact these self-care behaviors [142] and is associated with poor adherence to medication [143], which might worsen the management of metabolic factors and also increase the risk of future depressive episode.

Cognitive reserve, commonly defined as the capacity to switch between cognitive strategies, might also play a role in the association between the three risk factors and the onset of depression. There is evidence that people with depression have lower levels of cognitive reserve [144]. Low levels of cognitive reserve might also be associated with unhealthy lifestyle-related behaviors and management of metabolic conditions, which in turn might increase the risk of future depressive episodes.

We did not find a synergistic interaction between elevated blood glucose levels, cognitive function, and history of depression. The lack of association may be explained by the fact that individuals with diabetes at baseline were excluded from the study. The group with obesity as the

metabolic condition had the strongest association with the risk of depression. A strong association between depression and obesity has been previously established [145], and some evidence even suggests that of the metabolic factors, obesity is most strongly associated with depression [146]. Further investigation is necessary to understand the role of each individual risk factor comorbid with depression history and low cognitive function.

The main strengths of the study are the prospective design, the availability of metabolic factors and cognitive function at baseline, and the clinical interview for the assessment of depression at follow-up. The CIDI is a comprehensive, fully structured diagnostic interview, which allows for its administration by both clinicians and non-clinicians, and is capable of providing lifetime and current diagnostic assessments [147].

We acknowledge several study limitations. Information on cognitive function was not available for all participants in EMHS. Our sample consisted of primarily white participants (93.5 %), and evidence suggests that metabolic risk factors can vary across ethnicities [108-110]. Individuals with diabetes were not included, although diabetes is strongly associated with the risk of depression, so that could explain some of the weaker associations observed for elevated blood glucose group. Another limitation is that the CIDI interview was only conducted at one-time point thus, it remains unknown how this comorbidity impacts depression over time.

Furthermore, participants recruited for the CaG study were likely healthier than the overall cohort due to restrictions placed upon eligibility for blood assessments. Finally, as in all observational studies, there could be unmeasured confounding by unknown or unmeasured

predictors. For example, treatment of depression was not measured nor considered in the analyses were could have impacted the results.

In conclusion, we found that comorbidity of metabolic risk factors, depression history, and low cognitive function increases the risk of experiencing a depressive episode five years later in middle-aged adults. Although depressive history is a strong predictor of future depressive episodes, our findings show when comorbid with metabolic conditions, especially obesity, and low cognitive function, the risk of depression more than doubles. Our findings reveal a need for addressing comorbid conditions when treating depression, especially obesity and low cognitive function. Remediation of impaired cognitive function and metabolic conditions may play an important role in improving the outcome for middle-age patients with depression.

Author Statement Contributors

NS, SD and FF contributed to the design of the study, revision and analysis. FF drafted the initial version of the manuscript. All authors reviewed and approved the final version of the study.

Role of the Funding Source

None.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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5.6 Tables

Table 1 Baseline characteristics of the participants in the five groups, divided by each of the five metabolic conditions.

	Groups stratified by Metabolic Condition														
	Obesity					Hypertension					High Triglycerides				
GROUPS	***Ref***	***1. M***	***2. C***	***3. D***	***4. A***	***Ref***	***1. M***	***2. C***	***3. D***	***4. A***	***Ref***	***1. M***	***2. C***	***3. D***	***4. A***
Age, mean (SD)	53.0 (7.5)	54.6 (7.5)	53.1 (7.5)	52.8 (7.0)	54.9 (7.3)	51.8 (7.2)	55.9 (7.3)	52.9 (7.3)	52.8 (7.0)	55.7 (6.6)	53.2 (7.4)	54.3 (7.7)	53.7 (7.7)	51.8 (7.1)	55.7 (6.6)
Sex, female%	50.2	53.5	53.7	57.5	76.5	61.5	40.4	68.5	57.9	66.0	60.8	40.8	70.4	73.7	66.0
Education, %															
< high school	0.5	1.1	1.1	1.6	7.1	0.7	0.9	1.1	1.6	5.7	0.6	1.1	1.9	0.6	5.7
>= high school	99.5	98.9	98.9	98.4	92.9	99.3	99.1	98.9	98.4	94.3	99.4	98.9	98.1	99.4	94.3
Living alone, %	19.6	21.5	25.9	31.9	30.3	19.7	21.9	25.5	31.1	35.7	22.8	18.5	26.2	28.2	35.7
Physical Activity, low %	13.2	21.2	16.0	11.2	25	18.5	14.9	19.2	11.2	23.5	17.4	16.0	17.0	11.6	17.2
(Daily) Smoker %	12.4	8.8	12.0	18.8	9.5	11.0	8.1	12.9	18.7	17.0	9.1	10.6	8.8	19.3	17.0
	Low HDL Cholesterol					High Fasting Blood Glucose									
GROUPS	***Ref***	***1. M***	***2. C***	***3. D***	***4. A***	***Ref***	***1. M***	***2. C***	***3. D***	***4. A***					
Age, mean (SD)	53.7 (7.4)	53.7 (7.7)	54.6 (7.7)	52.8 (7.1)	55.7 (7.4)	52.4 (7.5)	55.4 (7.3)	52.6 (7.6)	51.8 (6.8)	54.7 (6.6)					
Sex, female %	55.0	47.4	61.9	66.3	66.0	49.4	54.3	55.9	65.7	73.3					
Education, %															
< high school	0.4	1.2	2.4	1.7	5.7	0.7	1.0	1.7	0.5	4.4					
>= high school	99.6	98.8	97.6	98.3	94.3	99.3	99.0	98.3	99.5	95.6					
Living alone,%	21.0	20.5	24.1	29.1	35.7	20.4	21.7	24.0	30.3	30.6					
Physical activity, low %	17.2	17.6	15.6	15.0	23.5	15.5	18.8	17.6	17.4	9.5					
Daily Smoker %	8.5	11.1	9.5	14.3	17.0	8.4	11.8	13.0	16.9	15.6					

† Ref represents the reference group without the specified metabolic condition, normal cognitive function and no history of depression 1.M represents the metabolic risk factor only group without a history of depression and normal cognitive function (these participants could have additional metabolic risk factors other than the specified factor), 2.C represents the low cognitive function only group, 3.D represents the depression history only group, and 4.A the comorbid/all three conditions group.

Table 2 Results from the logistic regression model where the dependent variable is the presence of depression in the last year and the four groups are the independent variables (reference group is also included as a comparison).

Obesity	**Low cognitive function**	**Depression history**	**No Depression (N)**	**Depression (N)**	**OR (95% CI)[a]**
No	No	No	518	38	Reference
Yes	No	No	407	36	**1.20 (0.71, 2.02)**
No	**Yes**	No	156	19	**1.39 (0.72, 2.67)**
No	No	**Yes**	146	40	**3.10 (1.81, 5.24)**
Yes	Yes	No	126	15	1.22 (0.57, 2.60)
Yes	No	Yes	119	38	3.02 (1.71, 5.35)
No	Yes	Yes	51	18	3.13 (1.43, 6.84)
Yes	**Yes**	**Yes**	26	16	**8.66 (3.83,19.59)**
Hypertension	Low cognitive function	Depression history	No Depression (N)	Depression (N)	OR (95% CI)
No	No	No	483	54	Reference
Yes	No	No	448	20	**0.47 (0.26, 0.84)**
No	**Yes**	No	159	19	**0.93 (0.50, 1.70)**
No	No	**Yes**	166	46	**1.97 (1.22, 3.20)**
Yes	Yes	No	128	15	0.92 (0.44, 1.92)
Yes	No	Yes	106	33	2.46 (1.41, 4.31)
No	Yes	Yes	40	18	2.97 (1.36, 6.46)
Yes	**Yes**	**Yes**	37	16	**3.96 (1.87, 8.34)**
High Triglycerides	Low cognitive function	Depression history	No Depression (N)	Depression (N)	OR (95% CI)
No	No	No	477	39	Reference
Yes	No	No	439	34	**0.88 (0.52, 1.50)**
No	**Yes**	No	145	14	**0.69 (0.31, 1.54)**
No	No	**Yes**	127	44	**2.96 (1.75, 5.01)**
Yes	Yes	No	139	19	1.56 (0.82, 2.96)
Yes	No	Yes	145	35	2.33 (1.35, 4.04)
No	Yes	Yes	39	16	3.70 (1.66, 8.28)
Yes	**Yes**	**Yes**	37	18	**4.89 (2.29,10.54)**
Low HDL Cholesterol	Low cognitive function	Depression history	No Depression (N)	Depression (N)	OR (95% CI)
No	No	No	468	36	Reference
Yes	No	No	450	37	**0.97 (0.58, 1.63)**
No	**Yes**	No	153	15	**0.77 (0.35, 1.67)**
No	No	**Yes**	140	35	**2.56 (1.47, 4.45)**
Yes	Yes	No	131	18	1.63 (0.84, 3.17)
Yes	No	Yes	132	44	2.95 (1.71, 5.09)
No	Yes	Yes	38	20	5.07 (2.34 10.99)
Yes	**Yes**	**Yes**	38	14	**3.94 (1.77, 8.80)**
Elevated Blood Glucose	Low cognitive function	Depression history	No Depression (N)	Depression (N)	OR (95% CI)
No	No	No	526	45	Reference
Yes	No	No	388	28	**0.83 (0.48, 1.43)**
No	**Yes**	No	157	20	**1.22 (0.66, 2.29)**
No	No	**Yes**	169	44	**2.41 (1.46, 3.98)**
Yes	Yes	No	127	13	0.88 (0.39, 1.97)

Yes	No	Yes	101	35	2.93 (1.67, 5.16)
No	Yes	Yes	45	19	4.73 (2.28, 9.81)
Yes	**Yes**	**Yes**	141	31	**3.28 (1.39, 7.73)**

† Odds ratio values reflect the difference in odds ratio of group vs. the reference group (none of the three conditions present).

‡ CI, confidence interval and OR, odds ratio. OR is adjusted for sex, education, smoking status, physical activity, and living status.

Chapter 6: Discussion

6.1 Restatement of objectives

Dementia and depression are leading causes of disability worldwide and have significant impacts on public health [1]. There is strong evidence suggesting an association between cognitive impairment and depression [148], which may be bidirectional. Persisting cognitive deficits in patients who have recovered from a first depressive episode are associated with poor response to antidepressant treatment [15, 16] and an increased risk of recurrence/chronicity of depression [33]. Depression, on the other hand, is known to cause vascular, inflammatory, and neurotrophic changes in the brain [32] that may increase the risk of cognitive impairment and dementia.

The pre-clinical stages of dementia have been found to begin a decade prior to the manifestation of memory impairments, and existing approaches might be intervening too late[149]; given that depression and cognitive impairment share similar risk factors, such as metabolic risk factors, it is important to examine whether comorbidity of metabolic risk factors, depression, and low cognitive function increases the risk of future episodes of depression or cognitive impairment. In particular, understanding whether comorbidities place certain individuals at higher risk for depression and cognitive decline in middle-age, prior to the development of dementia, is important for preventing dementia.

The purpose of this thesis was to help identify individuals who are at an increased risk for poor cognitive function and depression in middle-age. The first objective was to compare the risk of poor cognitive function in individuals with comorbid depressive symptoms and metabolic dysregulation compared to those with one of the conditions only. The second objective was to

examine whether comorbid low cognitive function and metabolic risk factors increase the five-year risk of experiencing a depressive episode and whether they do so independently of depressive history or not.

The focus was on the middle-age population as the aim is to identify those at risk as early as possible in order to intervene prior to the development of chronic depression or dementia.

6.2 Summary of findings

In Manuscript 1, our findings indicate that there is an association between comorbid depressive symptoms and metabolic dysregulation and poor cognitive function in middle-aged individuals (40-69 years old). Individuals with comorbid depressive symptoms and metabolic dysregulation showed the poorest performance on all three cognitive outcomes, and they were also at the highest risk for poor cognitive function. The risk in the comorbid group was double that of the reference group with neither condition indicating a synergistic association; this means that comorbid depressive symptoms and metabolic dysregulation interact with each other in such a way that when in combination, they pose a greater risk of poor cognitive function in middle-aged individuals.

In Manuscript 2, we demonstrated that middle-aged individuals with co-occurring metabolic risk factors, low cognitive function, and depression history had the highest risk of experiencing a depressive episode five years later in comparison to individuals with only one of three conditions. Moreover, we found that low cognitive function and metabolic risk factors are not associated with an increased risk of future depressive episodes independently of depression

history. When in combination with metabolic risk factors, especially obesity, and low cognitive function, however, the risk of a depressive episode is more than double of that of depression history, indicating that depression history, metabolic risk factors, and low cognitive function interact with one another to further increase the risk of future depressive episodes.

Overall, the two studies demonstrated that low cognitive function, depression, and metabolic risk factors interact with one another to increase the risk of both future depressive episodes and poor cognitive function.

6.3 Strengths and limitations

The strength of this thesis is that we found associations between comorbid conditions and depression/poor cognitive function in middle-aged individuals; these associations remained even after controlling for established risk factors for depression and cognitive impairment.

A strength of Manuscript 1 is that the fact that we examined the risk of poor cognitive function in individuals who are at risk but have not yet developed a chronic disease such as diabetes, which is a strong risk factor for dementia. Thus, the fact that we found an association means that even healthier individuals may be at risk for poor cognitive function in middle-age if they have co-occurring metabolic conditions and depressive symptoms.

A strength of Manuscript 2 is that the association between low cognitive function and depression was examined longitudinally, making it possible to observe the trajectory of the effect of low cognitive function on depression. In Manuscript 2, we also had a comprehensive measure of depression (the CIDI), rather than just information on depressive symptoms, which makes it possible to generalize the results to the clinical population.

A limitation of Manuscript 1 is the lack of longitudinal data. We were unable to make causal inferences about the role of comorbid depressive symptoms and metabolic dysregulation on cognitive function. Additionally, in Manuscript 1, we only had information on self-reported depressive symptoms, which do not allow us to make conclusions about the impact of clinical depression on cognitive function.

Limitations for Manuscript 2 include the fact that the CIDI interview was assessed at one time only, there may be recall bias for depression history, the sample sizes for the individual groups (all three conditions) were small, and metabolic factors and cognition were not assessed at the five-year follow-up.

In both manuscripts, the sample was composed of primarily ethnically white and healthier participants, as they were recruited from the metropolitan areas of Quebec and had to meet specific health requirements in order to participate in the study, such as not having cognitive or physical impairments. This introduced the risk of selection bias and could reduce the external validity of both studies. Lastly, there were a limited number of cognitive tasks measured in the two studies as only three cognitive domains were measured during the baseline at CARTaGENE. Thus, it remains unknown how these specified comorbidities impact other cognitive function domains not measured in the CaG. Additionally, in both manuscripts, there were missing data either on cognitive function and/or depression thereby reducing the overall sample size for the two manuscripts from the EMHS final sample, however, no differences were found between participants in the EMHS sample and the final samples for both studies (see appendix 1).

6.4 Implications of findings

Considering that comorbidity in old age has been associated with increased disability and mortality, reduced quality of life, and increased health care costs [2], our findings provide evidence that comorbidity has consequences even in middle-age and therefore, should be addressed as early as possible in order to avoid deficits in functioning in late adulthood. Specifically, patients at risk for dementia or showing signs of poor cognitive function in middle age should be simultaneously screened for depressive symptoms, and metabolic risk factors as a comorbidity of these two conditions might lead to a faster deterioration of their cognitive functioning. Similarly, patients with a history of depression should be screened for metabolic conditions and impaired cognitive functioning, factors which might increase their risk of experiencing future episodes of depression.

6.5 Future directions

Future studies should aim to understand the mechanism through which comorbid metabolic risk factors and depressive symptoms/low cognitive function interact with one another to increase the risk of chronic depression and dementia. More prospective studies are necessary to determine the causal relationships between depression, metabolic risk factors, and low cognitive functioning and to measure the deterioration of cognitive function over time, and not only at a one-time point.

Furthermore, considering that in Manuscript 2, we found differences between the effect of individual metabolic risk factors on risk of depression, future studies should further examine the effect of each metabolic factor rather than just focusing on metabolic syndrome. By

examining each metabolic risk factor individually, we might be able to further understand why some metabolic conditions, such as obesity, are more likely to interact with depression history and low cognitive function to increase the risk of future episodes of depression. Similarly, for Manuscript 1, it would be beneficial to examine the impact of each individual metabolic condition comorbid with depressive symptoms on cognitive functioning in order to determine whether specific metabolic risk factors are more likely to interact with depression to impair cognitive function. For example, hypertension is known as one of the main risk factors for dementia [56], while elevated blood glucose levels below the threshold for diabetes, might not necessarily be as harmful to cognitive functioning.

Moreover, cognitive impairment or low cognitive function observed in depression has been associated with poor response to treatment [11]. Likewise, individuals with depression are also less likely to adhere to their antihypertensive medication and oral hypoglycemic medication [150, 151]. Future studies should examine whether poor cognitive function/depression with other comorbidities, such as metabolic risk factors and depression history further reduces the response to treatment.

Future studies could also explore the idea of cognitive reserve and whether increasing cognitive reserve could modulate the association between neurodegeneration and depression in patients with cognitive impairment [152]. In patients who have experienced a depressive episode, cognitive function was predictive of depression severity at baseline and at follow-up; younger individuals with higher education levels had better cognitive functioning (more cognitive reserve) and therefore, were less likely to experience depressive episodes [153].

6.6 Conclusion

In conclusion, comorbid metabolic risk factors and depressive symptoms are associated with an increased risk of poor cognitive function, while comorbidity of low cognitive function and metabolic risk factors increases the risk of future episodes of depression but only in individuals with a history of depression. Therefore, our findings provide evidence that remediation of metabolic conditions comorbid with impaired cognitive functioning /depressive symptoms may play an important role in improving outcomes for patients with depression and cognitive impairment.

Chapter 7: References

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Appendix

Appendix I: Supplemental table (manuscript 2)

Comparison of the demographics of the final EMHS sample and the final sample of manuscript 2 (differences due to missing data on cognitive function and depression).

	Final Sample Manuscript 2 N=1788	**Final EMHS Sample N=2525**
Age, mean (SD)	53.6 (7.4)	53.9 (7.5)
Sex, female %	57.3	56.7
Education, % < high school % >= high school	 1.1 99.9	 1.1 99.9
Smoking status, never **%**	42.3	41.4
Physical activity, high %	43.2	42.0
Living alone, yes %	24.0	24.9
Hypertension, yes %	44.9	45.4
High fasting blood glucose, yes%	41.8	42.4
Obesity, yes %	44.3	44.8
Low HDL cholesterol, yes %	48.8	49.1
High triglycerides levels, yes %	49.0	49.4