Evaluating the associations of cardio-metabolic conditions and depression with cognitive decline: Longitudinal analysis of the Health and Retirement Study

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Abstract

Objective: Recent studies have shown strong associations between cardiovascular conditions and dementia. However, little is known on when changes in cognitive function begin. There is some evidence that cognitive decline for people with chronic somatic conditions might start in mid-life, but evidence from large longitudinal community-based studies with long follow-up data is still lacking. The role of mental conditions like depression is also not clear. For example, individuals with depression and diabetes have a higher risk for dementia than individuals with either depression or diabetes alone, but it is not clear if the comorbidity of depression with diabetes is associated with accelerated cognitive decline in the middle age. The aims of this thesis were:

a) to examine longitudinal cognitive function trajectories associated with the presence of cardio-metabolic conditions in middle-aged adults using data from the longitudinal US Health and Retirement Study (HRS).

b) to evaluate if elevated depressive symptoms and diabetes were associated with accelerate worse cognitive function trajectories in middle-aged adults in the HRS.

Methods: HRS is a prospective cohort study with a nationally representative sample of US adults 50 years and older. We included individuals who participated in HRS in 2002 with follow-up until 2016. For the first study, participants between ages 50-65 in 2002 with a minimum of two follow-up assessments and information about baseline cardio-metabolic conditions were included (n=5011). Cognitive function was assessed using a modified Telephone Interview for Cognitive Status (TICS-M) scored out of 27 points. Cognitive function trajectories were modelled for different numbers of cardio-metabolic conditions (heart disease, hypertension, diabetes and stroke). Linear mixed effects modelling was used to estimate the mean longitudinal trajectory of total cognitive score amongst the different groups. The analyses controlled for baseline age, sex, depression, education, marital status, physical activity, BMI, smoking and alcohol. For the second study, we included individuals aged 50 to 70 in 2002 with at least three follow-ups between 2004 and 2016, as well as information about diabetes diagnosis and a depression assessment in 2002 (n=7538). Latent growth modelling was performed to identify different classes of cognitive trajectories. Multinomial logistic regression was used to analyze the association between diabetes and

elevated depressive symptoms at baseline with the cognitive function trajectory groups, adjusting for baseline age, sex, education, marital status, physical activity, and smoking.

Results:
Study 1: Compared to the group without cardio-metabolic conditions at baseline (trajectory intercept 18.87 [95% confidence interval (CI) 18.29 to 19.45]), trajectory slope -0.17 [95% CI -0.22 to -0.13]), participants with one cardio-metabolic condition had a similar decrease in cognitive function over time (trajectory intercept 18.65 [95% CI 18.45 to 18.85], trajectory slope -0.17 [-0.20 to -0.15]). Participants with two cardio-metabolic conditions had a steeper cognitive decline (trajectory intercept 18.53 [95% CI 18.28 to 18.79], trajectory slope -0.21 [95% CI -0.23 to -0.18]); participants with three or more conditions had the greatest decline in cognitive function (trajectory intercept 18.62 [95% CI 18.21 to 19.03], trajectory slope -0.25 [95% CI -0.29 to -0.22]).
Study 2: We identified three trajectory classes using latent growth modelling adjusting for baseline age: high (40.5%), intermediate (44.2%) and low (15.2%). The high trajectory class had a high baseline cognitive score with a small decline over time; the intermediate class had a lower baseline score with a steeper decline while the low class had the lowest baseline score and the steepest decline. In reference to the high trajectory class, diabetes alone was associated with an odds ratio (OR) of 2.09 [95% CI 1.63 to 2.66] for being in the low trajectory class and an OR of 1.56 [95% CI 1.30 to 1.86] for being in the intermediate trajectory class. Having elevated depressive symptoms alone was associated with an OR of 1.97 [95% CI 1.51 to 2.56] for low class membership and 1.75 [95% CI 1.44 to 2.12] for intermediate class membership. Comorbidity was associated with an OR of 6.74 [95% CI 3.96 to 11.48] for being in the low trajectory group and an OR of 2.81 [95% CI 1.73 to 4.57] for being in the intermediate trajectory group.

Conclusions: Cognitive trajectories for those with two or more cardio-metabolic conditions were significantly worse compared to those with one or less, suggesting that cognitive decline may occur in middle-aged adults with multiple chronic conditions long before the onset of dementia. Elevated depressive symptoms and diabetes were individually associated with a low or intermediate class cognitive trajectory; comorbidity increased the risk of belonging to the low trajectory group.

Résumé

Objectif: Des études récentes ont montré de fortes associations entre les conditions cardiovasculaires et la démence. Cependant, on sait peu de choses sur le début des changements dans la fonction cognitive. Il existe des preuves que le déclin cognitif des personnes atteintes de maladies somatiques chroniques pourrait commencer au milieu de la vie, mais les preuves provenant de grandes études communautaires longitudinales avec de longues données de suivi font toujours défaut. Le rôle des conditions mentales comme la dépression n'est pas clair non plus. Par exemple, les personnes atteintes de dépression et de diabète ont un risque plus élevé de démence que les personnes atteintes de dépression ou de diabète seul, mais il n'est pas clair si la comorbidité de la dépression avec le diabète est associée à un déclin cognitif accéléré au moyen âge. Les objectifs de cette thèse étaient:

a) pour examiner les trajectoires longitudinales des fonctions cognitives associées à la présence de conditions cardio-métaboliques chez les adultes d'âge moyen en utilisant les données de la longitudinale US Health and Retirement Study (HRS).

b) pour évaluer si des symptômes dépressifs élevés et le diabète étaient associés à une accélération des trajectoires des fonctions cognitives chez les adultes d'âge moyen dans le HRS.

Conception: HRS est une étude de cohorte prospective avec un échantillon nationalement représentatif d'adultes américains de 50 ans et plus. Nous avons inclus des personnes qui ont participé à HRS en 2002 avec un suivi jusqu'en 2016. Pour la première étude, des participants âgés de 50 à 65 ans en 2002 avec au moins deux évaluations de suivi et des informations sur les conditions cardio-métaboliques de base ont été inclus (n = 5011). La fonction cognitive a été évaluée à l'aide d'une interview téléphonique modifiée pour l'état cognitif (TICS-M) avec 27 points. Les trajectoires des fonctions cognitives ont été modélisées pour différents nombres de conditions cardio-métaboliques (maladie cardiaque, hypertension, diabète et accident vasculaire cérébral). Une modélisation à effets mixtes linéaires a été utilisée pour estimer la trajectoire longitudinale moyenne du score cognitif total parmi les différents groupes. Les analyses contrôlaient l'âge de base, le sexe, la dépression, l'éducation, l'état matrimonial, l'activité physique, l'IMC, le tabagisme et l'alcool.

Résultats:
Étude 1: Comparé au groupe sans conditions cardio-métaboliques au départ (interception de trajectoire 18,87 [intervalle de confiance à 95% (IC) 18,29 à 19,45]), pente de la trajectoire -0,17 [IC à 95% -0,22 à -0,13]), participants avec une condition cardio-métabolique avait une diminution similaire de la fonction cognitive au fil du temps (interception de trajectoire 18,65 [IC à 95% 18,45 à 18,85], pente de la trajectoire -0,17 [-0,20 à -0,15]). Les participants avec deux conditions cardio-métaboliques ont eu un déclin cognitif plus prononcé (interception de trajectoire 18,53 [IC 95% 18,28 à 18,79], pente de la trajectoire -0,21 [IC 95% -0,23 à -0,18]); les participants avec trois conditions ou plus avaient le plus grand déclin de la fonction cognitive (interception de trajectoire 18,62 [IC 95% 18,21 à 19,03], pente de la trajectoire -0,25 [IC 95% -0,29 à -0,22]).

Étude 2: Nous avons identifié trois classes de trajectoires à l'aide de la modélisation de la croissance latente ajustée à l'âge de référence: élevée (40,5%), intermédiaire (44,2%) et faible (15,2%). La classe à trajectoire élevée avait un score cognitif de base élevé avec un léger déclin au fil du temps; la classe intermédiaire avait un score de base plus faible avec un déclin plus prononcé tandis que la classe basse avait le score de base le plus bas et le déclin le plus prononcé. En référence à la classe à trajectoire élevée, le diabète seul était associé à un rapport de cotes (OR) de 2,09 [IC à 95% 1,63 à 2,66] pour être dans la classe à trajectoire basse et à un OR de 1,56 [IC à 95% 1,30 à 1,86] pour être dans la classe de trajectoire intermédiaire. Le fait d'avoir des symptômes de dépression élevés seuls était associé à un OR de 1,97 [IC à 95% 1,51 à 2,56] pour les membres de la classe basse et 1,75 [IC à 95% 1,44 à 2,12] pour les membres de la classe intermédiaire. La comorbidité était associée à un OR de 6,74 [IC à 95% 3,96 à 11,48] pour être dans le groupe à trajectoire basse et à un OR de 2,81 [IC à 95% 1,73 à 4,57] pour être dans le groupe à trajectoire intermédiaire.

Conclusions: Les trajectoires cognitives des personnes atteintes de deux affections cardio-métaboliques ou plus étaient significativement moins bonnes que celles qui en avaient une ou moins, ce qui suggère qu'un déclin cognitif peut survenir chez les adultes d'âge moyen souffrant de multiples maladies chroniques bien avant le début de la démence. Des symptômes dépressifs élevés et le diabète étaient individuellement associés à une trajectoire

cognitive de classe basse ou intermédiaire; la comorbidité augmentait le risque d'appartenance au groupe à faible trajectoire.

Preface

This thesis is an original work of Dominik Yang. No part of this thesis has been previously published. Two manuscripts are included in this thesis, of which the first has been prepared for submission to the Journal of Epidemiology and Community Health. The second paper was formatted for submission to the journal of Aging and Mental Health.

The motivation of this thesis came from my time working at the University of Ottawa Heart Institute Division of Cardiac Surgery, where I interacted with many elderly patients suffering from both heart disease and cognitive impairment. This led to my interest in the association between physical and mental illnesses and exploring the relationship between cardio-metabolic conditions and cognitive decline.

Contribution of Authors

All chapters of this thesis have been personally written by me, with comments and edits suggested by my supervisor Dr. Norbert Schmitz by review.

This thesis consists of two manuscripts that I authored. Both studies used data from the US health and Retirement Study of University provided by the University of Michigan and funded by the National Institutes of Health (NIH).

For the first manuscript, Dr. Norbert Schmitz advised me with the idea of the study and helped prepare the dataset. Dr. Norbert Schmitz, Dr. Sonya Deschenes and Dr. Paramita Saha-Chaudhuri instructed me on mixed effects modelling methodology. Dr. Amanda Sonnega provided information on the HRS dataset and study design. Dr. Louise Pilote reviewed the manuscript and provided suggestions and feedback on both the analysis and writing.

For the second manuscript, Dr. Norbert Schmitz was involved in concept creation, assisted with the group-based trajectory modelling, and assisted with the composition of the manuscript. Dr. Sonya Deschenes helped with reviewing the paper.

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I am indebted to Dr. Sonya Deschenes for her feedback and suggestions during the planning and review of my thesis, her assistance with study methodologies, as well as providing references and textbooks to aid in my analyses.

I would also like to express my very great appreciation to my thesis advisor Dr. Louise Pilote for her valuable and constructive suggestions during the planning and development of this research project. Her critiques and recommendations not only helped improve the quality of my work, but also opened my eyes to the rigorousness of epidemiologic research.

I would like to offer my special thanks to the National Institute on Aging for funding the Health and Retirement Study and the University of Michigan for conducting the study. Without their contributions to the research world, I would not have been able to use their data for my thesis.

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I would also like to thank Dr. Dimitra Panagiotoglou for providing me the necessary skills to work with administrative data and SAS software, and Dr. Kristian Filion for teaching me how to perform systematic reviews and meta-analyses.

Finally, I am deeply indebted to my classmates, friends, and family. All of them have supported me throughout my academic career and were my motivation to pursue higher education.

Many thanks to everyone who has helped me with the preparation of this thesis. Thank you for the patience in guiding me through this process and your unwavering support throughout the struggles, including the recent quarantine and pandemic.

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List of Abbreviations

1. 3C – Three-City (3C) Study
2. ADAMS – Aging, Demographics, and Memory Study
3. AHA – American Heart Association
4. AIC – Akaike Information Criterion
5. BIC – Bayesian Information Criterion
6. BMI – Body mass index
7. CES-D – Center for Epidemiologic Studies Depression Scale 8
8. CI – Confidence interval
9. CIDI-SF – Composite International Diagnostic Interview – Short Form
10. CIND – Cognitively impaired but not demented
11. GBTM – Group-based trajectory modelling
12. HPA – Hypothalamic-pituitary-adrenal
13. HRS – Health and Retirement Study
14. IC – Intervalle de confiance
15. IMC – Indice de Masse Corporelle
16. MAR – Missing at random
17. MCAR – Missing completely at random
18. NIH – National Institutes of Health
19. nlme – Linear and Nonlinear Mixed Effects Models package for R software
20. OR – Odds ratio
21. REML – Restricted maximum likelihood
22. SD – Standard deviation
23. SE – Standard error
24. SES – Social economic status
25. STROBE – Strengthening the Reporting of Observational Studies in Epidemiology
26. TICS-M – modified Telephone Interview for Cognitive Status
27. UK – United Kingdom
28. US – United States

1 | Introduction

Dementia is a debilitating illness that impacts not only those affected by it, but also the people around them – caretakers, family members and close friends. With more and more people living until old age, there is a rise in age related diseases such as dementia.[1, 2] In the past few decades, numerous studies have been published suggesting potential causes and risk factors. Some of the strongest evidence show cardio-metabolic conditions like diabetes and hypertension are important risk factors of dementia. This relationship between the body and mind quickly generated research interest, inspiring many studies and clinical trials to elucidate the relationship between cardiovascular disease and dementia. Following this surge in research interest, several scientists now believe that the two diseases share a common origin – cardio-metabolic conditions.[3-5] Dementia is not an illness that occurs overnight. It takes years, even decades, to manifest. Therefore, it is necessary to understand when changes in cognition occur in those at risk for dementia.

Current literature has strong support for the link between cardio-metabolic conditions and late life dementia, but not many studies have examined changes in cognition during the middle age. In this thesis, I tackled this issue by examining cognitive function trajectories of individuals in midlife and assessing whether the presence of cardiometabolic conditions accelerated the decline in cognition over time. In addition, a second study was performed to evaluate whether depression could worsen cognitive decline in those with diabetes. Depression is a well known risk factor of dementia and is also known to worsen the prognosis of diabetes.[6] Therefore, there is a lot of interest in whether comorbidity of depression and diabetes worsens cognitive decline in midlife.

The two studies in this thesis look at the association between cardiovascular conditions (factors related to coronary disease and stroke) and cognitive decline in midlife, and the role of depressive symptoms in the relationship between diabetes and cognitive decline.

2 | Literature review

In the early 2000s, lots of research begun on the relationship between the cardiovascular disorders and mental disorders. In early 2000, one study concluded that transient ischemic attacks (mini-strokes), hypertension and hyperlipidemia accelerate cognitive decline and may lead to dementia.[7] Other studies around that time found that diabetes was also associated with cognitive impairment.[8, 9] In 2009, a study was published showing hypertension and diabetes in middle-age was associated with risk of subsequent dementia hospitalisation.[3] Those with cardiovascular disease without stroke had a higher risk of dementia and Alzheimer's disease.[10] During this time period, not enough studies examined the link between stroke and dementia,[11] although some showed that stroke could cause changes in brain volume and decreased cognitive performance.[11]

Since then, researchers have built upon this foundation and explored the relationships in much more detail. A meta-analysis of observational studies concluded that diabetes increased the risk of all-type dementia, vascular dementia and Alzheimer's disease.[12] In the case of diabetes, cognitive impairment seemed to be caused by disturbance of the cerebral insulin pathways, accumulation of advanced glycation end products, increased blood-brain barrier permeability and inflammation, and endothelial dysfunction.[13, 14] Insulin receptors in the brain are located mostly in the hippocamps and cerebral cortex which are important for memory, so disturbances of these pathways could lead to problems with memory. Insulin also helps promote expression of insulin degrading enzyme which helps break down and prevent beta amyloid plaque build-up.[12] Although diabetes is linked with increased all-type dementia, a certain subgroup of dementia is only associated with diabetes-related mechanisms that differ from Alzheimer's disease or vascular dementia.[15] Hypertension, especially in midlife, increases cognitive decline and dementia later in life.[16, 17] Some evidence has been shown that controlling blood pressure could reduce the risk of vascular dementia.[16] Heart disease in midlife was also shown to be associated with dementia through mechanisms such as decreased cerebral blood flow leading to chronic hypoperfusion, cerebral infarction, white matter lesions and small vessel disease.[18, 19] It must be noted that heart disease itself may not be the cause of dementia, rather atherosclerosis could be the underlying root of both heart disease and dementia.[19] Finally, stroke and dementia have been shown to be tightly intertwined: stroke can accelerate neurodegeneration and

neurodegeneration can cause stroke.[20] However, since stroke is more common than dementia, almost one third of dementias may be preventable if we had first prevented stroke.[21] As information continues to evolve with ongoing research, potential therapeutic targets to prevent dementia include protecting the blood-brain barrier, preventing amyloid plaque build-up and inflammation, decreasing vascular risk and maintaining healthy lifestyle habits.

Recently, a large cross-sectional study using the UK Biobank with 474 129 participants aged 40-70 showed that cardio-metabolic diseases were associated with poorer non-demented cognitive ability among the domains of reasoning, reaction time and memory. An additive interaction was demonstrated between increasing number of cardio-metabolic diseases and worse cognitive abilities.[4] The Three-City (3C) Study, a prospective cohort study from France that ran from 1999-2016, showed that better health metrics including smoking, diet, physical activity, body mass index, blood pressure, total cholesterol, and fasting glucose among elderly aged 65 and over were associated with a decreased risk of cognitive decline and dementia (up to a reduced incidence of 0.96 cases per 100 person-years).[22] This study was repeated using the Whitehall II study cohort with individuals age 50 at baseline and concluded that better health metrics at midlife reduced the risk of dementia later in life (up to a reduced incidence of 1.9 cases per 1000 person years).[23] These studies provide promising results, suggesting that controlling cardio-metabolic health earlier in life may help in preventing dementia. However, limitations in cohort study data prevent causal conclusions from being made.

Aside from cohort studies, a large randomized control trial called SPRINT MIND recently concluded.[24] It was designed to assess whether controlling hypertension could provide benefits to cardiovascular events and all-cause mortality. As a secondary objective, the trial found that lowering systolic blood pressure below 120 mmHg decreased the combined rate of mild cognitive impairment and probable dementia by 3.9 cases per 1000 person-years. However, the study was considerably underpowered because of early trial termination due to clear benefits for cardiovascular events and all-cause mortality along with the low incidence of dementia identified from their sample.[24]

Aside from cardio-metabolic conditions, depression is another common condition that has been linked with cognitive impairment and dementia independent of vascular disease.[25, 26] Depression is also strongly linked with diabetes, where it is two to three times more

prevalent in people with diabetes.[6] Patients with both depression and diabetes have a much greater risk of dementia than having diabetes alone.[27] Potential mechanisms that explain this relationship could be that the regions of the brain responsible for emotional regulation and cognition could be affected by hyperglycemia, and decreased glucose levels in brain cells could result in neurotoxicity and neuroplasticity.[28] Depression can accelerate neuronal damage through hypothalamic pituitary adrenal (HPA) axis deregulation, inflammation and changes in neuronal signalling.[28] There may be behavioural pathways involved as well, since depression is associated with dementia risk factors like physical inactivity, obesity and smoking.[29-32]

There are numerous covariates that need to be addressed in order to limit bias due to confounding. Increasing age is associated with cardiovascular disease,[33] cognitive decline and dementia.[1, 34] Sex and gender differences are also present in both cardio-metabolic and cardiovascular disorders [35-37] and dementia.[38-40] Men seem to be more at risk of cardiovascular disease, however women have higher cardiovascular mortality.[37] The frequency of dementia is higher in women, however this could be due to more women living till older age[40] and women having double the risk of depression compared to men.[41] This may be due to women having different symptoms not being captured by current medical practice.[37] Lower education is associated with both cardiovascular disease[42] and dementia.[43] Body mass index (BMI) is associated with both cardio-metabolic disease[44] and cardiovascular disease morbidity and mortality.[45] In relation to dementia, higher BMI in midlife or in long follow-up periods was associated with increased risk of dementia, however in late life or short follow-up periods high BMI was seen as protective.[46, 47] The protective effect is likely an consequence of reverse causation, since in the 14 years before dementia onset, BMI has been shown to decrease as a symptom of pre-dementia.[48] Marital status is associated with cardiovascular disease and its prognosis[49] as well as dementia.[50, 51] Married individuals are at lower risk of both diseases compared to all non-married individuals, with divorced or separated individuals at highest risk.[50] Physical activity in midlife has been shown to lower the risk of dementia[52, 53], however an individual-participant meta-analysis addressing potential reverse causation suggests that physical activity is only associated with dementia in the subgroup of people with cardio-metabolic diseases.[5] A meta-analysis of physical activity in elderly with Alzheimer's disease found improved cognition associated with exercise,[54] however there is no association between midlife physical activity and Alzheimer's disease.[52] There are some

mixed notions with respect to physical activity and dementia, but there is evidence that physical activity is associated with both cardio-metabolic diseases[55, 56] and dementia and was thus considered to be an important covariate. Alcohol has a U-shaped relationship with both cardiovascular disease[57] and dementia,[58] where no consumption (<1 unit/week) or excessive consumption (>14 units/week) might increase the risk of these diseases while light to moderate drinking (1-2 units a day) could be considered as "protective".[58, 59] A caveat is that there was no distinction as to whether non-drinkers chose not to drink or were forced to abstain due to other medical conditions. Smoking is associated with increased risk of dementia, however prolonged smoking cessation (10 or more years) greatly reduced this risk.[60, 61]

3 | Study Objectives

The main purpose of this thesis was to identify changes in cognitive function in the middle age in relation to cardiovascular risk factors. Previous research identified cardiovascular conditions as risk factors of dementia and late life cognitive impairment, therefore understanding when changes begin to occur would help in developing prevention strategies by allowing us to target the right age to intervene. Two studies were performed to address this issue.

The first study analyzed the association between four common cardiovascular risk factors (diabetes, heart disease, hypertension and stroke) with cognitive change over a period of 14 years of follow-up data from a US nationally representative sample of adults 50-65. The primary objective was to evaluate whether cognitive function changes in those with one or more cardiovascular risk factors were worse than those without cardiovascular risk factors. The secondary objective was to estimate the individual association of each cardiovascular risk factor on cognitive function changes.

As a continuation of the first study, we were interested in the role of depression in this association. For the second study, we analyzed the association between depression, diabetes and cognitive decline to see if depression worsened the cognitive change in those with diabetes.

In terms of cognitive function changes, we addressed two aspects. The first was whether cognitive function differed at baseline between those with and without the exposures of interest, while the second aspect was whether average yearly decline in cognition is accelerated in the exposed groups. Both of these aspects (intercept and slope) were the main outcomes of this thesis

and were used to complete the objectives of the two studies. In order to assess whether a change in cognition could be defined as accelerated cognitive decline, we looked at the cognitive function at the end of follow-up and the trajectory of cognitive function over time since there could be instances where one had a higher cognitive function at the start of the study but a much worse trajectory.

4 | Study Methodology

All the analysis and results were based on the US Health and Retirement Study (HRS) data collected from 2002-2016.[16] HRS is an ongoing study conducted by the Survey Research Center at the University of Michigan, which began in 1992.[16] The study began in 1992, and has been collecting data every 2 years from then on. A new cohort of people is introduced every 6 years, and each cohort is representative of US households containing at least one person aged 50 or over. It was initially created as a national resource to analyse changes in health and economic conditions associated with aging. The data can be linked to administrative records such as Veteran's Administration or Medicare data. Biomarker data was introduced in 2006, however our study uses data from the core survey, which consists of interview questions on a broad range of topics such as health, welfare and cognition. We selected 2002 as the baseline year since that was the year when many variables were recoded to be more consistent from wave to wave.

The study follows a multi-stage area probability sample design with geographical stratification and oversampling of certain subgroups such as African-Americans and Hispanic households.[62] Sample weights were provided to correct for differential probability of selection and non-response to allow for population-level conclusions. If a participant was unable to answer questions themselves, a proxy respondent was invited, usually a spouse or immediate family member. These consist of approximately 9% of respondents each wave, mostly in those 80 or over and were excluded in our analyses.

Since the data used for analysis was longitudinal in nature and contained repeated measurements, the first study used mixed effects modelling to estimate linear trajectories of cognitive function over time.[63] This was performed using the "nlme" package in R version 3.5.3.[64] Mixed effects models work by estimating both a fixed effect estimate which is the population average (between clusters), while accounting for random effects of each individual's

unique trajectory (within clusters). Another name for this method is multi-level modelling, where the first level consists of individual trajectories, while the second level is an average of the individual trajectories. Each participant was assumed to have a random intercept and a random slope, so a minimum of three time points was required to estimate these two parameters. A population estimate was obtained using restricted maximum likelihood (REML) variance estimation.[65] Within-subject variance was assumed to be conditionally independent given the random effects. Essentially, there should be no serial correlation within subjects and normal errors are assumed. Missing data does not need to be imputed using multi-level modelling. Incomplete data can be used in a way that leads to unbiased estimates given missing at random (MAR) or missing completely at random (MCAR) assumptions, and also given we can estimate a trajectory for each individual (as stated earlier, minimum three observations needed for slope).

For the second study, latent growth modelling was used, sepcifically group-based trajectory modelling (GBTM).[66] This method applies maximum likelihood estimation using a quasi-Newton procedure to estimate the likelihood of an individual's repeated observations. It applies finite mixture modelling to group individuals into classes with similar cognitive function trajectories. Instead of specifying groups beforehand, this approach is more data driven. The most suitable model for the study is selected by specifying the number of groups and the order of polynomial for each group's cognitive function trajectory, then assessing model selection criteria while taking into account the context of the research.[67] There are two aspects of the equation for GBTM: 1) the probability of group membership and 2) the probability of the observed measurements within that group membership. Regression models are estimated via maximization of a likelihood function that then predicts the probability of group membership using a generalized logit model. Group membership is based on time stable covariates and additional time-dependent covariates can be specified in the model. Individuals do not belong to a group like in a conventional cluster analysis but are rather assigned a probability of fitting in that group. Individuals are assigned to groups based on likelihood of group membership, and this can further be used to associate back to individual characteristics. Like in the multi-level modelling scenario, repeated measurements were assumed to be independent conditional on the group. Missing data is handled using maximum likelihood estimation which generates unbiased parameter estimates assuming MAR. This method can be performed using the "proc traj" package in SAS 9.4.[68]

5 | Manuscript 1

Cardio-metabolic conditions and cognitive decline: a 14-year follow-up of the Health and Retirement Study

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Abstract (244 words)

Objective: Recent studies have shown strong associations between cardio-metabolic conditions and dementia. However, little is known on when changes in cognition begin to occur. The aim of this study was to examine changes in longitudinal cognitive function trajectory associated with cardio-metabolic conditions in middle-aged adults using US longitudinal cohort data from Health and Retirement Study (HRS).

Design: HRS is a nationally representative sample of US adults 50 years and older. Cognitive function was assessed using the Modified Telephone Interview for Cognitive Status (TICS-M). Cognitive function trajectories were modelled in association with baseline cardio-metabolic conditions (heart disease, hypertension, diabetes and stroke) in individuals from the 2002-2016 waves of HRS. Multi-level modelling was used to estimate population mean trajectories of cognitive function amongst those with different numbers of cardio-metabolic conditions, controlling for baseline age, sex, depression, education, marital status, physical activity, body mass index, smoking and alcohol use.

Results: 5011 participants were included in the analysis (mean age 59.6, 35.5% male). 45.7% of the study population had no cardio-metabolic conditions at baseline. Participants with two or more cardio-metabolic conditions experienced a steeper cognitive decline than participants without cardio-metabolic conditions (difference in slope: two conditions: -0.04 [95 CI -0.06 to -0.01]; three conditions: -0.08 [95 CI -0.12 to -0.05]).

Conclusions: Among those with two or more cardio-metabolic conditions, greater declines in cognitive function were observed compared to those without cardio-metabolic conditions. These results indicate that cognitive decline is observed in middle-age adults with chronic conditions long before the onset of dementia.

What is already known on this subject?

- Midlife cardio-metabolic risk factors increase the risk of subsequent dementia
- Increasing number of cardio-metabolic risk factors have an additive effect on the risk of dementia
- Cognitive decline greatly increases the risk of dementia and usually precedes dementia onset

What this study adds?

- Individuals with two or more cardio-metabolic conditions are at increased risk of accelerated cognitive decline at midlife
- The cognitive function trajectory worsens with increasing number of comorbid cardio-metabolic conditions
- Cognitive decline has been shown to begin even in midlife, thus public health policies should target preventative strategies towards a younger population

INTRODUCTION

Emerging research has suggested that an increasing number of cardio-metabolic diseases may have an additive deleterious effect on reasoning, reaction time and memory.[1] Midlife obesity, hypertension and high cholesterol each increased the risk of dementia almost two-fold, with a combination of these risk factors increasing the risk for dementia in an additive manner.[2] Poor health behaviors (i.e. smoking, poor diet, and physical inactivity) and metabolic problems (i.e. high body mass index, high blood pressure, high total cholesterol, and high fasting glucose) are associated with an increasing risk of dementia.[3, 4] These findings suggest that a high prevalence of cardio-metabolic diseases may lead to a rise in cognitive impairment and dementia.

Many studies have evaluated whether targeting cardiovascular risk factors could improve risk of dementia. SPRINT MIND, a sub study of a large randomized control trial (RCT) for the treatment of hypertension, found that lowering systolic blood pressure below 120 mmHg may decrease the rate of probable dementia by 1.4 cases per 1000 person-years [5]. However, the study was considerably underpowered because of early trial termination due to clear benefits for cardiovascular events and all-cause mortality along with the low incidence of dementia identified from their sample. Another RCT was performed to assess whether a multi-domain intervention could reduce incidence of all-cause dementia in community-dwelling elderly aged 70-78 by targeting cardiovascular risk factors. However, they did not find any effect of the intervention on the risk of dementia.[6, 7] Nevertheless, many multi-domain lifestyle intervention studies have concluded promising results in delaying or preventing cognitive impairment in healthy older adults,[8-11] with a higher adherence showing greater improvements.[8] These results lend credence to the notion that changes in cognition may start long before older age and can be prevented, thus more research is needed to elucidate how cognition is affected in the middle-aged population.

Dementia places a heavy burden on healthcare and welfare expenditure as well as social support services.[12, 13] It is a serious condition that impairs functioning and is associated with poor quality of life among those with dementia and their caretakers.[14-16] However, changes in cognition often occur long before the onset of dementia,[17] and decline has been shown to accelerate preceding mild cognitive impairment and dementia.[18] Cognitive decline also greatly increases the risk of dementia.[19] Therefore, it is important to study these early changes, ideally

as early as midlife. Although several studies have demonstrated an association between cardiovascular conditions and risk of dementia, little is known about how cardio-metabolic conditions affect the longitudinal trajectory (change in cognitive function over time) of cognitive function starting in midlife. The aim of this study was to examine the association between the number of cardio-metabolic conditions and the longitudinal trajectories of cognitive function in middle-aged adults using data from the US Health and Retirement Study (HRS), a prospective cohort study.

METHODS

Data Source

Data from the HRS (2002-2016) were used for the present analysis. HRS is an ongoing prospective cohort study which began in 1992.[20] We included all participants aged 50-65 years with data at our study baseline (2002). The baseline year was set as 2002 because many study variables and definitions were reformatted to be more consistent from wave to wave, and additional numeracy questions were added to the core survey that year. HRS is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. It is a biennial, multi-stage, area probability sample design involving geographical stratification and clustering among US community-dwelling populations and weighted to reflect all US households containing at least one person in the age-eligible range (50 and above). Oral or written consent was provided by all participants. Interviews were performed either face-to-face or by telephone. Individuals were followed biennially from date of entry until their deaths or voluntary withdrawal from the study. Given that less than three observations does not allow for random slope and may cause overfitting, participants were excluded from analyses if they recorded less than 3 cognitive function measurements (to ensure enough data points to provide each individual their own intercept and slope); if they disputed their exposure status in subsequent waves; if they did not have data at baseline (2002); and if they were missing baseline data on cardio-metabolic diseases or covariates of interest.

Exposure Measures

The cardio-metabolic conditions included in the analysis were hypertension, stroke, diabetes and heart disease and were assessed at baseline. Disease status was assessed by asking, “Has a doctor ever told you that you have/had (disease)?” Follow-up interviews asked, “Since

we last talked to you (in the last wave), has a doctor told you that you have/had (disease)?" Heart disease consisted of heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems. All exposure data were self-reported. Response options were either "Yes" or "No", with "Yes" being coded as 1 and "No" being coded as 0. Those who responded with "Yes" were considered to have the disease from that time point onwards. Any participants who disputed previous wave responses were excluded from analysis.

Cognitive function measures

The primary measure of cognitive function was determined as the sum of three individual cognitive tests, described below, for a total cognitive score ranging from 0 to 27 points.[21] This score has been used in previous studies.[22-26]. The tests included serial 7s subtraction (5 points), immediate and delayed word recall (20 points), and backwards counting from a given number (2 points). Serial 7s subtraction required participants to subtract 7 from a given number five times in succession with one point per correct subtraction. Immediate word recall gave participants 10 simple words and had them repeat the words for up to 10 points. Participants were then asked to recall those same 10 words after a delay consisting of other interview questions, also for up to 10 points. Total recall, the sum of both immediate and delayed recall, has been shown to be the most sensitive test for detecting change in memory due to aging.[27] Finally, participants received 2 points if they could count backwards from 20 to 0 and none should they have failed. This assessment was validated by comparing score cut-offs with dementia diagnosis in the Aging, Demographics, and Memory Study (ADAMS).[28]

Covariates

Covariates included sex (male/female), depression (Center for Epidemiologic Studies Depression Scale 8 (CES-D 8), an 8 item questionnaire),[29] age at baseline, highest level of education (less than high school/high school/some college/college degree/postgraduate degree), marital status (never married/widowed/separated or divorced/married), vigorous physical activity (1 day a week or less/more than once a week), continuous body mass index (BMI), smoking (never/former/current) and alcohol use (not drinking/1 or more drinks a day).

Statistical analysis

Data analyses were performed using R version 3.5.3 and the "nlme" package.[30] Descriptive analysis was performed according to the number of cardio-metabolic conditions. Multi-level linear models were used to estimate the mean longitudinal trajectories of total cognitive score among those with cardio-metabolic conditions compared to those without. Each participant was assumed to have their own intercept and slope estimate, which could only be obtained with a minimum of three observations per individual. Excess data points were not required, therefore even those with missing data at certain time points could still be included. A population estimate was obtained using restricted maximum likelihood (REML) variance estimation, which provides unbiased estimates given the missing at random (MAR) assumption. First, we assessed the association between the number of cardio-metabolic conditions and cognitive score using an unadjusted interaction model with time, then ran the same model adjusting for covariates. In addition, we examined the individual associations between each cardio-metabolic condition and cognitive score using an unadjusted model, a model adjusting for covariates and a third model adjusting for covariates and the presence of other cardio-metabolic conditions. Significance for model variables was tested using a t-test to determine whether changes to intercept and slope were statistically significant (p-value < 0.05 and confidence intervals do not contain the reference or null).

Sensitivity analyses were performed. First, heart disease and hypertension were re-coded as only being true if participants stated they had the condition and were taking medication for the condition. This was because those not on medication may have mis-reported their status. Finally, there were 56 people with severe cognitive impairment at baseline (<6 at baseline),[21] which meant that their responses to other questions may not be valid as they could have forgotten what happened or misunderstood the questions. These participants were excluded.

RESULTS

Study population characteristics

There were 5011 participants included in the final analysis, with a mean of 5.7 observations per person and 431 with 3 observations only. **Figure 1** details the selection process. Mean baseline age was 59.6 years (SD=3.83) with males comprising 35.5% of the analysis sample. Prevalence of heart disease at baseline was 13.9%, hypertension was 45.7%, diabetes

was 13.1% and stroke was 2.9%, with 45.7% of participants with no condition. **Table 1** shows the descriptive statistics for the number of cardiometabolic diseases. The proportion of males, smokers (current and former), non-drinkers, participants with less than high school education, with cognitively impairment at baseline and no vigorous physical activity was higher in groups with two or more cardio-metabolic conditions compared to groups with one or less. Groups with more cardio-metabolic conditions also had a higher average summary depression score compared with the group without any cardio-metabolic conditions.

Table 1: Descriptive statistics of baseline values for HRS participants with at least 3 cognition measures during 2002-2016 according to number of cardiometabolic conditions (n=5011)

Number of conditions	**0 (n=2292)**	**1 (n=1829)**	**2 (n=726)**	**3 or 4 (n=164)**	**Total (n=5011)**
Baseline age: Mean (SD)	59.2 (3.86)	59.8 (3.83)	60.3 (3.63)	59.7 (3.55)	59.6 (3.83)
Sex:					
Male	765 (33.4%)	655 (35.8%)	297 (40.9%)	64 (39.0%)	1781 (35.5%)
Female	1527 (66.6%)	1174 (64.2%)	429 (59.1%)	100 (61.0%)	3230 (64.5%)
Baseline Cognition:					
Normal (12-27)	2136 (93.2%)	1655 (90.5%)	610 (84.0%)	130 (79.3%)	4531 (90.4%)
Mildly Impaired (7-11)	139 (6.1%)	147 (8.0%)	108 (14.9%)	30 (18.3%)	424 (8.5%)
Severely Impaired (0-6)	17 (0.7%)	27 (1.5%)	8 (1.1%)	4 (2.4%)	56 (1.1%)
Education:					
Postgraduate Degree	309 (13.5%)	183 (10.0%)	49 (6.7%)	11 (6.7%)	552 (11.0%)
College Degree	430 (18.8%)	299 (16.3%)	299 (16.3%)	18 (11.0%)	848 (16.9%)
High School Diploma	1163 (50.7%)	942 (51.5%)	942 (51.5%)	77 (47.0%)	2553 (50.9%)
Less than High School	390 (17.0%)	405 (22.1%)	405 (22.1%)	58 (35.4%)	1058 (21.1%)
Vigorous Physical Activity:					
Yes	564 (24.6%)	297 (16.2%)	104 (14.3%)	14 (8.5%)	979 (19.5%)
No	1728 (75.4%)	1532 (83.8%)	622 (85.7%)	150 (91.5%)	4032 (80.5%)
Marital Status:					
Married	1701 (74.2%)	1341 (73.3%)	515 (70.9%)	112 (68.3%)	3669 (73.2%)
Widowed	188 (8.2%)	164 (9.0%)	70 (9.6%)	20 (12.2%)	442 (8.8%)
Divorced or Separated	327 (14.3%)	261 (14.3%)	123 (16.9%)	25 (15.2%)	736 (14.7%)
Never Married	76 (3.3%)	63 (3.4%)	18 (2.5%)	7 (4.3%)	164 (3.3%)
Smoking:					
	403 (17.6%)	263 (14.4%)	102 (14.0%)	25 (15.2%)	793 (15.8%)

Current	23 (1.0%)	32 (1.7%)	24 (3.3%)	8 (4.9%)	87 (1.7%)
Former	1866 (81.4%)	1534 (83.9%)	600 (82.6%)	131 (79.9%)	4131 (82.4%)
Non-smoker					
Alcohol:					
Yes	1372 (59.9%)	936 (51.2%)	324 (44.6%)	41 (25.0%)	2673 (53.3%)
No	920 (40.1%)	893 (48.8%)	402 (55.4%)	123 (75.0%)	2338 (46.7%)
Depression: Mean (SD)	1.08 (1.73)	1.36 (1.91)	1.74 (2.12)	2.53 (2.55)	1.33 (1.91)
Cognitive score: Mean (SD)	17.5 (3.9)	16.9 (4.1)	16.0 (4.2)	15.5 (4.7)	17.0 (4.1)

Association of cardio-metabolic conditions in midlife with cognitive score

Table 2: Multi-level model estimates for the number of cardio-metabolic conditions

Parameter	**Unadjusted**	**Adjusted****
	Coefficient [95% CI]	Coefficient [95% CI]
No condition (n = 2292)		
Intercept	17.25 [17.11, 17.39]	18.87 [18.29, 19.45]
Slope	-0.11 [-0.13, -0.09]	-0.17 [-0.22, -0.13]
One condition (n = 1829)		
Intercept	16.87 [16.70, 17.04]*	18.65 [18.45, 18.85]*
Slope	-0.11 [-0.13, -0.09]	-0.17 [-0.20, -0.15]
Two conditions (n = 726)		
Intercept	16.62 [16.39, 16.85]*	18.53 [18.28, 18.79]*
Slope	-0.14 [-0.16, -0.12]*	-0.21 [-0.23, -0.18]*
Three or four conditions (n = 164)		
Intercept	16.59 [16.20, 16.98]*	18.62 [18.21, 19.03]
Slope	-0.19 [-0.23, -0.16]*	-0.25 [-0.29, -0.22]*

* p-value < 0.05 and 95% confidence intervals, tested against the no condition reference group
** adjusted models controlled for age, marital status, sex, education, depression, body mass index, smoking, alcohol and vigorous physical activity. Full model values are available in supplementary figures

Exploratory data analysis and model diagnostics determined the association between the number of cardio-metabolic conditions and cognitive score to be linear, which is in line with prior literature.[3, 31, 32] In an unadjusted linear mixed effects model, higher number of cardio-

metabolic conditions was associated with a lower baseline cognitive score and a more negative yearly change in cognitive score (**Table 2**). The average baseline cognitive score in participants with no conditions was 17.25 [95% CI 17.11 to 17.39], with a yearly mean change of -0.11 [-0.13 to -0.09]. In participants with one condition, the cognitive score was lower by -0.38 [-0.55 to -0.21] at baseline, however there was no significant change in slope. For those with two conditions, cognitive function score was lower by -0.63 [-0.86 to -0.40] at baseline and the slope decreased by -0.03 [-0.05 to -0.01]. In the group of three to four conditions, baseline cognitive score was lower by -0.66 [-1.05 to -0.27] and yearly cognitive score change decreased by -0.08 [-0.12 to -0.05]. After adjusting for covariates, the baseline differences were attenuated, with the baseline difference in those with three to four conditions no longer remaining significant. However, the changes in slope remained the same after adjustment. **Figure 2** illustrates the association produced by the adjusted model detailed in **Table 2**. At the last assessment, mean cognition scores of those with one condition were similar to those without condition, while those with two or more conditions had significantly lower cognition scores.

Table 3: Difference in intercept and slope for each condition compared to not having the condition

Parameter	**Model 1 (Unadjusted)**	**Model 2 (Adjusted)****	**Model 3 (Adjusted)****
Heart disease			
Intercept	-0.06 [-0.28, 0.15]	0.14 [-0.09, 0.37]	0.17 [-0.06, 0.40]
Slope	-0.03 [-0.05, -0.01]*	-0.03 [-0.05, -0.01]*	-0.02 [-0.04, 0.00]*†
Diabetes			
Intercept	-0.18 [-0.40, 0.04]	-0.03 [-0.27, 0.21]	-0.01 [-0.26, 0.23]
Slope	-0.04 [-0.06, -0.02]*	-0.05 [-0.07, -0.03]*	-0.04 [-0.07, -0.02]*
Hypertension			
Intercept	-0.38 [-0.54, -0.22]*	-0.23 [-0.41, -0.05]*	-0.28 [-0.47, -0.10]*
Slope	-0.02 [-0.04, -0.01]*	-0.02 [-0.04, 0.00]	-0.01 [-0.03, 0.01]
Stroke			
Intercept	-1.07 [-1.51, -0.63]*	-0.73 [-1.19, -0.28]*	-0.75 [-1.21, -0.29]*
Slope	-0.02 [-0.06, 0.02]	-0.04 [-0.08, 0.00]	-0.03 [-0.07, 0.01]

P-values were tested against the group without the cardio-metabolic condition

* Marked values indicate statistical significance

** Adjusted models controlled for age, marital status, sex, education, depression, body mass index, smoking, alcohol and vigorous physical activity in Model 2. Further adjustment to account for comorbid cardio-metabolic conditions was added in Model 3. Full model estimates are available in supplementary figures.
† 95% CI rounded to two decimal points contains the null value, however p-value <0.05

When modelling the unadjusted associations between each individual cardio-metabolic condition and cognitive score, we found a significantly lower baseline cognitive score among those with hypertension -0.38 [-0.54 to -0.22] and stroke -1.07 [-1.51 to -0.63] (**Table 3**). Significant decreases in yearly cognitive change were also observed in those with heart disease (-0.03 [-0.05 to -0.01]), diabetes (-0.04 [-0.06 to -0.02]) and hypertension (-0.02 [-0.04, -0.01]). After adjustment for covariates, the baseline cognitive score changes were attenuated, and hypertension was no longer significantly associated with a decrease in slope. Further adjustment for the other cardio-metabolic conditions attenuated the association of heart disease and slope, however the association remained statistically significant (p-value = 0.047).

For sensitivity analyses, recoding disease status to account for medication did not significantly change any of the estimates. Removing the 56 individuals with a cognitive score <6 at baseline also did not change the estimates. When stratifying by sex, we found similar trajectories for both males and females, however females had a higher baseline cognitive score average.

DISCUSSION

Association of cardio-metabolic conditions and cognitive decline

We found that those with multiple cardio-metabolic conditions at baseline were subject to cognitive decline. Those with an increased number of these conditions were observed to have a worse cognitive score trajectory, although just having one condition did not seem to have significant differences compared to having no conditions. This suggests that with two or more cardio-metabolic conditions at mid-life, cognitive decline seems to be a concern. After individually assessing the impact of each cardio-metabolic condition even after adjusting for the presence of other cardio-metabolic conditions, individuals with hypertension and stroke saw lower cognitive scores at baseline, whereas those with heart disease and diabetes showed a greater decline in cognitive score each year. Heart disease can be caused by hypertension and

diabetes,[33, 34] so some of its association with cognitive decline may be lost after adjusting for diabetes and hypertension. At the final assessment, those with stroke had the lowest cognitive score compared to the other cardio-metabolic conditions.

There have been many proposed reasons as to why an increased number of cardio-metabolic conditions would lead to accelerated cognitive decline. Cardio-metabolic conditions increase the risk of cardiovascular disease, which may impair blood flow to the brain inducing hypoperfusion and vascular dementia.[35, 36] Our results support this proposed mechanism since we found stroke was associated with the biggest impact on cognitive decline in our study. Studies have suggested that this may be a case of reverse causation, where those with poorer cognitive function would have a worse time taking care of their health.[37] Poor health is also associated with changes in personality[38] and mental health problems like depression[39], which complicates the exact mechanism of action.[40] However, what is accepted is that there is evidence that cardio-metabolic diseases primarily affect cognitive decline by impacting cerebrovascular blood flow.[35]

The proportion of people living until old age is rising and therefore age-related cardiometabolic conditions such as heart disease, diabetes, hypertension, and stroke are also on the rise.[41] According to the American Heart Association (AHA) 2019 update of the Heart Disease and Stroke statistics, the prevalence of hypertension among US adults is over 45%, diabetes prevalence is 13.5%, and stroke prevalence is 2.5% for those above the age of 20.[41] Compared to the AHA statistics, the observed prevalence of conditions in our HRS sample was very similar (hypertension = 45.7%, diabetes = 13.1% and stroke = 2.9%).

In context with other studies

Numerous studies have shown an association between cardio-metabolic risk and dementia. However, most of these studies were either cross-sectional in nature[1] or had a sample from an elderly population.[3] In the previous studies that examined a middle-aged population, vascular risk factors have been shown to increase the risk for dementia and Alzheimer's Disease.[2, 4, 42, 43] In some studies, mid-life risk factors were better predictors of cognitive decline and dementia than late-life predictors,[42, 44, 45] and this was most likely due to reverse causation, where the pre-dementia phase may influence changes in cardio-metabolic health.[46, 47] Although so much evidence exists to support the association between mid-life

cardiovascular conditions and dementia, limited research has been done on the extent of changes during mid-life. This study shows that cognitive decline may be accelerated in the middle age among those with multiple cardio-metabolic conditions, suggesting that interventions may need to be targeted at an earlier age.

Studies performed in France,[3] the UK[1, 4] and Korea[42] have all shown associations between cardiovascular health and dementia, which complement our findings using the HRS data from the US. However, these nations are all wealthy and developed, and more research should be done to examine these associations in lower-income countries.

Many clinical trials have been performed to target cardio-vascular risk factors using multi-domain interventions in hopes of reducing the incidence of dementia, with some producing promising results[5, 11, 48] while others not so much.[6, 7] The drawback of the unsuccessful interventions was that they targeted an elderly population of 70-78 years old, whereas we are now beginning to understand that important changes in cognition may be occurring long before such an age. Therefore, multi-domain intervention attempts should not be discouraged, but the target age group should be expanded to include younger participants.

Strengths and limitations

The strengths of the study include the longitudinal nature of the dataset spanning up to 14 years of follow-up with an average of over 5 repeated measurements per individual. This allows temporal associations to be explored. Since repeated measurements are correlated, mixed effects models were run with interaction terms to estimate a mean effect using REML. Using a mixed effects model allowed the use of incomplete data by only requiring a minimum of 3 data points per individual to establish a regression estimate, regardless of other missing timepoints, minimizing the effects of loss-to-follow up or missed visits. This ensured a large enough sample size to run complex models with many parameters to adjust for all relevant covariates. Finally, the dataset used is publicly available and free to use by the generous contributions of University of Michigan and the NIH, with clear documentation of questionnaires, protocols and codebooks.

Limitations to the study include potential bias with self-report data and excluding disputed responses. Residual confounding is ever present, since there will always be something unaccounted for due to lack of a priori knowledge. Some potential confounders not accounted for

in this study include diet and SES,[49, 50] however education can be used as a proxy for SES,[51] and BMI a proxy of diet.[52, 53] Although this study specified mid-life risk factors, the mean age was 59 and the range of ages spanned from 50-65, so there was some variation in age in the sample. However, for sample size concerns, we kept the age range slightly large. We only specified baseline chronic conditions and did not include the onset of chronic conditions over time. Thus, several people in the no-condition group may have developed some conditions over time. There was no information on gender and stratifying by sex risked losing power due to the decreased sample size, which is why we were unable to confidently perform sex-stratified analysis. Finally, although the HRS total cognitive score is sensitive enough to detect change and has been validated, it does not qualify as a comprehensive or clinical assessment of cognition. [54]

CONCLUSION

In summary, the cognitive decline was accelerated in those with two or more cardio-metabolic conditions compare to those without cardio-metabolic conditions. This study adds further evidence to support the current body of literature surrounding the association between mid-life cardio-metabolic conditions and cognitive decline due to the longitudinal nature of the data. These findings should inspire efforts into targeted prevention of cardio-metabolic conditions at younger adults, since these conditions not only lead to cardiovascular disease, but may also cause cognitive decline in the middle-age.

FOOTNOTES

Contributors: DY and NS participated in designing the study, generating hypotheses, preparing the data and writing the paper. DY wrote the first draft of the report. DY, NS and SD analyzed the data, interpreted the data and critically reviewed the paper, with support from LP. DY and NS had full access to anonymized individual-participant data from the HRS. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data sharing: All HRS data used in this study are freely available from https://hrs.isr.umich.edu/.

Transparency: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported and no important aspects of the study have been omitted.

Dissemination plans: The dissemination plan targets a wide audience, including members of the public, patients, health professionals, and experts in the specialty through various channels: written communication, conferences and social media.

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FIGURE LEGENDS

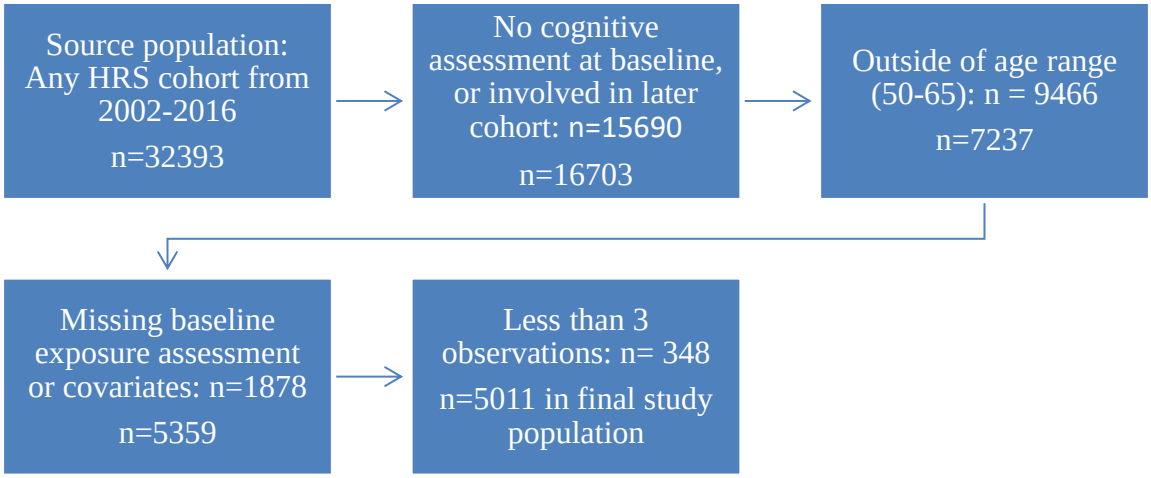

Figure 1: Selection of study sample from the Health and Retirement Study datasets

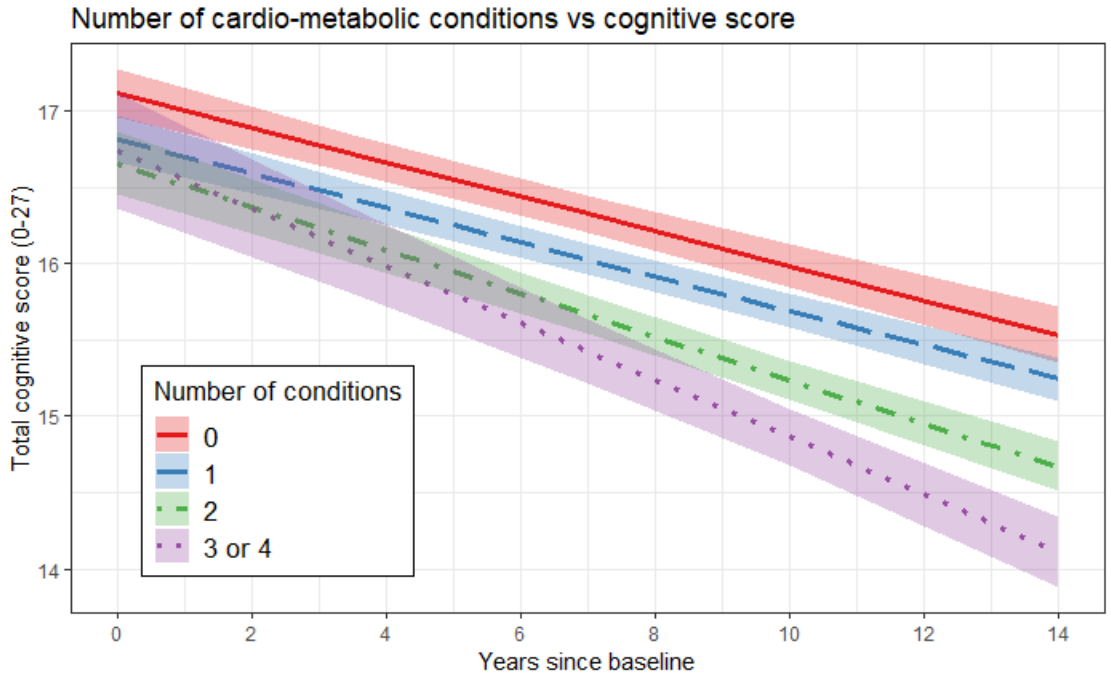

Figure 2: Linear estimated longitudinal trajectories of cognition by number of cardio-metabolic conditions adjusted for baseline age, sex, depression, education, marital status, physical activity, body mass index, smoking and alcohol use. Shaded areas represent the 95% prediction interval per number of conditions.

6 | Bridging Chapter

Our first study concluded that the cognitive trajectories for those with two or more cardio-metabolic conditions were significantly worse in comparison with the trajectory of those with no conditions, suggesting that accelerated cognitive decline in participants with multiple cardio-metabolic comorbidities may occur in middle age. Diabetes is the condition with a particularly interesting relationship with cognitive decline since it may act through a mechanism separate from the other three conditions assessed. Heart disease, stroke and hypertension all affect blood flow to the brain, whereas diabetes acts through insulin related pathways, impaired glucose, beta-amyloid deposition and inflammation among many others. From our study, we were able to determine that people with diabetes were at risk of accelerated cognitive decline, since the slope was worse in participants with diabetes.

We wanted to further analyze the subgroup with diabetes especially with relation to depression. Diabetes and depression have a close bi-directional relationship,[6] and both are associated with dementia, therefore there is great interest in seeing whether people with both diabetes and depression have worse changes in cognitive function compared to participants with just diabetes or depression alone. Using the same dataset as the previous study, the HRS dataset from 2002-2016, we aimed to identify distinct groups of cognitive function trajectories using group-based trajectory models (GBTM). This method identifies a specified number of groups from the dataset which are grouped together by their similarity in trajectory over time. Using this method, we could establish different trajectory groups and estimate the risk of being classified in one group compared to another given the presence of depression and diabetes.

7 | Manuscript 2

Comorbidity of diabetes and elevated depressive symptoms on the risk of cognitive decline: a 14-year follow-up from the Health and Retirement Study

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Comorbidity of diabetes and elevated depressive symptoms on the risk of cognitive decline: 14-year follow-up from the Health and Retirement Study

Objective: Diabetes and depression are both risk factors for cognitive decline, and the relationship between diabetes and depression has been shown to be bidirectional. The purpose of this study was to evaluate whether depression and diabetes were associated with worse cognitive function trajectories in middle-aged and elderly adults compared to no depression or diabetes.

Methods: Participants were from the Health and Retirement Study (HRS), a US longitudinal cohort study, aged 50-70 in 2002 and followed until 2016. Cognitive function was assessed using a modified Telephone Interview for Cognitive Status. Group-based trajectory modelling was used to identify classes of cognitive function trajectories adjusting for baseline age. Multinomial logistic regression was used to estimate the association between diabetes and depression at baseline with the cognitive function trajectory classes. The analysis adjusted for baseline age, sex, education, marital status, physical activity and smoking.

Results: We identified three trajectory classes using latent growth modelling: high baseline cognitive function with a stable trajectory over time (40.5%), intermediate baseline cognitive function with a decrease in cognitive function over time (44.2%) and low baseline cognitive function with a steep decrease over time (15.2%). Compared to the high cognitive function trajectory class, diabetes alone was associated with an odds ratio (OR) of 2.09 [95% CI 1.63 to 2.66] for being in the low cognitive function trajectory class, while elevated depressive symptoms was associated with an OR of 1.97 [95% CI 1.51 to 2.56], and diabetes and depression comorbidity was associated with an OR of 6.74 [95% CI 3.96 to 11.48].

Conclusions: Three levels of cognitive function trajectory were identified – high, intermediate, and low. Diabetes and elevated depressive symptoms were individually associated with the low cognitive function trajectory class; comorbidity greatly increased this risk.

Keywords: diabetes, depression, community, cognitive decline, trajectory

1. Introduction

Diabetes is a well-established risk factor for cognitive decline and dementia, and elevated glucose levels have also been shown to be associated with dementia in those without diabetes (Biessels et al., 2006; Crane et al., 2013; Gregg et al., 2000; Rawlings et al., 2014; Schnaider Beeri et al., 2004). Diabetes and pre-diabetes are associated with accelerated progression of mild cognitive impairment to dementia (Xu et al., 2010). Some studies have found that diabetes prevention and control of glucose levels during midlife could benefit late-life cognitive decline (Rawlings et al., 2014). However, not all those with diabetes may experience accelerated cognitive decline, and therefore it is necessary to further examine which subgroup of people with diabetes have a heightened risk of cognitive decline. The prevalence of depression is twice as high in people with diabetes compared to those without (Sartorius, 2018). Comorbidity also worsens prognosis and mortality of the conditions (Sartorius, 2018).

The relationship between diabetes and depression is likely to be bi-directional (Pan et al., 2010; Ratliff & Mezuk, 2015), and depression and diabetes are both associated with cognitive decline (Hassing et al., 2004; Rock et al., 2014; Yang et al., 2020). A 40-month cohort study found depression in patients with type 2 diabetes was associated with greater cognitive decline in three different cognition tests (Sullivan et al., 2013). A recent systematic review concluded that higher depressive symptoms in those with diabetes was associated with poorer cognitive function than compared to those with fewer symptoms (Danna et al., 2016). However, it remains to be elucidated when decline in cognition occurs among those with comorbidity of diabetes and high depressive symptoms and to what extent having both diabetes and depression affects cognitive function over time. Therefore, the aim of the study was to examine longitudinal data from the US Health and Retirement Study (HRS) to estimate different levels of cognitive function trajectories over time and whether depression and diabetes are associated with worse cognitive function trajectories in middle-aged and elderly adults in the HRS.

2. Methods

2.1: Data Source

Data from the HRS (2002-2016) were used for the present study. We included individuals who were between 50-70 years at baseline in 2002 (n=7538). 2002 was the year when many study variables were renamed for consistency (Amanda et al., 2014). The HRS (is sponsored by

the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. It is a multi-stage clustered sample design reflective of all US households containing at least one person in the age-eligible range (50 and above). All participants consented to the study with follow-up either face-to-face or by telephone performed every two years from date of entry until death or voluntary withdrawal. A comprehensive overview of the dataset is made available by researchers at the University of Michigan (Amanda et al., 2014). Participants were excluded from analyses if they recorded 4 or less cognitive function measurements (minimum 4 points required for latent trajectory analysis), did not have a depression assessment or diagnosed diabetes at baseline, if they were outside the age range of 50-70 at baseline or if they had a proxy respondent. STROBE cohort reporting guidelines were used (von Elm et al., 2014).

2.2: Exposure Measures

Diabetes status was assessed by asking, "Has a doctor ever told you that you have diabetes or high blood sugar?" Participants who responded "Yes" at baseline were coded as having diabetes, participants who responded "No" were coded as not having diabetes. Depression was assessed by HRS using the CES-D 8 measurement tool (Steffick, 2000), a questionnaire consisting of 8 items with a yes or no response. All "yes" responses were summed per person to provide a summary score, with scores ranging from 0-8. A cut-off of 3 or more symptoms has been proposed to indicate a probable diagnosis of depression (Turvey et al., 1999), however the estimated equivalent to the traditional 16+ cut-off on the full 20-item CES-D (scores ranging from 0-60) for the 8-item CES-D was determined to be 4 or more symptoms (Steffick, 2000). Therefore, those with a score of 4 or more were coded as having high levels of depressive symptoms while those with a lower score were considered not depressed.

2.3: Cognitive function measures

Cognitive function was assessed using the HRS global score of cognitive function, derived from a modified Telephone Interview for Cognitive Status (TICS-M) (Cook et al., 2009), which is comprised of three individual cognitive tests for a total range of 0 to 27 points (Crimmins et al., 2011). The three tests were: serial 7s subtraction (5 points); immediate and delayed word recall (20 points); backwards counting (2 points). Serial 7s subtraction was a test of whether the participants were able to continuously subtract 7 from a given number five times

in a row. Immediate and delayed word recall consisted of providing participants with 10 simple words to memorize and repeat both immediately after hearing them and after a few minutes of other interview questions for up to 10 points each. Backwards counting assessed the ability to count backwards from a given number by 20, with 2 points awarded if successful. TICS-M was validated by comparing global score cut-offs with dementia diagnoses in the Aging, Demographics, and Memory Study (ADAMS) (Langa et al., 2005).

2.4: Covariates

Covariates included baseline age, sex (male/female), highest level of education (less than high school/high school/some college/college degree/postgraduate degree), marital status (never married/widowed/separated or divorced/married), vigorous physical activity (1 day a week or less/more than once a week), and smoking (never/former/current). These covariates were included to adjust for potential confounding effects as they have been considered critical confounders in previous studies and systematic reviews on diabetes, depression and cognitive function (Danna et al., 2016; Yang et al., 2020).

2.5: Statistical analysis

Participants were categorized as having neither diabetes nor elevated depressive symptoms, only diabetes, only elevated depressive symptoms, and diabetes with elevated depressive symptoms. A data-driven approach called latent growth analysis was performed using the "proc traj" procedure in SAS 9.4 to define different trajectory groups that share a similar trajectory over time (Jones et al., 2001). A discrete mixture model was estimated for clustering the cognition data into groups using a general quasi-Newton procedure of maximum likelihood estimation (Jones et al., 2001). Missing data was handled using maximum likelihood estimation which generates unbiased parameter estimates assuming MAR. Akaike's information criterion (AIC) and Bayesian information criteria (BIC) was used to identify the optimal number of groups, where a smaller value represents a better fit. We began by testing a two-group model, then sequentially adding a group until we could determine the best group by fit. Based on prior cognition research using latent trajectories, three was generally the most suitable number of groups (Elovainio et al., 2017; Hayden et al., 2011; Marioni et al., 2015). We also tested for the order of polynomial for each group's cognitive function trajectory (i.e. linear vs quadratic vs cubic). However, other aspects were considered to prevent over or under-fitting the data: a)

whether the groups had enough representation (>10% proportion of group membership); b) whether adding an extra group added valuable information (if two groups are too similar then it may not be providing new information); and c) whether the shape of the trajectory makes sense in the context of cognitive function changes over time.

Multinomial logistic regression was used to estimate the odds ratio (OR) of belonging to the low or intermediate groups compared to the high group with 95% confidence intervals (CI). An unadjusted model was first conducted followed by a model adjusting for age, sex, education, marital status, vigorous physical activity and smoking.

3. Results

There were 32393 participants with data between 2002 and 2016 from the HRS, with 10234 between ages of 50 to 70 in 2002. Of the 10234, 38 did not have a diabetes diagnosis, 563 did not have a depression assessment, and 2095 had less than 4 time points. Therefore, the final analytic sample consisted of 7538 participants. Descriptive statistics of the study sample are provided in Table 1. Females were more likely to have elevated depressive symptoms only or both diabetes and elevated depressive symptoms than to have diabetes only or neither condition. Having no degree was most common in the group with both conditions, whereas college or professional degrees were most likely in the neither conditions group. The proportion of married participants was lower in the group with both conditions as well as in the elevated depressive symptoms group compared to diabetes only and neither. Physical activity was lowest in the group with both conditions, and the diabetes only group had a higher proportion of physical activity compared to the group with elevated depressive symptoms while the group with neither condition had the highest proportion of physical activity. Smoking was lowest in the group with elevated depressive symptoms. Most participants belonged in the group with neither diabetes nor elevated depressive symptoms (n=5605, 74.4%), whereas all the other exposure variants only amounted to a quarter of the sample.

[Table 1 near here]

The trajectory with three groups and a linear shape was selected as the best-fitting model with an AIC of -123537.4 and a BIC of -123847.6, which was a better fit than the four-group and five-group models and a slightly worse fit than the two-group model. However, the three-group model provided more information than the two-group model while maintaining a proportional

group probability, while the four-group and five-group models gave rise to some groups with very small proportions that are very similar to one another. Higher orders of polynomials were not significantly different to the linear shape and risked over-fitting the data.

[Figure 1 near here]

Figure 1 shows the final three-trajectory model. The high cognitive function trajectory had the highest baseline cognitive function value and the slowest decline. The intermediate cognitive function trajectory had a lower baseline value and a steeper decline, whereas the low cognitive function trajectory had the lowest baseline value and the most accelerated cognitive decline. Most participants belonged to intermediate functioning (44.2%) or high functioning (40.5%) while only 15.2% belonged to low functioning. The trajectory of the high cognitive function group had an intercept of 19.55 [standard error (SE) 0.059] and a slope of -0.22 [SE 0.01]. The intermediate cognitive function group had a slope of 16.50 [SE 0.06] and a slope of -0.43 [SE 0.01]. The low cognitive function group had an intercept of 11.79 [SE 0.10] and a slope of -0.54 [SE 0.18]. The mean cognitive function score over time per group is shown in Table 2.

[Table 2 near here]

The association of diabetes and elevated depressive symptoms with cognitive function trajectory groups are shown in Table 3. The OR represents the risk of being classified into the low cognitive function group compared with the risk of classifying into the high cognitive function group. The group with neither diabetes nor elevated depressive symptoms was set as the reference exposure. In all cases, the OR of belonging to the low group was greater than the OR of belonging to the intermediate cognitive function group. All ORs were attenuated with adjustment however remained statistically significant. The group with both diabetes and elevated depressive symptoms had the highest OR of being part of the low function class and intermediate function class. While diabetes or elevated depressive symptoms alone were also associated with more likely membership of the low and intermediate cognitive function class compared to the high functioning class, there was no significant difference in OR between the two.

[Table 3 near here]

4. Discussion

Three cognitive function trajectories were identified through latent class analysis that spanned the years 2002-2016 using data from the HRS with at least 4 repeated measures of cognitive function. All three identified trajectories demonstrated a decrease in cognitive function over time, however with the trajectories could still be classified into low, intermediate and high cognitive function trajectories. Diabetes alone was equally associated with poorer cognitive function trajectories compared to elevated depressive symptoms alone, however both combined resulted in an even greater likelihood of poorer cognitive function trajectory.

Other studies of cognitive trajectories in both middle aged (Whitehall II) or elderly cohorts (Paquid, Religious Orders Study) using latent growth modelling have found 3 levels of classes to be the best fit; with a low, intermediate and high class as we have observed (Elovainio et al., 2017; Hayden et al., 2011; Marioni et al., 2015). The result is also consistent with a studies that reported significantly reduced cognitive function in people with diabetes suffering from depression (Guerrero-Berroa et al., 2018; Sullivan et al., 2013). A few mechanisms have been proposed that help explain this observed association. Hypoglycemia and insulin resistance causes decreased intracellular glucose levels in the brain, which results in neurotoxicity and brain dysfunction (Rosenblat et al.). Depression could potentially facilitate neural damage via hypothalamic pituitary adrenal (HPA) axis dysregulation, lowering of brain-derived neurotrophic factor levels as well as inflammatory pathways (Rosenblat et al.). Increased levels of formaldehyde in tissues are also associated with depression, diabetes and neuro-degeneration (Hipkiss, 2017). These findings may suggest that depression and diabetes may play a role in metabolic pathways that increase formaldehyde production, which would induce neurotoxicity due to overproduction of intracellular reactive oxygen species (Songur et al., 2010).

The strengths of the study include the longitudinal nature of the data spanning up to 14 years of follow-up with a minimum of 4 repeated measurements per individual. Latent class analysis uses mixture models which accounts for unobserved heterogeneity in a population while identifying homogenous subgroups. Cognitive assessment measures have been validated (Crimmins et al., 2011; Mary Beth et al., 2005), as well as the CES-D score (Karim et al., 2015; Missinne et al., 2014; Van de Velde et al., 2009). Several covariates were accounted for.

Limitations to the study include potential bias with self-report data. Diabetes was ascertained based on high blood sugar, and thus could contain those with pre-diabetes, leading to mis-classification. Also, CES-D 8 has been cited to be a measure of psychological distress rather than depression syndrome measured by Composite International Diagnostic Interview-short form (CIDI-SF) (Dang et al., 2019). Thus, our study can only conclude the associations of elevated depressive symptoms rather than those of diagnosed depression. While other studies have suggested medication could improve cognitive decline in both diabetics and those with depression, medication use was not considered in this study due to unreliability of the self-report data and a lack of a proper control group of those with the disease but not on medication. The population was on the older side, with mean age of 62, while cognitive decline has been shown to start much earlier (Salthouse, 2009).

5. Conclusion

Three levels of cognitive function trajectory were identified – low, intermediate and high. Elevated depressive symptoms and diabetes were individually associated with a low or intermediate cognitive function trajectory; comorbidity of diabetes and elevated depressive symptoms increased the risk of belonging to both the low and intermediate cognitive function trajectory group. These results may inspire future studies to consider both metabolic diseases, mental health and cognitive aging together instead of treating them as separate issues.

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7. Tables and Figures

Table 1: Descriptive statistics of baseline characteristics for HRS participants in 2002 according to diabetes and depression status (n=7538)

	Neither condition (n=5605)	**Elevated depressive symptoms only (n=815)**	**Diabetes only (n=919)**	**Both conditions (n=199)**	**Total (n=7538)**
Baseline age: Mean (SD)	62.2 (4.93)	61.6 (5.07)	63.1 (4.68)	62.7 (4.64)	62.3 (4.92)
Sex (%):					
Male	38.6	25.0	47.0	25.6	37.8
Female	61.4	75.0	53.0	74.4	62.2
Education (%):					
Postgraduate Degree	11.3	3.4	8.0	3.0	9.8
College Degree	17.2	12.4	13.6	6.5	16.0
High School Diploma	57.1	52.0	51.4	42.7	55.5
Less than High School	14.3	32.1	26.9	47.7	18.7
Vigorous Physical Activity (%):					
Yes	51.7	32.4	40.8	22.6	47.5
No	48.2	67.5	59.1	77.4	52.4
Marital Status (%):					
Married	45.7	56.0	73.2	45.7	70.5
Widowed	26.6	16.8	12.0	26.6	12.0
Divorced or Separated	22.6	22.5	11.6	22.6	14.2
Never Married	4.5	4.7	3.0	4.5	3.1
Smoking (%):					
Yes	14.9	22.9	10.9	13.6	15.2
No	84.6	76.2	88.6	86.4	84.2

If percentages don't add up to 100%, this is due to missing values, however missing values never exceeded 1% in any category

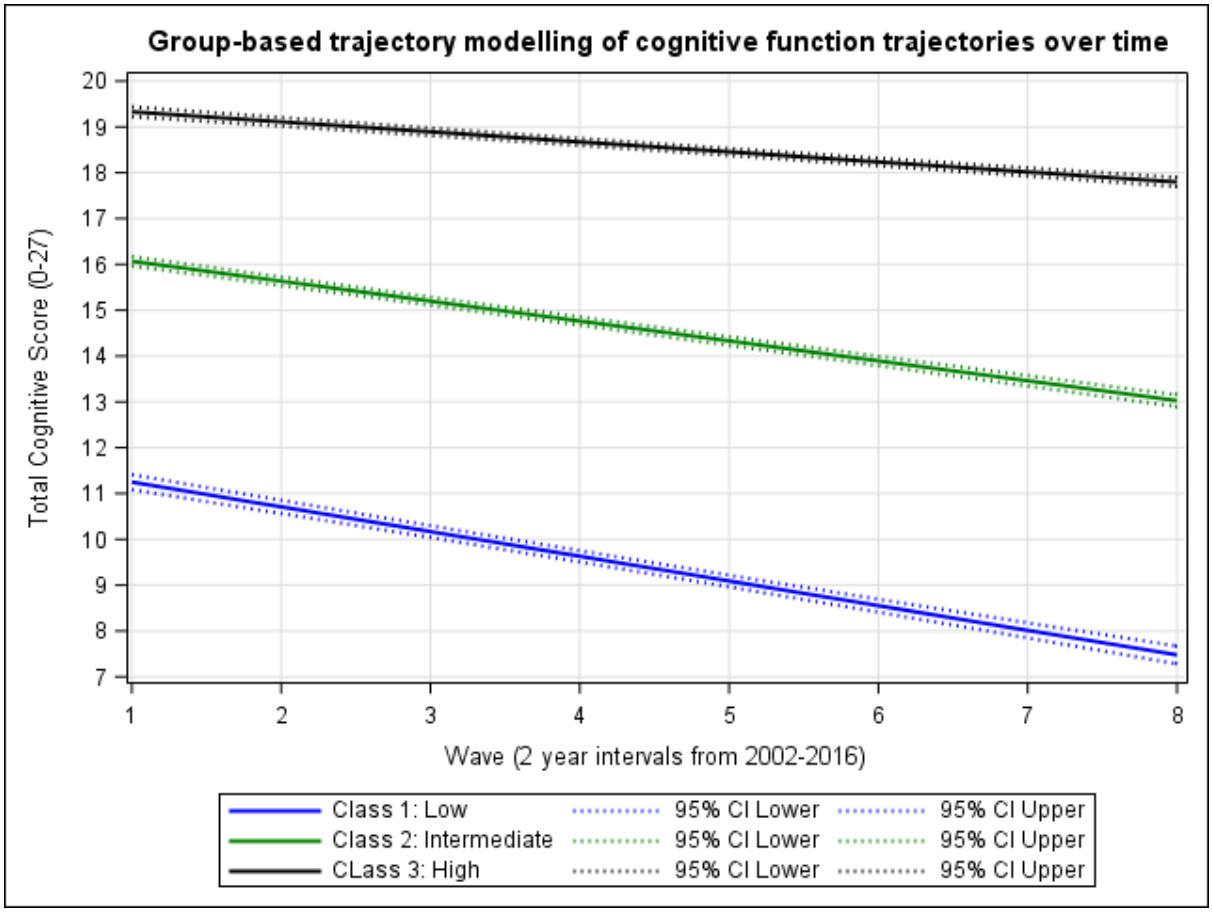

Figure 1: Group based trajectories of cognitive function over time with three specified groups

Table 2: Mean cognitive function score per group at each wave from 2002-2016

Group	**Mean (SD) cognitive function score out of 27**							
Wave	1	2	3	4	5	6	7	8
Low class	11.2 (3.5)	10.5 (3.4)	10.0 (3.3)	9.9 (3.3)	8.8 (3.1)	8.3 (3.1)	8.0 (3.1)	7.5 (3.1)
Intermediate class	15.9 (3.0)	15.5 (2.7)	15.3 (2.8)	14.9 (2.8)	14.2 (2.8)	13.7 (2.9)	13.5 (2.9)	12.9 (3.1)
High class	19.4 (2.9)	19.0 (2.7)	19.0 (2.7)	18.9 (2.6)	18.5 (2.8)	18.2 (2.8)	18.2 (2.9)	17.8 (3.0)

Table 3: Multinomial logistic regression analysis for the association of diabetes and elevated depressive symptoms with cognitive function trajectories from 2002-2016: Odds ratio of belonging to a certain trajectory class compared to the high trajectory class

Exposure group compared to neither	**Cognitive function trajectory group**	
	Low vs high [95% CI]	Intermediate vs high [95% CI]
Elevated depressive symptoms only		
Unadjusted	3.06 [2.47, 3.79]	1.87 [1.57, 2.22]
Adjusted*	1.97 [1.51, 2.56]	1.75 [1.44, 2.12]
Diabetes only		
Unadjusted	3.09 [2.52, 3.78]	1.82 [1.55, 2.14]
Adjusted*	2.09 [1.63, 2.66]	1.56 [1.30, 1.86]
Comorbidity		
Unadjusted	14.39 [9.09, 22.77]	3.71 [2.36, 5.86]
Adjusted*	6.74 [3.96, 11.48]	2.81 [1.73, 4.57]

*Adjusted for age, sex, education, marital status, vigorous physical activity and smoking.

8 | Discussion

Cognitive function is bound to decline as we age. However, in healthy adults this decline should be minimal. In our first study, we saw that cognitive function in the group without cardio-metabolic conditions decreased by around 1.5 points out of 27 over a 14-year period. In the second study, healthy individuals were more likely to belong to the high cognitive function trajectory group and experienced a decrease of around 1 point out of 27 over a 14 -year period. This relatively stable decline has been shown in similar longitudinal studies.[69] With the addition of cardio-metabolic conditions, the decline over time worsened. With only one condition, the change was not noticeable, however with two or more conditions the decline was accelerated. Previous cross-sectional studies have proposed an additive effect on cognitive decline with increasing number of cardio-metabolic diseases,[4] which was supported by our findings since the greater the number of cardio-metabolic conditions, the greater the decline in cognitive function over time.

Seeing as cardio-metabolic conditions are risk factors for cardiovascular disease, this means that the higher the risk of cardiovascular disease, the higher the risk of accelerated cognitive decline. This concept is well established among studies in the elderly.[70] What this study adds, is that changes in cognitive function can occur as early as midlife. Many studies have looked at midlife risk factors and subsequent dementia.[71, 72] However, they neglect the cognitive changes during the transition from midlife risk factor assessment to dementia diagnosis. This is where my thesis fills the gap. Dementia is a progressive disorder and changes in cognitive abilities can begin over a decade before dementia diagnosis.[73] There is evidence that accelerated decline precedes mild cognitive impairment and dementia,[73] which means the risk of dementia is increased in those with accelerated cognitive decline.[74, 75] By studying the changes in cognition in middle-aged adults, we were able to determine that changes in cognitive function can be detected early on.

An amplified association of comorbid diabetes and depression with cognitive decline was seen in previous studies.[76, 77] This is consistent with our results, where those with comorbidity were at increased risk of having a worse cognitive function trajectory. The caveat is that we did not have a proper diagnosis of depression; and relied on a cut-off score for the CES-D 8 questionnaire. However, using elevated depressive symptoms as a proxy for depression

resulted in findings that support current literature and should still be taken as evidence for a comorbid effect of depressive symptoms and diabetes on worsening cognition.

The HRS cognitive test, TICS-M, places a huge emphasis on immediate and delayed recall.[78] Immediate recall usually follows a gradual linear decline over time while delayed recall has been shown to remain relatively consistent until just before dementia diagnosis where there is a sudden accelerated decline.[74] In terms of characterizing which group of individuals experiencing cognitive decline would be at greatest risk of developing dementia, evidence suggests those with language impairment and declining episodic and working memory are at greatest risk.[74] Although our study did not examine changes in specific cognitive aspects, episodic and working memory comprised 20 out of the 27 points of the global cognitive score we used to assess cognitive function.[78] Therefore, cognitive function changes we measured should reflect cognitive decline associated with risk of dementia.

Prevention of dementia has been difficult.[79] However, in the last decade, progress has been made in identifying modifiable risk factors for dementia. According to the recent Lancet Commission on Dementia report,[80] modifiable risk factors may account for up to 35% of all dementia cases. Several of these modifiable risk factors are similar to those for cancer and cardiovascular disease, including metabolic factors, health behaviours (physical inactivity and smoking), and social factors (limited social interaction). Focussing on the management of chronic conditions (diabetes, hypertension etc.) as well as behavioral and social factors may reduce morbidity and mortality associated with chronic conditions and might also decrease the risk or delay the onset of dementia.

The strengths of my thesis include the longitudinal nature of the data which allowed for more complex modelling that could handle correlated and missing data. This made it possible to compare trajectories between different groups. There was a long follow-up time of 14 years, which allowed us to establish long-term relationships between our variables of interest. Also, we controlled for most of the well-established confounders in our analyses.

There were many limitations to the study as well. Depression and the cardiovascular conditions were self-reported and not based on a clinical assessment. CES-D 8 only asks about experiences in the past week, so participants with depressive episodes or currently taking treatment for depression may not be captured.[81] Also, there was no information on history of

depression. Finally, the dataset had a lower age limit of 50, meaning our study population consisted mostly of people nearing the end of mid-life and early late-life. To fully explore the changes in mid-life, the preferable lower age limit should be around 40 years old.[82]

9 | Conclusion

Using data from HRS conducted in the US, we concluded that having multiple cardio-metabolic conditions worsened cognitive trajectories in middle-aged adults, and that comorbidity of diabetes and elevated depressive symptoms greatly increased the risk of belonging to the low-class trajectory in middle-aged to elderly adults (low baseline cognitive function with accelerated decline). These results suggest the complex nature of cognitive aging and expands on the many factors involved with cognitive decline.

The hope of this thesis is to inspire further research exploring potential treatment and prevention methods in middle-aged or even younger participants, such as clinical trials for behavioural factor interventions with long follow-ups to assess cognitive changes over time while participants age. These can include multi-domain interventions promoting exercise, diet habits, smoking cessation, social interaction etc. This would strengthen the evidence for shared mechanisms between cardiovascular disease and dementia, as well as elucidate the role depression plays in this association. Since our study was limited to data from the US and did not have a proper assessment of depression diagnosis, future studies could examine the roles of cardio-metabolic conditions and depression in other countries to see if our results would be generalizable to the rest of the world. Finally, although cognitive decline increases the risk of dementia, not everyone will develop dementia. Therefore, it would be interesting to follow-up with the participants from the present study and obtain dementia diagnosis information to help identify what factors may be protective against dementia in those suffering from cognitive decline.

Cognitive aging and cardiovascular aging seem to be two separate entities. However, they may share more similarities than we once thought. This could open possibilities to prevent cognitive decline and cardiovascular disease with the same prevention and treatment methods.

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11 | Appendix

STROBE Checklist for Manuscript 1

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors
Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	2
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			

Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a (not matched)
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5-6
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	5,7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6-7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6-7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	6-7
Statistical methods	#12c	Explain how missing data were addressed	7
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	5
Statistical methods	#12e	Describe any sensitivity analyses	7

Results

Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	8
Participants	#13b	Give reasons for non-participation at each stage	n/a (reasons not given)
Participants	#13c	Consider use of a flow diagram	7
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a (correlated data, so not everyone has data at same time points)
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	7
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9-10
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
Main results	#16b	Report category boundaries when continuous variables were categorized	n/a/ (kept as continuous
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a (not calculating risks)

Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5

STROBE Checklist for Manuscript 2

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	2
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3

Methods

Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a (not matched study)
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	4,5
Bias	#9	Describe any efforts to address potential sources of bias	5
Study size	#10	Explain how the study size was arrived at	3,6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5

Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a (did not assess subgroups)
Statistical methods	#12c	Explain how missing data were addressed	5
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	6
Statistical methods	#12e	Describe any sensitivity analyses	n/a (did not perform)
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	6
Participants	#13b	Give reasons for non-participation at each stage	n/a (reasons not specified)
Participants	#13c	Consider use of a flow diagram	n/a (written in text)
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	6
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a (latent modelling and correlated data, so

			not everyone has data at each time point)
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	6
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	7
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
Main results	#16b	Report category boundaries when continuous variables were categorized	n/a (did not categorize continuous outcomes)
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a (odds ratio, not risk)
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a (did not perform)
Discussion			
Key results	#18	Summarise key results with reference to study objectives	7
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	8

Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	8
Generalisability	#21	Discuss the generalisability (external validity) of the study results	8
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4