Investigating the Relationship Between Metabolic Syndrome and the Risk of Developing Dementia



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DPhil Publications, Recognitions and Awards:

Peer-Reviewed Research Articles:

1. **Qureshi D**, Collister J, Allen N, Kuźma E, Littlejohns T. Association between metabolic syndrome and risk of incident dementia in UK Biobank. (2023). Published in ***Alzheimer's & Dementia***. https://doi.org/10.1002/alz.13439

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4. **Qureshi D**, Kuźma E, Allen N, Littlejohns T. Metabolic syndrome and risk of incident dementia: a systematic review and meta-analysis of prospective cohort studies. (2024). *Manuscript In Preparation.*

Conference Presentations and Abstracts:

1. **Qureshi D**, Allen N, Littlejohns T, Kuźma E. Association between metabolic syndrome with incident dementia: a systematic review and meta-analysis of prospective cohort studies (Zum Zusammenhang zwischen metabolischem Syndrom und Demenzrisiko: Ein systematisches Review und eine Meta-Analyse prospektiver Kohortenstudien). (2024, September). ***Gemeinsamer Jahreskongress DGGG & DGG 2024***. Kassel, Germany. https://www.gerontologie-geriatrie-kongress.org/programm/session/beste-eingereichte-beitraege-geriatrie.html

2. **Qureshi D**, Luben R, Hayat S, Talarico R, Allen N, Kuźma E, Littlejohns T. (2024, July). Metabolic syndrome and risk of incident dementia in EPIC-Norfolk: the role of age and exposure duration. ***Alzheimer's Association International Conference (AAIC)***. Philadelphia, USA.

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4. **Qureshi D**, Topiwala A, Allen N, Kuźma E, Littlejohns T. (2024, March). Metabolic syndrome in association with brain structure and cognition in 32,864 UK Biobank participants. ***Alzheimer's Research UK (ARUK) Conference***. Liverpool, UK.

5. **Qureshi D**, Topiwala A, Allen N, Kuźma E, Littlejohns T. (2023, December). Association of metabolic syndrome with brain structure and cognition in 32,864 UK Biobank participants. ***UK Biobank Scientific Conference***. London, UK.

6. **Qureshi D**, Collister J, Allen N, Kuźma E, Littlejohns T. (2023, July). Association between metabolic syndrome and incident dementia in UK Biobank. ***2023 Alzheimer's Research UK (ARUK) Thames Valley Network Dementia Research Day***. St Anne's College, Oxford, UK.

7. **Qureshi D**, Collister J, Allen N, Kuźma E, Littlejohns T. (2023, July). Investigating the association between metabolic syndrome and incident dementia: a prospective population-based cohort study of UK Biobank participants. ***Alzheimer's Association International Conference (AAIC)***. Amsterdam, Netherlands. https://doi.org/10.1002/alz.071957

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Protocols:

1. **Qureshi D**, Kuźma E, Allen N, Littlejohns T. Association between metabolic syndrome and incident dementia: a systematic review and meta-analysis of prospective cohort studies. (2024). ***The International Prospective Register of Systematic Reviews***. URL

Media Coverage of DPhil Research:

DPhil article published in *Alzheimer's & Dementia* was featured in **200+** news outlets worldwide, reaching over **1 billion views**. This work received coverage in prominent newspapers, including:

The Independent: "Poor metabolic health 'linked with 12% higher risk of dementia later in life"'

The Daily Mail: "Poor metabolic health 'linked with 12% higher risk of dementia later in life"'

The Evening Standard: "Poor metabolic health 'linked with 12% higher risk of dementia later in life"'

The Mirror: "Dementia risk in later life could be increased by common health issue 25% of adults have"

Oxford University Home Page: "Poor metabolic health could increase risk of developing dementia later in life"

Oxford University Twitter Page: "Researchers @Oxford_NDPH have found that having poor metabolic health was related to an increased risk of developing dementia in a study of more than 176,000 individuals."

DPhil article published in *Diabetes Care* was also featured online in various social media channels, reaching over **80 million views** globally:

Oxford University Home Page: "Poor metabolic health linked to worse brain health"

Oxford University Twitter Page: "An @Oxford_NDPH study has found that people with worse metabolic health are more likely to have memory and thinking problems, and worse brain health."

Oxford University LinkedIn Page: received 300+ reactions and 30+ reposts

MSN: "Poor metabolic health linked to worse brain health"

Reddit r/Science: received ~1,000 upvotes and 30+ comments

Diabetes Core Update – Podcast (August 2024): "a monthly audio podcast devoted to presenting and discussing the latest clinically relevant articles from American Diabetes Association's four scholarly journals, as well as notable articles from other journals related to diabetes research and care. Intended for the busy health care professional, Diabetes Core Update examines how the latest research and information published in ADA journals and beyond are relevant to clinical practice and can be applied in a treatment setting."

Awards Related to DPhil Research:

Conference Fellowship Award **July 2023**

Alzheimer's Association International Conference (AAIC): Awarded competitive conference (among 1000s of submissions) fellowship award to cover costs to attend AAIC 2023 in Amsterdam, Netherlands.

Best Poster Prize Winner **July 2023**

Alzheimer's Research UK (ARUK): Voted best poster (1 in 50+) at the ARUK Thames Valley Dementia Research Day 2023, St Anne's College, Oxford.

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Statement of Contributions:

DQ developed all pre-specified analysis plans and conducted all analyses presented within this doctoral thesis. DQ led and contributed to the conception, design, conduct and structure of each objective, with all supervisors (TJL, NA, EK) making key contributions to each of these aspects. DQ drafted all content presented in this thesis (including any content related to relevant peer-reviewed publications and conference abstracts), which was critically reviewed and edited by all supervisors (TJL, NA, EK). TJL and NA played key roles in the acquisition of the data used in this work. For the systematic review, NR (Nia Roberts; Senior Librarian at University of Oxford) provided support in the development of each search strategy for the three databases used. EK acted as a second reviewer for the article screening process conducted using Covidence software. TJL acted as a second reviewer for the quality assessment of identified studies. For the UK Biobank analyses, members of the Translational Epidemiology Unit provided key guidance regarding the creation of confounding variables and dementia as an outcome. Ben Lacey (Associate Professor at University of Oxford) and Robert Clarke (Emeritus Professor at University of Oxford) provided expert clinical input regarding capture of medications to define specific components within the exposure definition. For EPIC-Norfolk analyses, members of the MRC Epidemiology Unit at Cambridge University, Robert Luben and Shabina Hayat, provided guidance in creation of the pre-specified analysis plan, variable selection process, and critically reviewed and edited the associated manuscript. Statistical guidance on trajectory modelling was provided by Robert Talarico (Senior Research Methodologist and Statistician at Institute for Clinical Evaluative Sciences). Anya Topiwala (Consultant Psychiatrist at University of Oxford) provided expert guidance on UK Biobank neuroimaging analyses. DQ is the guarantor of this work, and as such, had full access to all data presented in this thesis and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

List of Abbreviations:

β: Standardised Beta coefficient

3C Study: Three-City Study

ACC/AHA: American College of Cardiology/American Heart Association Task Force Guideline

ACCORDION MIND: Extension of the Memory in Diabetes (MIND) sub-study of the Action to Control Cardiovascular Risk in Diabetes

ACE: Angiotensin-Converting Enzyme

AD: Alzheimer's disease

AHA/NHLBI: American Heart Association and the National Heart, Lung, and Blood Institute

ANOVA: Analysis of Variance

APOE: Apolipoprotein E

ASPREE: ASPirin in Reducing Events in the Elderly

BDS: Backward Digit Span Task

BIANCA: Brain Intensity AbNormality Classification Algorithm

BIC: Bayesian Information Criterion

BP: Blood Pressure

CaPS: Caerphilly Prospective Study

CDR: Clinical Dementia Rating

Chi^2: Cochran's Chi-squared test

CI: Confidence Interval

CSBA: Conselice Study of Brain Ageing

DASH: Dietary Approaches to Stop Hypertension

df: Degrees of Freedom

DSM: Diagnostic and Statistical Manual of Mental Disorders

DXA: Dual-energy X-ray Absorptiometry

EPHPP: Effective Public Health Practice Project

EPIC: European Prospective Investigation into Cancer

FAST: FMRIB's [Functional Magnetic Resonance Imaging of the Brain] Automated Segmentation Tool

FI: Fluid Intelligence Score

FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability trial

FIRST: FMRIB's [Functional Magnetic Resonance Imaging of the Brain] Integrated Registration and Segmentation Tool

FLAIR: Fluid-Attenuated Inversion Recovery

FMRIB: Functional Magnetic Resonance Imaging of the Brain (Analysis Group at Oxford University)

GBP: British Pound Sterling

H & Y Stage: Hoehn and Yahr Stage

HbA1c: Glycated Hemoglobin A1c

HDL: High density lipoprotein.

HR: Hazard ratio

I^2: I-squared Statistic

ICD: International Classification of Diseases

ICD-9: International Classification of Diseases, Ninth Revision

ICD-10: International Classification of Diseases, Tenth Revision

IDF: International Diabetes Foundation

IDP: Imaging Derived Phenotype

INV-202: Novel cannabinoid receptor-1 (CB1R) inverse agonist

ILSA: Italian Longitudinal Study on Ageing

IQR: Interquartile Range

KNHI: Korean National Health Insurance Service - National Health Information Database

MetS: Metabolic Syndrome

MET: Metabolic Equivalent of Task

MPC: Matrix Pattern Completion Test

MRI: Magnetic Resonance Imaging

NCEP-ATP III: National Cholesterol Education Program – Adult Treatment Panel III

NfL: Neurofilament Light Chain

NHS: National Health Service

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association

NINDS-AIREN: National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN)

NR: Not Reported

OR: Odds Ratio

PAL: Paired Associate Learning Task

PDD: Parkinson's Disease Dementia

pHR: Pooled Hazard Ratio

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

PROSPERO: The International Prospective Register of Systematic Reviews

PRS: Polygenic Risk Score

P-tau: Phosphorylated tau

Q (m): Q For Moderators

Ref: Reference Group

SD: Standard Deviation

SDS: Symbol Digit Substitution Task

SHR: Sub-distribution Hazard Ratio

SIGN: Scottish Intercollegiate Guidelines Network

SLAS: Singapore Longitudinal Ageing Study

SNP: Single Nucleotide Polymorphisms

SPRINT MIND: Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension - Memory in Diabetes

TG: Triglycerides

TMT: Trail Making Test

TNHIRD: Taiwan National Health Insurance Research Database

TwSHHH: Taiwanese Survey on Prevalence of Hypertension Hyperglycemia and Hyperlipidemia

UK: United Kingdom

UPDRS: Unified Parkinson's Disease Rating Scale

URL: Uniform Resource Locator

VaD: Vascular Dementia

WC: Waist Circumference

WHO: World Health Organisation

WMH: White Matter Hyperintensity

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THESIS ABSTRACT

BACKGROUND: Metabolic syndrome (MetS) may be a risk factor for dementia, however, the relationship remains inconclusive. This thesis sought to clarify the association between MetS and incident dementia.

METHODS: **First**, a systematic review was conducted (up to Feb-2022), identifying prospective studies evaluating associations of MetS and risk of incident dementia. **Second**, UK-Biobank prospective analyses of 176,249 dementia-free adults aged ≥60 years with up to 15-years of follow-up investigated associations of MetS (defined using the 2009 Harmonized Criteria) with incident all-cause dementia (ascertained through medical records) using multivariable Cox-regression. **Third**, EPIC-Norfolk prospective analyses were conducted in 20,150 adults (50-79 years) with up to 25-years of follow-up, employing similar methods as Objective 2, and additionally exploring the impact of age and duration/trajectory of living with MetS on dementia risk. Group-based trajectory modelling was performed to identify MetS trajectories. **Fourth**, an updated systematic review and meta-analysis was performed, incorporating UK-Biobank and EPIC-Norfolk findings, plus newly published literature (up to Feb-2024). **Fifth**, associations of MetS with neuroimaging and cognition were explored in 37,395 dementia-free adults from UK-Biobank using multivariable linear-regression.

RESULTS: The systematic review revealed inconsistent evidence, owing to small sample sizes, short follow-up, and inadequate confounder adjustments across studies. In UK-Biobank analyses, MetS was associated with a 12% increased risk of all-cause dementia (HR, 1.12, 95%CI: 1.06-1.18); risk also varied by follow-up length, number of MetS components, and *APOE*-ε4 carrier status. EPIC-Norfolk analyses found similar trends, and additionally revealed that mid-life MetS was associated with dementia risk (HR, 1.21 [1.05-1.39]), but was attenuated in late-life (HR, 0.96 [0.81-1.14]). A prolonged MetS duration was also associated with heightened dementia risk (HR, 1.26 [1.13-1.40]). In meta-analyses, MetS was associated with all-cause dementia (pHR, 1.12, [1.08-1.15]), but not Alzheimer's (pHR, 0.91 [0.72-1.15]) or vascular dementia (pHR, 1.40 [0.96-2.06]). Lastly, MetS was associated with lower total and region-specific brain volumes, increased cerebrovascular pathology, and poorer performance across all cognitive domains.

CONCLUSIONS: This thesis provides robust evidence indicating that MetS is an independent risk factor for dementia. Targeting MetS might be a useful strategy for dementia prevention. Further research is necessary to explore these associations in diverse populations and understand the pathways linking MetS to different dementia subtypes.

CHAPTER 1

Introduction

CHAPTER SUMMARY

Dementia remains a leading cause of death worldwide, despite recent efforts and advancements in available treatments and interventions. Current dementia prevention strategies have emphasised a recent focus on trying to understand and identify which modifiable risk factors for dementia can be effectively targeted to possibly help prevent or delay progression towards the disease. One of the emerging topics in this area concerns the role of metabolic syndrome (MetS) in the development of dementia. MetS is a condition characterised by a cluster of cardiometabolic and vascular symptoms that tend to co-occur in individuals. Globally, it is estimated that approximately 1 in 4 adults live with MetS and this is expected to increase over time. Previously, MetS has been implicated as a potential risk factor for the development of many different health conditions. In recent years, there has been considerable interest among the scientific community to establish whether MetS plays any role in the risk of developing cognitive and neurodegenerative diseases, including dementia. Given both the high prevalence of MetS, and the growing number of dementia cases globally, untangling this relationship is of great importance from a public health perspective; this is especially pertinent because MetS consists of several modifiable traits, and therefore, it may be an important target for dementia prevention strategies. However, current evidence indicates that the relationship between MetS and dementia remains unclear.

In this Chapter, the concept of MetS is introduced, and the importance of studying its potential link with dementia is discussed in detail. Specific knowledge gaps on this topic are also highlighted, which further sets the stage for discussing the purpose of conducting this DPhil research and outlining its specific objectives.

BACKGROUND

Importance

Dementia is a term used to describe a progressive neurodegenerative condition that is characterised by a gradual loss in cognitive and functional impairments which ultimately interfere with the ability to carry out activities of daily living.[1-3] There are several different types of dementia, among which the most common are Alzheimer's disease (resulting from plaques and tangles in the brain), vascular dementia (caused by reduced blood flow to the brain), Lewy Body dementia (often caused by abnormal protein buildup in the brain), and frontotemporal dementia (resulting from degeneration of the frontal and temporal lobes).[4] However, it is important to acknowledge that in many cases, dementia presents with mixed pathology, characterised by both vascular and neurodegenerative components.[5-7] For example, diagnoses of mixed Alzheimer's and vascular dementia are frequently observed, with the amyloid deposition inherent in Alzheimer's also contributing to vascular pathology.[8] Cases of mixed Alzheimer's with Lewy body dementia are also frequently observed.[9] Therefore, the clinical diagnosis of specific dementia subtypes is challenging and may lack reliability due to a high risk of misclassification[10] resulting from a significant overlap in the clinical presentation and characteristics of different dementia pathologies.[10-12] This is further complicated by varying levels of cognitive reserve across individuals, whereby different socio-behavioural factors (e.g., education, occupation type, and engagement in cognitively-stimulating activities) influence how 'resilient' a person's brain is in coping with progressing dementia pathology.[13,14] Therefore, from a population health perspective, all-cause dementia remains a highly useful concept to explore, as it reflects the combined impact of multiple interacting dementia pathologies for which their detrimental effects may further vary by different levels of cognitive reserve. Concerningly, the global prevalence of dementia is rapidly increasing at an alarming rate, and is expected to grow from about 50 million

currently to 150 million by 2050.[15] Dementia is also the seventh leading cause of death worldwide, with 1.6 million deaths resulting from the disease in 2019 alone.[16] It is also major contributor to physical dependency and disability; among individuals aged 60 years and older, dementia was ranked among the top 10 causes of years of healthy life lost due to disability.[16] There is also a tremendous economic and societal impact associated with dementia; in 2019, the global costs related to dementia were estimated to be approximately $1.3 Trillion (equivalent of ~£1 Trillion), and these estimates are projected to increase dramatically in the near future.[16]

There are currently few treatment options available for dementia, warranting an urgent need to understand and identify which risk factors can be effectively targeted to help prevent or delay its progression. Recent health guidelines have emphasised the need to invest in preventative strategies to help curb the number of dementia cases worldwide.[16,17] One of these strategies includes identifying and targeting modifiable risk factors which are amenable to change through lifestyle and behavioural modifications.[16-18] Having a better understanding of these modifiable risk factors can help shed light on the potential mechanisms through which they might be implicated in the development of dementia, and this information could aid healthcare providers and policymakers in devising better strategies to prevent or delay the onset of this devastating disease.

Several potentially modifiable cardiometabolic and vascular risk factors for dementia have been previously identified, including diabetes, obesity, hypertension, and hyperlipidaemia.[17-21] Elevated waist circumference and blood pressure are known to be associated with an increased risk of dementia in mid-life but not late-life.[22-24] Dyslipidaemia and hyperglycaemia, specifically in mid-life, have also been associated with an increased risk for developing dementia.[22,25] These

different conditions tend to co-occur in individuals, and this clustering is commonly described as *Metabolic Syndrome*, or *MetS*.[26] MetS has become a serious public health concern, affecting approximately 20-25% of adults globally.[26] Generally, the presence of at least three out of the five following symptoms constitutes a diagnosis of MetS: (1) a large waist circumference; (2) high triglycerides; (3) high blood pressure; (4) high blood glucose; and (5) reduced high-density lipoprotein (HDL) cholesterol.[26] The prevalence of MetS increases with age, with some research indicating that 40% of individuals aged ≥60 years meet the diagnostic criteria for MetS.[27,28] MetS is also strongly associated with an increased risk of developing cardiovascular disease, cerebrovascular disease, and type-2 diabetes.[26] Moreover, the presence of a greater number of individual MetS components has been associated with further progression of these conditions and risk of future complications.[26] MetS is characterised by several modifiable traits, and therefore, the condition could be considered an important target for dementia prevention. Given both the high prevalence of MetS, and the growing number of dementia cases globally, untangling this relationship is of great importance from a public health perspective.[17,18,26]

A Brief History of MetS

The concept of MetS has been around for almost a century, with early scientists noting that there was a constellation of several known risk factors for cardiovascular disease and type-2 diabetes that seemed to cluster together in the same individuals, more often than chance alone.[29-31] In 1988, during his seminal Banting Lecture, Dr Gerald Reaven (an American Endocrinologist and Stanford Professor) noted that there were several risk factors that commonly cluster together – dyslipidaemia, hypertension, and hyperglycaemia – which may have a common aetiology based on insulin resistance.[32] Dr Reaven initially described this clustering as "*Syndrome* X", and over the years, this constellation of symptoms has now become commonly

known as "*Metabolic Syndrome"* or "*MetS"*.[32,33] Since then, several different terms have been used synonymously to describe MetS, such as "Reaven syndrome", "Insulin resistance syndrome", "Cardiometabolic syndrome", "The deadly quartet", and many more.[34,35]

Definitions of MetS

Several different definitions of MetS have been proposed by various public health organisations over the years. In 1998, the first formal definition for MetS was proposed by the World Health Organisation (WHO) consultation group in an attempt to establish an internationally recognised definition for the condition.[36] The WHO definition stressed the importance of insulin resistance as a major underlying risk factor. Thus, the WHO made insulin resistance a requirement for the diagnosis of MetS, plus two of the following risk factors: obesity, hypertension, elevated triglyceride levels, reduced HDL cholesterol levels, or microalbuminuria.[36] Since then, there have been several proposed criteria for the diagnosis of MetS; in addition to the WHO criteria, the other two most popular definitions commonly used in research and clinical practice were proposed by the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III)[37] and the International Diabetes Foundation (IDF).[38] For the NCEP-ATP III criteria, no single factor was made a requirement, but rather, the presence of any three of the five mentioned factors (stated above) constituted a diagnosis of MetS.[37] In contrast, the IDF criteria dropped the WHO requirement for insulin resistance but made abdominal obesity one of the necessary risk factors (plus any two of the other factors) for MetS diagnosis.[38] The IDF criteria specifically emphasised the importance of adopting different values for waist circumference among various ethnic groups due to differences in populations, such as varying body composition.[38] Finally, in 2009, the IDF and several other major organisations issued a joint interim statement in an attempt to unify the criteria for MetS

diagnoses, which was proposed as the "Harmonized Criteria".[26] In this new Harmonized Criteria, it was stated that *"three abnormal findings out of 5 would qualify a person for the metabolic syndrome. A single set of cut points would be used for all components except waist circumference"* with variations based on specific ethnic group and sex.[26] Further details regarding the Harmonized Criteria for MetS can be found below, in **Table 1.1**. A detailed description and comparison of several different definitions for MetS proposed over the years are also provided in **Appendix 1.1**.

Table 1.1: 2009 Harmonized Criteria for a MetS diagnosis

	Harmonized Criteria (2009)[26]
Absolutely required	None
Criteria	Any 3 or more of the following:
Abdominal obesity	Elevated WC (population and country-specific) ‡
Elevated blood glucose	Fasting glucose ≥ 100 mg/dL (5.6 mmol/L) OR Drug treatment of elevated glucose
Elevated triglycerides	TG ≥ 150 mg/dL (1.7 mmol/L) OR Drug treatment for elevated TG
Reduced HDL cholesterol	HDL-C < 40 mg/dl (1.0 mmol/L) in men and < 50 mg/dl (1.3 mmol/L) in women OR Drug treatment for reduced HDL-C
Elevated blood pressure	SBP ≥ 130 and/or DBP ≥85 mmHg OR Antihypertensive drug treatment in a patient with a history of hypertension

DBP = Diastolic Blood Pressure, HDL-C = High Density Lipoprotein Cholesterol, SBP = Systolic Blood Pressure, TG = Triglycerides, WC = Waist Circumference

‡ Waist circumference must be: for Europeans, > 94 cm in men and > 80 cm in women; and for South Asians, Chinese, and Japanese, > 90 cm in men and > 80 cm in women. For ethnic South and Central Americans, South Asian data are used, and for sub-Saharan Africans and Eastern Mediterranean and Middle East (Arab) populations, European data are used.

Prevalence of MetS

MetS is on the rise and has become recognised as a serious public health concern in many different countries.[39-44] Global estimates indicate that about 1 in 4 adults live with MetS.[45] Wong et al. conducted a recent systematic review of 426 studies reporting the incidence and

prevalence of MetS among 14.6 million individuals worldwide.[28] The authors reported that the overall worldwide prevalence of the condition was 25.3% (95% Confidence Interval [CI] = 24.2% to 26.4%), with an incidence of 32.0 per 1,000 person-years (95%CI = 27.8 to 36.2).[28] The prevalence of MetS was found to be the greatest among Caucasians, residents in urban settings, and those living in low-middle income countries.[28] Furthermore, these prevalence rates for MetS appear to increase with age.[46] MetS prevalence estimates also vary across regions, with its prevalence reported to be about 21.3% in China, 27.8% in Spain, and 34.3% in the US, and ranging from 16.7% to 51% in Middle Eastern Countries.[47-53] Variations in MetS incidence and prevalence rates between different racial and ethnic populations have also been documented.[54-57] With the rapid increase in rates of obesity (which promotes insulin resistance), the prevalence of MetS has continued to increase in the last few decades.[58-61]

Burden of MetS

The economic burden of MetS is also substantial. While global costs are difficult to estimate, it has been suggested that the costs (both direct and indirect) associated with the syndrome are likely in the trillions.[62] Additionally, several US-based studies have found that the annual costs associated with MetS are 60% greater than those without the condition.[63-65] Other work using data from several European countries found that the mean annual costs per patient were roughly three-fold greater in those with MetS when compared to those without MetS.[66] These elevated costs are largely due to the fact that a MetS diagnosis can often lead to a variety of complications which are major causes for morbidity and mortality. MetS increases the risk of developing type-2 diabetes mellitus, cardiovascular disease, cerebrovascular disease, and is associated with an increased risk of all-cause mortality.[26] Specifically, MetS is associated with a five-fold greater risk of developing type-2 diabetes.[45] Those with MetS are also three times as

likely to have a heart attack or stroke, and two times more likely to die from these conditions than those without MetS.[45] Despite these concerning trends, the American Heart Association and the American Stroke Association have identified MetS as the most potentially modifiable risk factor for cardiovascular and cerebrovascular disease.[67,68] The modifiable nature of MetS and its importance in mitigating future disease risk has also been stressed in health guidelines published by the IDF.[69] Therefore, addressing MetS and its components might prove to be useful for preventing a host of different diseases that it is associated with worldwide.

MetS and Risk of Dementia: Current Insights and Knowledge Gaps

Current Evidence

Recent research has indicated a potential relationship between MetS and the risk of developing dementia. Individually, each component of MetS has been previously studied in the context of dementia risk.[17] However, the combined contribution of these components in the development of dementia remains unclear. Previous systematic reviews and meta-analyses on this topic yield equivocal results. A 2019 meta-analysis by Atti et al. found no statistically significant pooled association between MetS and incident all-cause dementia among six longitudinal studies (Hazard Ratio [HR], 1.12, 95% CI: 0.94, 1.33). The authors also conducted a further meta-analyses of four studies investigating subtypes and found no significant association of MetS with incident Alzheimer's disease (HR, 0.80, 95% CI: 0.66, 1.08), but did find a significant positive association with incident vascular dementia (HR, 1.37, 95% CI: 1.01, 1.86).[70] Another meta-analysis conducted in 2021 by Zuin et al. examined MetS and risk of Alzheimer's disease only and found no association among four prospective studies (HR, 0.80, 95% CI: 0.61, 1.05).[71] However, most of the individual studies published on this topic to-date have had insufficient statistical power or a short follow-up length of <5 years, making them more susceptible to

reverse causation bias. Reverse causation may occur in this context due to the long prodromal period of dementia which can result in reductions in the levels of different components of MetS, such as blood pressure and weight.[17] These changes are thought to be driven by autonomic dysfunction that arises as dementia progresses, causing fluctuations in the balance between sympathetic and parasympathetic activity and ultimately affecting individual levels of MetS components.[72,73] Consequently, these biological processes inherent in the preclinical stages of dementia may lead to an underestimation of the association between MetS and dementia risk, particularly in studies with short follow-up periods. Furthermore, few studies have incorporated important confounding factors, most notably Apolipoprotein-E (*APOE*)-ε4 genotype – the strongest genetic risk factor for dementia[74] which is also associated with an increased risk of developing MetS.[75] It is well understood that individual cardiometabolic and vascular risk factors are highly correlated with each other, often making it difficult to isolate their individual effects on disease development.[76] Therefore, investigating these questions is particularly pertinent in the context of MetS (as a whole) and dementia, as the conditions inherent in MetS more accurately reflect the real-world clustering of known individual risk factors that frequently occur together rather than in isolation.[77]

MetS Across the Life Course

It is well known that different risk factors for dementia, including those inherent in MetS, show varying associations across the life course.[17] For instance, the presence of hypertension has been shown to be associated with an increased risk of dementia at mid-life, but not late-life[17,77]; moreover, a prolonged exposure to this risk factor (over a mean 16-year period) has also been shown to elevate dementia risk.[78] However, there still remains a limited understanding of the influence of age and duration of exposure to MetS (as a whole) on dementia risk, particularly as

most studies lack the breadth and depth of data and sufficient follow-up length to address such questions.[70] Knowledge of the role of age and duration of exposure to MetS could potentially help identify periods of increased vulnerability and the possible cumulative damage that MetS may exert in the context of dementia risk. Gaining such insights can help understand whether there is a critical window of opportunity to intervene in those living with MetS, which could ultimately inform prevention strategies to curb future cognitive dysfunction and dementia in these populations.

MetS and Brain Health

Prior to the clinical onset of dementia, several different aspects of brain health might be affected as well, but this remains unclear in the context of MetS and dementia risk. In MetS, the different individual components share universal mechanisms that result in cognitive dysfunction and dementia, through the potential involvement of both vascular injury and neurodegeneration.[79,80] Hence, the pathogenesis behind this relationship may be multifactorial with individual MetS components contributing jointly and synergistically to dementia risk; this may involve features such as insulin resistance, vascular endothelial damage and oxidative stress in combination with chronic low-grade inflammation (all of which are known to be involved in the development of MetS) which impact the brain and promote the development of cognitive dysfunction and dementia.[79,80] However, insights regarding early changes in brain health (in terms of both the neuropathological and cognitive basis) implicated in the relationship between MetS and dementia are still not fully understood.[81] Gaining such insights can provide clarity on how MetS might contribute to brain changes that may potentially result in the subsequent development of dementia.

DPhil Thesis Objectives

Given these knowledge gaps, further research is necessary to disentangle the complexity of the relationship between MetS and dementia. Therefore, this DPhil research thesis sought to investigate and clarify the association between MetS and the risk of developing dementia. Specifically, the objectives of this doctoral work (outlined in **Figure 1.1**) are as follows:

1) **To perform** a systematic review of prospective studies investigating the association between MetS and risk of incident all-cause dementia and key dementia subtypes.

   ⇒ Purpose: to provide an up-to-date synthesis and understanding of existing literature, setting the foundation to identify key knowledge gaps to address in this DPhil work.

2) **To investigate** the association between MetS and incident all-cause dementia among UK Biobank participants.

   ⇒ Purpose: to leverage a large, well-characterised cohort to provide a comprehensive investigation of the relationship between MetS and dementia risk.

3) **To explore** the role of age and duration of exposure to MetS on dementia risk using data from the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort.

   ⇒ Purpose: to repeat analyses from Objective 2 in a novel cohort, and additionally leverage the cohort's unique strengths of a wider baseline age and longer follow-up to understand how timing and length of exposure to MetS might influence dementia risk. This will provide key insights into potentially critical periods for intervention and dementia prevention.

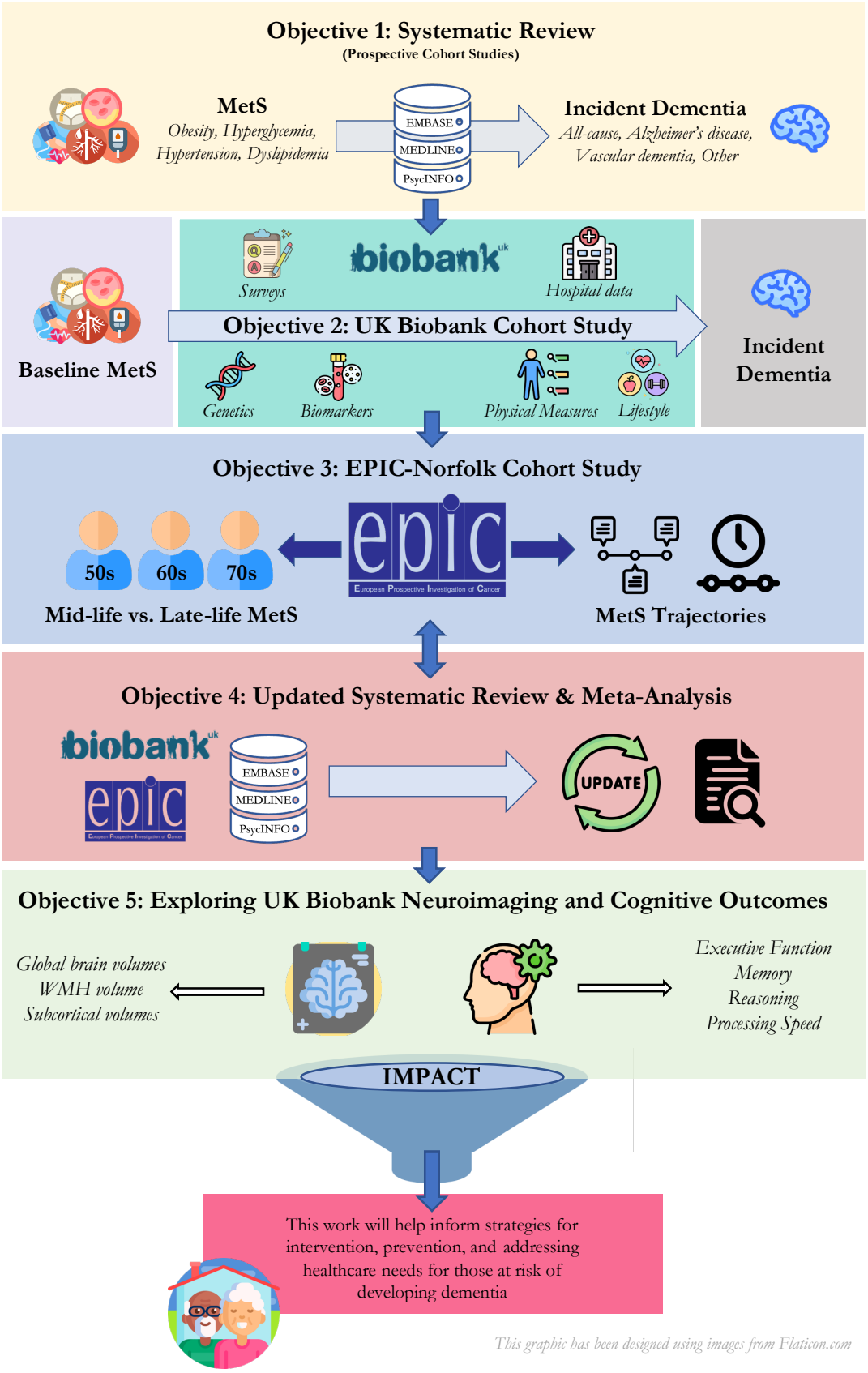
4) **To conduct** an update of the systematic review (from Objective 1) and perform a meta-analysis on this topic to specifically incorporate novel findings from Objectives 2-3 and any additional literature published on the association between MetS and incident dementia.

   ⇒ Purpose: to integrate new evidence (generated from this DPhil) with existing published research in the broader literature, providing improved clarity on the current evidence base regarding the association of MetS and dementia risk.

5) **To examine** the impact of MetS on brain health in dementia-free adults using neuroimaging and cognitive function data available in UK Biobank.

   ⇒ Purpose: to understand the influence of MetS on early changes in brain health prior to the clinical onset of dementia, providing new insights into how MetS might be implicated in the subsequent development of dementia.

Figure 1.1: Visual outline of doctoral research objectives



CHAPTER 2

A Systematic Review of Prospective Studies on the Relationship Between Metabolic Syndrome and Incident Dementia

CHAPTER SUMMARY

This chapter systematically reviews current evidence from prospective cohort studies examining the association between MetS and the risk of developing dementia. Searches were conducted using Medline, Embase and PsycINFO databases (from inception to February 2022) for prospective cohort studies examining the association of MetS with incident dementia, including all-cause dementia, Alzheimer's disease, vascular dementia or other dementias. Backward and forward citation searches of included studies were also conducted to identify any additional publications.

The search strategy identified 5,603 articles eligible for screening. Screening was conducted independently by two reviewers using Covidence software. After removing 1,838 duplicates, a total of 3,700 articles were excluded based on title and abstract screening, resulting in 65 publications for full-text review. Among these studies, 10 met the inclusion criteria for the systematic review. Five of these studies were from Europe, four from Asia, and one from the United States. Risk of bias was assessed using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies.

All-cause dementia was reported in nine studies; five reported a positive association (increased risk), among which two reached statistical significance. Five studies reported on Alzheimer's disease, among which one reported a significant positive association (increased risk) while another study reported a significant negative association (reduced risk). Five studies reported on the outcome of vascular dementia; four reported a positive association (increased risk) among which three reached statistical significance. Additionally, one study reported on

Parkinson's disease-dementia and found a significant positive association (increased risk). A total of two studies were rated as 'strong' quality, six as 'moderate', and two as 'weak'.

Overall, studies identified in this systematic review indicated that the relationship between MetS and risk of dementia remains inconsistent, likely owing to the large variations observed in study characteristics such as differences in sample sizes, follow-up length, and lack of comprehensive confounder adjustments across studies.

BACKGROUND

Previous systematic reviews and meta-analyses examining the relationship between MetS and dementia have produced equivocal results. A systematic review published in 2019 (Atti. et al.) consisted of longitudinal studies on the association of MetS with incident all-cause dementia, Alzheimer's disease and vascular dementia (search up to August 31, 2018).[70] The review found six relevant longitudinal studies reporting on the relationship between MetS and incident all-cause dementia or key subtypes, among which five studies were published more than a decade ago (prior to 2012). The subsequent meta-analysis conducted by the authors found no statistically significant pooled association between MetS, incident all-cause dementia (HR: 1.12, 95% CI: 0.94, 1.33) and Alzheimer's disease (HR: 0.80, 95% CI: 0.66, 1.08), but found a significant positive association with vascular dementia (HR: 1.37, 95% CI: 1.01, 1.86).[70] A more recent systematic review was also conducted, specifically in 2021 (Zuin et al.), but this work focused on capturing studies examining the association of MetS and Alzheimer's disease only (search up to July 30, 2020).[71] The subsequent meta-analysis conducted by the authors found no association among prospective studies (HR: 0.80, 95% CI: 0.61, 1.05); however, these findings were based on only four studies, all of which were published more than a decade ago (prior to 2012).[71] More recently, various prospective studies have been conducted which may help to clarify whether MetS is a risk factor for dementia, and thus, a further comprehensive investigation of the existing literature on this topic is warranted.

Therefore, the main objective of the work presented in this Chapter was to systematically review the results of all prospective studies that have investigated the association between MetS and incident all-cause dementia, including key subtypes. This Chapter provides a detailed

overview of current evidence regarding the association between MetS and dementia risk, serving as a key foundation for the remainder of the work presented throughout this thesis.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines which provide a standardised protocol for performing systematic reviews.[82] This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO); Registration Number: CRD42024549846 (further details can be found here: URL).

Search Strategy and Study Selection

Following a pre-defined protocol (see **Appendix 2.1**), searches were developed for Medline, Embase, and PsycINFO via OvidSP. Full search strategy details are available in **Appendices 2.2-2.4**. Relevant subject headings and free-text terms were included, and all searches were peer-reviewed by an experienced librarian (Nia Roberts, Senior Outreach Librarian at The University of Oxford Bodleian Health Care Libraries) prior to execution. Selection of the relevant MetS (exposure) search terms were informed by: (1) key papers discussing standardised definitions of MetS (see sources cited in **Appendix 1.1**)[26,36-38,83-86]; (2) review articles discussing MetS[44,87-98]; and (3) search strategies of the top 50 most-cited systematic reviews focused on MetS (identified via Web of Science)[99-148]. The dementia (outcome) search terms were informed by: (1) review articles discussing dementia and/or key dementia subtypes[17,149-151]; and (2) search strategies used in previous systematic reviews where all-cause dementia and/or key dementia subtypes were the main outcome.[77,152-201] Study design search terms were informed by: (1) a search strategy used in a previous systematic review of prospective

studies[201]; and (2) the Scottish Intercollegiate Guidelines Network (SIGN) search filters for systematic reviews.[202] The searches were conducted on February 9th, 2022, supplemented by backward and forward citation searches of included studies via Web of Science.

This systematic review was restricted to prospective studies (in English, among adults ≥18 years) investigating the association between MetS and risk of incident all-cause dementia or key dementia subtypes (e.g., Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementia). The comparison group was no prevalent MetS. The inclusion and exclusion criteria (outlined below) for the exposure of MetS were defined broadly to encompass all possible established standardised definitions used for MetS diagnoses in adults (see **Appendix 1.1** for further details). Two reviewers (DQ & EK) independently screened titles and abstracts based on the inclusion and exclusion criteria, and independently reviewed the full-text articles of potentially relevant studies. Any discrepancies were resolved by discussion, if necessary, with a third reviewer (TJL).

Inclusion and Exclusion Criteria

Studies were <u>included</u> in this systematic review if they met the following criteria:

1) Study population: participants were 18 years or older at study baseline;
2) Study design: prospective;
3) Exposure: MetS defined as (i) a self-reported diagnosis, or a diagnosis confirmed through medical history (i.e., medical records); or (ii) any combination of ≥ 3 out of the following 6 components (or an appropriate proxy indicator for any component): obesity, elevated fasting blood glucose, elevated triglyceride levels, elevated blood pressure, reduced HDL cholesterol, or microalbuminuria*;

4) Outcome: incident dementia or key dementia subtypes (e.g., Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementia); and
5) Language restriction: studies published in English.

Studies were excluded from the systematic review if they met the following criteria:

1) Studies which do not define the presence or absence of MetS using the following 5 components (or an appropriate proxy indicator): obesity, elevated fasting blood glucose, elevated triglyceride levels, elevated blood pressure, reduced HDL cholesterol;
2) Studies which define the presence or absence of MetS using a combination of measures outside of the following 6 components: obesity, elevated fasting blood glucose, elevated triglyceride levels, elevated blood pressure, reduced HDL cholesterol, and microalbuminuria*;
3) Studies with no comparison group or comparison group other than 'no MetS';
4) Studies with outcomes that are not directly dementia-related (e.g., neuroimaging or biomarkers);
5) Studies using only a single cognitive instrument or self-reported dementia to define incident dementia or key dementia subtypes;
6) Animal studies;
7) Case reports, narrative reviews, letters, editorials, opinions, book chapters;
8) Conference abstracts; and
9) Duplicate publications using the same data.

*Note: microalbuminuria was included in the list of components to capture studies that used the original WHO standardised criteria for defining MetS, alongside other established MetS criteria.

Data Extraction

Study characteristics and fully adjusted results were extracted by one reviewer (DQ) and checked by a second reviewer (EK). Key data items included: study author, publication year, country/region, data source, race and/or ethnicity, study design, setting, analytic sample size, proportion of females, mean (Standard Deviation [SD]) or median (Interquartile Range [IQR]) baseline age in years, mean (SD) or median (IQR) follow-up length in years, MetS criteria used in the identified study, dementia outcomes reported, outcome assessment details, number and percentage of MetS cases, number and percentage of incident dementia cases (all-cause and/or key subtypes), effect estimates and 95% CIs, and confounder adjustments. Any discrepancies were resolved by discussion, if necessary, with a third reviewer (TJL). Corresponding authors of nine studies were contacted for clarification or additional data that was not fully reported.[203-211] A response was received from two corresponding authors[207,211], among which one provided additional data or clarification[207], while the other was unable to provide clarification due to data access issues.[211] No response was received for the other remaining seven studies.[203-206,208-210]

Assessment of Risk of Bias

Two reviewers (DQ, TJL) independently assessed the risk of bias using the EPHPP Quality Assessment Tool for Quantitative Studies.[212] The components of the tool were rated as outlined in previously described methods (further details are provided in **Appendix 2.1**).[201] Any discrepancies were resolved by discussion, if necessary, with a third reviewer (EK). Overall risk of bias and potential sources of bias (i.e., selection bias, study design, confounders, blinding, data collection, withdrawals and drop-outs [attrition bias]) were rated as 'strong', 'moderate', or 'weak' according the dictionary provided with the tool.[212] According to the tool's provided guidance, studies with no weak component ratings received a 'strong' overall rating. Studies with only one

weak component rating received a 'moderate' overall rating, while studies with two or more weak component ratings received a 'weak' overall rating.

RESULTS

The final searches resulted in 5,603 records. After removing 1,838 duplicates, 3,700 articles were excluded based on title and abstract screening which resulted in 65 publications for full-text review, of which 10 met the inclusion criteria for the systematic review (see **Figure 2.1**). No additional studies were identified via backward and forward citation searches.

Key characteristics of included studies are provided in **Table 2.1**. Five studies were from Europe[203,205,209-211], four from Asia[204,206,208,213], and one from the United States.[207] Eight studies used data from research cohorts[203-205,208-211,213], while two studies used data from medical records cohorts.[206,207] The most commonly adopted definition for ascertaining MetS was the NCEP-ATP III criteria (eight studies).[203-205,207,209-211,213] MetS prevalence ranged from 7% to 55% across studies. All-cause dementia or key subtypes were ascertained using a combination of: medical records, anti-dementia prescription drug use, or adjudication following established criteria for dementia, neuropsychological evaluations, neurological exams and/or brain magnetic resonance imaging (MRI). Analytic sample sizes varied between the studies, ranging from a sample of 59 participants in a memory clinic cohort study[203] to 4,106,590 participants from the largest medical records cohort study.[206]

Mean baseline age was widespread; one study exclusively included participants aged <65 years[211], five studies included both participants aged <65 and 65+ years[203,204,206,208,213], and four studies exclusively included participants aged 65+ years.[205,207,209,210] The proportion of females

included across studies ranged between 39.5%[203] to 67.3%[207], and one study included males only.[211] Follow-up length varied considerably, ranging from a mean of 3.4 years[203] to up to 21 years.[211] Age and sex/gender were adjusted in the multivariate analysis of all but one study (which included males only).[211] Seven studies included adjustment for smoking status[204,206-208,210,211,213], six adjusted for education[205,207-210,213], five for alcohol consumption[204,206,210,211,213], three for *APOE*-ε4 carrier status[205,207,208], and one study adjusted for socioeconomic status (specifically, social class).[211]

Figure 2.1: Flow chart of study selection and exclusion

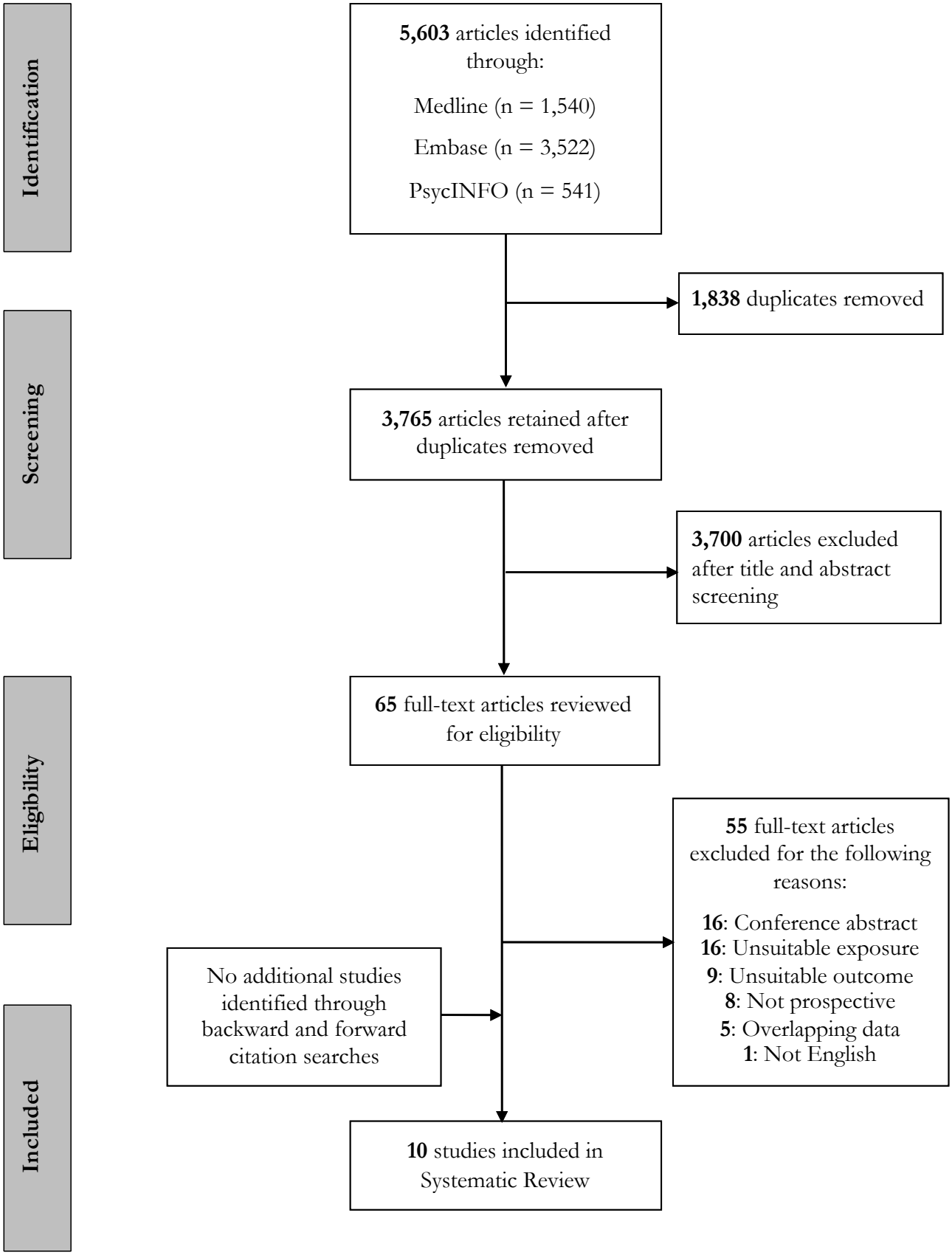


Table 2.1: Characteristics of all included studies

Study author, publication year	Region (data source)	Race/Ethnicity	Study design	Setting	Analytic sample size	% Female	Mean baseline age in years (SD)	Mean follow-up length in years (SD)	Exposure: MetS criteria	Outcomes Reported	Outcome Assessment
Creavin et al., 2012[211]	UK (CaPS)	NR	Research Cohort	Community	N = 1,131	0.0%	57.7 (53.6 - 61.4)§§***	Up to 21***	NCEP-ATP III	All-cause dementia	Adjudicated based on DSM-IV, NINCDS-ADRDA, NINDS-AIREN
Exalto et al., 2015[203]	Netherlands (ADC)	NR	Research Cohort	Memory clinic	N = 59	39.5%#	66.7 (9.7)#	3.4 (1.1)	NCEP-ATP III revised AHA/NHLBI	All-cause dementia	NR
Fan et al., 2017[204]	Taiwan (TwSHHH)	100% Asian¶¶	Research Cohort	Community	N = 3,458	53.0%	54.5 (10.7)†	9.2††	NCEP-ATP III revised AHA/NHLBI	All-cause dementia	Medical records, ICD-9-CM: 290.0, 290.1x, 290.2x, 290.3, 290.4x, 294.1, 331.0, 331.1, 331.2
Forti et al., 2010[205]	Italy (CSBA)	NR	Research Cohort	Community	Age <75 years: N = 466 Age ≥75 years: N = 283	Age <75 years: 51.3% Age ≥75 years: 56.9%	Age <75 years: 69.3 (3.0)† Age ≥75 years: 79.8 (3.8)†	3.9 (0.8)	NCEP-ATP III	All-cause dementia AD VaD	Adjudicated based on DSM-IV, NINCDS-ADRDA, NINDS-AIREN[XX]
Lee et al., 2020[206]	South Korea (KNHI)	100% Asian¶¶¶	Medical Records Cohort	Community	N = 4,106,590	45.5%	55.8 (10.1)	4.9 (NR)	Harmonized Criteria	All-cause dementia AD VaD	Neuropsychological exam, antidementia drug prescriptions, and medical records (ICD-10: AD [F00 or G30], VD [F01], or other dementia [F02, F03, G23.1 or G31])
Ng et al., 2016[208]	Singapore (SLAS)	100% Asian	Research Cohort	Community	N = 1,936	64.8%*	64.9 (6.8)*	3.8 (NR) §§	IDF	All-cause dementia	Adjudicated based on DSM-IV
Muller et al., 2007[207]	USA (Medicare – Manhattan)	29.9% White 30.8% African American 39.3% Hispanic	Medical Records Cohort	Community	N = 1,833	67.3%	76.1 (6.0)	4.4 (2.5)	NCEP-ATP III	All-cause dementia AD VaD	Adjudicated based on DSM-IV, CDR ≥1, NINCDS-ADRDA
Peng et al., 2018[213]	China (Multicentre study)	100% Asian	Research Cohort	Community	N = 787	43.1%	67.1 (7.2)	5 (NR)	NCEP-ATP III	PDD	Adjudicated based on Movement Disorder Task Force (2007) criteria##

Raffaitin et al., 2009[209]	France (3C Study)	NR	Research Cohort	Community	N = 7,077	61%††	73.4 (4.9)††	Up to 4 (NR)	NCEP-ATP III	All-cause dementia AD VaD	Adjudicated based on DSM-IV, NINCDS-ADRDA, Hachinski score, MRI, history of vascular disease
Solfrizzi et al., 2010[210]	Italy (ILSA)	NR	Research Cohort	Community	N = 2,097	47.3%	72.9 (5.6)	Up to 3.5 (NR)	NCEP-ATP III	All-cause dementia AD VaD Other dementias^#	Adjudicated based on DSM-III-R, NINCDS-ADRDA, and ICD-10 ¶

CaPS: Caerphilly Prospective Study, ADC: Amsterdam Dementia Cohort, TwSHHH: Taiwanese Survey on Prevalence of Hypertension Hyperglycemia and Hyperlipidemia, TNHIRD: Taiwan National Health Insurance Research Database, CSBA: Conselice Study of Brain Ageing, KNHI: Korean National Health Insurance Service - National Health Information Database, SLAS: Singapore Longitudinal Ageing Study, 3C Study: Three-City study, ILSA: Italian Longitudinal Study on Ageing, MetS: Metabolic syndrome, NCEP-ATP III: National Cholesterol Education Program - Adult Treatment Panel III, AHA/NHLBI: American Heart Association and the National Heart, Lung, and Blood Institute, IDF: International Diabetes Foundation, DSM: Diagnostic and Statistical Manual of Mental Disorders, NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NINDS-AIREN: National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN), NR: Not reported, ICD-9: International Classification of Diseases, Ninth Revision, ICD-10: International Classification of Diseases, Tenth Revision CDR: Clinical Dementia Rating, SD: Standard deviation, AD: Alzheimer's disease, VaD: Vascular dementia, PDD: Parkinson's disease dementia

§§: Median (Interquartile Range), #: Reported for 86 participants, *: Reported for 1,519 participants (primary sample), ***: Among phase 2 participants (n=2,398) – chosen based on balance between longest follow-up and largest sample size, † : Combined mean and SD, ||: Calculated based on other available data. ††: Reported for 7,087 participants, &: Additional information provided by the authors, ^#: Defined as dementia in other diseases classified elsewhere (e.g., dementia in Pick's disease, Creutzfeldt - Jakob disease, Huntington's disease, Parkinson's disease, human immunodeficiency virus [HIV], or other disease)

XX: Ravaglia, Giovanni, and Paola Forti. "The Conselice study of brain ageing." Immunity & Ageing. Vol. 7. No. 1. BioMed Central, 2010.
¶¶: Information taken from Chen, Y. C., et al. "Impact of metabolic syndrome components on incident stroke subtypes: a Chinese cohort study." Journal of Human Hypertension 28.11 (2014): 689-693.
¶¶¶: Information taken from Kim, Yun Gi, et al. "Association of Depression With Atrial Fibrillation in South Korean Adults." JAMA network open 5.1 (2022): e2141772-e2141772.

Table 2.2-2.5 provide the main results of included studies by different types of dementia outcomes. All-cause dementia was reported in nine studies[203-211] (**Table 2.2**); five studies reported a positive association (increased risk)[204,206,208,209,211], among which two reached statistical significance.[204,206] Five studies reported on Alzheimer's disease[205-207,209,210] (**Table 2.3**) among which results were mixed; one study reported a significant positive association (increased risk)[206], while another study reported a significant negative association (reduced risk) – specifically among participants aged 75 years or older.[205] Five studies reported on vascular dementia[205-207,209,210] (**Table 2.4**); four of these studies reported a positive association (increased risk)[205,206,209,210], among which three reached statistical significance.[206,209,210] Additionally, one study reported on Parkinson's disease-dementia (**Table 2.5**) and found a significant positive association (increased risk).[213]

Table 2.2: Studies reporting outcome: All-cause dementia

Study author, publication year	Number and % of MetS cases	Number and % of incident all-cause dementia	Effect estimate (95% CI)	Confounder adjustments
Creavin et al., 2012[211]	NR	NR	OR: 1.54 (0.89 - 2.66)[#] p = NR	Age, social class, smoking, alcohol intake, National Adult Reading Test
Exalto et al., 2015[203]	23 (39.0%)	10 (16.9%)	HR: 0.50 (0.10 - 2.40) p = NR	Age, gender
Fan et al., 2017[204]	1,122 (32.4%)	76 (2.2%)	Persistent MetS, HR: 1.12 (0.57 - 2.21), p = 0.752 Improved MetS, HR: 0.88 (0.27 - 2.88), p = 0.829 Worsened MetS, HR: 2.22 (1.32 - 3.72), p = 0.003	Age, sex, smoking, alcohol intake, physical activity, betel quid chewing, heart disease, stroke, depression
Forti et al., 2010[205]	<75 years: 133 (28.5%) ≥75 years: 63 (22.3%)	<75 years: 35 (7.5%) ≥75 years: 52 (18.3%)	<75 years: HR: 0.74 (0.34 - 1.63) p = NR ≥75 years: HR: 0.54 (0.25 - 1.15) p = 0.11	Age, sex, education, APOE-ε4 carrier status, physical activity, hyperhomocysteinemia, and inflammation status, history of cardiovascular disease, history of stroke
Lee et al., 2020[206]	1,880,175 (45.8%)	~19,286 (0.5%)[||]	HR: 1.12 (1.11 - 1.14) p = NR	Age, sex, smoking, alcohol intake, physical activity, stroke, depression, chronic kidney disease
Ng et al., 2016[208]	443(29.2%)[*]	26 (1.3%)	HR: 1.37 (0.60 - 3.12), p = 0.49	Sex, age, education, APOE-ε4 carrier status, smoking, and physical/social/productive activities score
Muller et al., 2007[207]	1,005 (54.8%)	236 (12.9%)	HR: 0.9 (0.60 - 1.10) p > 0.1[&]	Age, sex, education, ethnicity, APOE-ε4 carrier status, smoking, cohort
Raffaitin et al., 2009[209]	NR	208 (2.9%)	HR: 1.28 (0.92 - 1.80) p = 0.15	Age, gender, education, study centre
Solfrizzi et al., 2010[210]	918 (43.8%)	88 (4.2%)	HR: 1.00 (0.61 - 1.65) p = NR	Age, sex, education, alcohol intake, smoking, fibrinogen, non-HDL cholesterol, ratio of apolipoprotein B to apolipoprotein A-I, coronary artery disease, stroke

MetS: Metabolic syndrome, NCEP-ATP III: National Cholesterol Education Program - Adult Treatment Panel III, NR: Not reported, OR: Odds Ratio, HR: Hazard Ratio, CI: Confidence Interval, HDL: High density lipoprotein, APOE: Apolipoprotein E, SHR: Sub-distribution Hazard Ratio

||: Calculated based on other available data, *: Reported for 1,936 participants in supplementary analysis, &: Additional information provided by the authors. #: among phase 2 participants (n=2,398) – chosen based on balance between longest follow-up and largest sample size.

Table 2.3: Studies reporting outcome: Alzheimer's disease

Study author, publication year	Number and % of MetS cases	Number and % of incident AD	Effect estimate (95% CI)	Confounder adjustments
Forti et al., 2010[205]	<75 years: 133 (28.5%) ≥75 years: 63 (22.3%)	<75 years: 18 (3.9%) ≥75 years: 35 (12.4%)	<75 years: HR: 0.84 (0.29 - 2.44) p = NR ≥75 years: HR: 0.33 (0.12 - 0.94) p = 0.04	Age, sex, education, APOE-ε4 carrier status, physical activity, hyperhomocysteinemia, and inflammation status, history of cardiovascular disease, history of stroke
Lee et al., 2020[206]	1,880,175 (45.8%)	~14,509 (0.4%)||	HR: 1.09 (1.07 - 1.11) p = NR	Age, sex, smoking, alcohol intake, physical activity, stroke, depression, chronic kidney disease
Muller et al., 2007[207]	1,005 (54.8%)	147 (8.0%)	HR: 0.90 (0.60 - 1.30) p > 0.1&	Age, sex, education, ethnicity, APOE-ε4 carrier status, smoking, cohort
Raffaitin et al., 2009[209]	NR	134 (1.9%)	HR: 0.81 (0.50 - 1.31) p = 0.39	Age, gender, education, study centre
Solfrizzi et al., 2010[210]	918 (43.8%)	47 (2.2%)	HR: 0.83 (0.42 - 1.63) p = NR	Age, sex, education, alcohol intake, smoking, fibrinogen, non-HDL cholesterol, ratio of apolipoprotein B to apolipoprotein A-I, coronary artery disease, stroke

MetS: Metabolic syndrome, NCEP-ATP III: National Cholesterol Education Program - Adult Treatment Panel III, HR: Hazard Ratio, CI: Confidence Interval, HDL: High density lipoprotein, APOE: Apolipoprotein E, AD: Alzheimer's disease, NR: Not Reported, ||: Calculated based on other available data, &: Additional information provided by the authors.

Table 2.4: Studies reporting outcome: Vascular dementia

Study author, publication year	Number and % of MetS cases	Number and % of incident VaD	Effect estimate (95% CI)	Confounder adjustments
Forti et al., 2010[205]	<75 years: 133 (28.5%) ≥75 years: 63 (22.3%)	<75 years: 14 (3.0%) ≥75 years: 15 (5.3%)	<75 years: HR: 0.79 (0.23 - 2.79) ≥75 years: HR: 1.54 (0.42 - 5.69) p = 0.51	Age, sex, education, APOE-ε4 carrier status, physical activity, hyperhomocysteinemia, and inflammation status, history of cardiovascular disease, history of stroke
Lee et al., 2020[206]	1,880,175 (45.8%)	~2,475 (0.06%)||	HR: 1.27 (1.22 - 1.32) p = NR	Age, sex, smoking, alcohol intake, physical activity, stroke, depression, chronic kidney disease
Muller et al., 2007[207]	1,005 (54.8%)	73 (4.0%)	HR: 0.80 (0.50 - 1.30) p > 0.1&	Age, sex, education, ethnicity, APOE-ε4 carrier status, smoking, cohort
Raffaitin et al., 2009[209]	NR	40 (0.6%)	HR: 2.42 (1.24 - 4.73) p = 0.01	Age, gender, education, study centre
Solfrizzi et al., 2010[210]	918 (43.8%)	25 (1.2%)	HR: 3.71 (1.40 - 9.83) p = NR	Age, sex, education, alcohol intake, smoking, fibrinogen, non-HDL cholesterol, ratio of apolipoprotein B to apolipoprotein A-I, coronary artery disease, stroke

MetS: Metabolic syndrome, NCEP-ATP III: National Cholesterol Education Program - Adult Treatment Panel III, HR: Hazard Ratio, CI: Confidence Interval, HDL: High density lipoprotein, APOE: Apolipoprotein E, VaD: Vascular dementia, NR: Not Reported.

||: Calculated based on other available data, &: Additional information provided by the authors.

Table 2.5: Studies reporting outcome: Other dementias

Study author, publication year	Number and % of MetS cases	Number and % of incident dementia	Effect estimate (95% CI)	Confounder adjustments
Peng et al., 2018[213]	204 (25.9%)	105 (13.3%)	Parkinson's Disease Dementia: OR: 2.12 (1.57 - 2.83) p = 0.003	Age, sex, education, body mass index, coronary artery disease, lacunar infarction, white matter lesions, smoking, alcohol intake, baseline UPDRS score and H&Y stage
Solfrizzi et al., 2010[210]	918 (43.8%)	16 (0.8%)	Other dementias^#: HR: 0.23 (0.06 - 1.08) p = NR	Age, sex, education, alcohol intake, smoking, fibrinogen, non-HDL cholesterol, ratio of apolipoprotein B to apolipoprotein A-I, coronary artery disease, stroke

MetS: Metabolic syndrome, NCEP-ATP III: National Cholesterol Education Program - Adult Treatment Panel III, OR: Odds Ratio, HR: Hazard Ratio, CI: Confidence Interval, UPDRS: Unified Parkinson's Disease Rating Scale, H & Y Stage: Hoehn and Yahr Stage, HDL: High density lipoprotein, APOE: Apolipoprotein E, VaD: Vascular dementia, ^#: Defined as dementia in other diseases classified elsewhere (e.g., dementia in Pick's disease, Creutzfeldt - Jakob disease, Huntington's disease, Parkinson's disease, human immunodeficiency virus [HIV], or other disease), NR: Not Reported

Analyses Conducted Among Identified Studies

All of the identified studies from this systematic review examined (as a focus of their primary analysis) the association between MetS and risk of developing incident dementia (or key subtypes). However, there were some key differences in the types of secondary and subgroup analyses carried out across the identified studies. Insights regarding the impact of these various factors (outlined below) on the association of MetS and dementia are necessary to fully and comprehensively understand these relationships.

Age: Understanding the age-specific associations is important as risk factors and biological mechanisms implicated in the development of dementia can vary significantly based on different age groups (as detailed previously in Chapter 1).[17] Among the identified studies in this review, age-specific associations were only reported in three out of the ten studies; two of these studies reported these findings in the context of MetS status assessed over multiple time points, with one revealing a positive (non-significant) association between 'persistent' or 'worsened' MetS and all-cause dementia in those aged 65+ years[204], while the other study reported a weaker association in those aged 65+ years when compared to those <65 years for outcomes of all-cause dementia, Alzheimer's disease and vascular dementia.[206] The third study examined binary MetS as the exposure and found no differences in age-based associations for all-cause dementia and Alzheimer's disease, but did report a stronger positive association for vascular dementia when comparing participants aged 75+ years to those aged <75 years.[205]

Sex: Exploring sex-specific differences is also important, as biological, physiological and other differences between males and females could influence associations with dementia risk.[214]

However, only one out of the ten studies examined the sex-based associations of MetS and dementia, reporting no significant effect modification by sex.[208]

APOE-ε4 Carrier Status: Assessing the impact of *APOE*-ε4 carrier is important as well, particularly since it is strongly associated with dementia risk, and this factor could interact with MetS to modify any potential relationship with dementia.[215-218] However, only one out of the ten studies investigated the specific impact of *APOE*-ε4 carrier status on the association between MetS and dementia, observing no statistically significant effect modification by *APOE*-ε4 carrier status.[208]

MetS Components: Understanding the role of individual components is critical since each of the MetS components may influence risk for dementia in unique ways.[17,18] Moreover, further examination of the number of MetS components present in individuals with MetS is also important since this can help understand whether the MetS-dementia relationship can be explained by a potential dose-response association, or more so a threshold-related effect. Almost all studies (eight out of ten) examined the impact of individual MetS components on dementia risk.[205-211,213] While variations were observed in trends for individual components and dementia risk, the strongest associations were consistently observed for the components of high blood glucose and high blood pressure across six out of the eight studies.[205-208,211,213] Interestingly, only two out of the ten studies examined the relationship between the number of MetS components present and dementia risk.[209,213] One study reported no significant association between the number of MetS components and risk of incident all-cause dementia[209], while the other study observed a dose-response relationship between MetS and Parkinson's disease dementia.[213]

Duration of MetS: Evaluating the duration of exposure to MetS is also crucial, as such information can help understand the longitudinal course of its impact on the development of dementia, and this can generate insights about which populations may be at greatest risk. Two out of the ten studies included data on repeat measures of MetS to understand how exposure status across multiple time points may impact dementia risk.[204,206] One study measured MetS status across two time points over a 2-year period and found that both persistent and non-persistent MetS was associated with an increased risk of dementia.[206] However, another study measuring MetS at two time points over a 5-year period found that only non-persistent MetS was associated with an increased dementia risk.[204] An understanding of the impact of MetS status over many years is limited, and further studies that investigate these trends can provide key insights regarding the longitudinal patterns of MetS and their impact across different life stages – which can then be used to inform dementia prevention strategies.

Follow-up length: Follow-up length is of great importance when studying risk factors for dementia because of its long prodromal phase and potential susceptibility to reverse causation bias.[219] Notably, none of the ten studies examined how variation in follow-up length may impact the association between MetS and dementia risk. This is likely because the follow-up length across most studies was relatively short, which did not allow for such analyses to be performed.

Given the limited number of studies that have conducted the aforementioned types of analyses, further investigation and clarification of the role of these factors is necessary to fully understand how they might be implicated in the potential link between MetS and the risk of developing dementia. The insights and gaps described above helped to shape some of the analyses that were conducted in the prospective studies presented in later Chapters.

Risk of Bias and Quality Assessment

Among the 10 studies that were identified in this systematic review, a total of two studies were rated as 'strong' quality[205,210], six as 'moderate'[203,207-209,211,213] and two as 'weak'[204,206] (**Table 2.6**) according to the EPHPP tool. Studies classified as having a moderate rating were subject to selection bias (n=4)[207-209,213], lack of sufficient confounder adjustment (n=1)[203] or were subject to potential attrition (n=1).[211] Studies with a weak rating did not describe the validity and reliability of data collection methods (n=2) or exhibited a lack of sufficient confounder adjustment (n=2).[204,206]

Table 2.6: Quality assessment ratings for all studies included in systematic review

Study Author, Publication Year	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawals and Drop-outs	Global Rating
Creavin et al., 2012[211]	STRONG	MODERATE	STRONG	MODERATE	STRONG	WEAK	MODERATE
Exalto et al., 2015[203]	MODERATE	MODERATE	WEAK	MODERATE	STRONG	STRONG	MODERATE
Fan et al., 2017[204]	MODERATE	MODERATE	WEAK	MODERATE	WEAK	STRONG	WEAK
Forti et al., 2010[205]	MODERATE	MODERATE	STRONG	MODERATE	STRONG	MODERATE	STRONG
Lee et al., 2020[206]	MODERATE	MODERATE	WEAK	MODERATE	WEAK	MODERATE	WEAK
Muller et al., 2007[207]	WEAK	MODERATE	STRONG	MODERATE	STRONG	STRONG	MODERATE
Ng et al., 2016[208]	WEAK	MODERATE	STRONG	MODERATE	STRONG	STRONG	MODERATE
Peng et al., 2018[213]	WEAK	MODERATE	STRONG	MODERATE	STRONG	STRONG	MODERATE
Raffaitin et al., 2009[209]	WEAK	MODERATE	MODERATE	MODERATE	STRONG	STRONG	MODERATE
Solfrizzi et al., 2010[210]	STRONG	MODERATE	STRONG	MODERATE	STRONG	MODERATE	STRONG

Further details regarding the quality assessment components and their specifications are provided under the heading "Risk of bias (quality) assessment" in **Appendix 2.1**.

DISCUSSION

Findings from this systematic review suggest that current evidence regarding the relationship between MetS and the risk of developing incident dementia remains inconclusive. The mixed findings are likely due to several potential biases evident across identified studies, which include: limitations in sample size and follow-up duration, variation in exposure measurement, and differences in confounder adjustments (these items are discussed later in this section).

Comparison with Previous Systematic Reviews

To date, only two systematic reviews have been conducted on the topic of MetS and the risk of developing dementia, specifically in 2019 (Atti et al.)[70] and 2021 (Zuin et al.).[71] Atti et al. reported several types of dementia outcomes from six prospective studies. Zuin et al. focused solely on Alzheimer's disease and included data from four prospective studies. However, the evidence generated from these reviews come mostly from data which is more than a decade old, with the majority of identified studies published prior to 2012 (see **Appendix 2.5**). In contrast, the systematic review presented in this thesis Chapter incorporates more recent evidence on this topic, with inclusion of four additional studies published after 2012 with traits such as inclusion of larger sample sizes and previously understudied subgroup analyses, such as the impact of number of MetS components on dementia risk. Therefore, this review offers a more up-to-date and comprehensive overview of the literature on MetS and dementia risk, incorporating a broad range of dementia-related outcomes; the latter aspect can help understand not only the state of current evidence, but can also provide insights regarding potential differential associations with varying dementia subtypes, each of which are known to possess different mechanisms of development.[220] However, based on the overall characteristics and quality ratings of the identified

studies, as well as the precision of their findings (which potentially contribute to the mixed results observed), additional research on MetS and dementia risk is warranted.

Potential Reasons for Differences in Study Findings

Results from this systematic review indicate large variation among studies in terms of study characteristics, overall quality, and generalisability. Potential reasons resulting in the variability and equivocal nature of findings among the identified studies could be due to several methodological factors, including: 1) small sample sizes and short follow-up periods; 2) differences in ascertainment of MetS; and 3) lack of inclusion of important confounder adjustments. These considerations are discussed in further detail below.

Sample Size and Follow-up Duration

Among the ten studies identified in this review, seven studies had a relatively small sample size (i.e., ~2,000 participants or less)[203,205,207,208,210,211,213], and short follow-up durations of up to 5 years or less (eight studies).[203,205-210,213] These factors could have possibly contributed to the constrained number of incident dementia cases ascertained (<250 cases). The short follow-up duration across studies is particularly problematic in the context of dementia, which is known to have a long prodromal phase where symptoms may not become apparent until much later into the disease's progression.[221] Moreover, early subclinical changes in disease pathology could disrupt autonomic function, thereby impacting individual levels of MetS components (e.g., lowering blood pressure or reducing weight).[72,73] Such subclinical changes can also influence behavioural risk factors such as decreased physical activity or reduced engagement in usual daily hobbies which could subsequently affect MetS components.[222-224] Consequently, reverse causation remains a significant concern in these studies as most of them may not adequately

capture the long-term development of dementia, which could potentially lead to an underestimation of the association between MetS and dementia risk. Longer follow-up periods are necessary for accurately determining the temporality of the relationship between MetS and dementia risk. Interestingly, while the largest study identified in this systematic review consisted of >4 million participants, it was based on a medical records cohort. While large, such cohorts present many limitations as they are not typically designed for research purposes (i.e., administrative data). These limitations include: high levels of missingness, lack of appropriate confounder data, inconsistencies in the standardisation of data collection procedures, and susceptibility to selection bias.[225] Therefore, further studies leveraging larger samples and longer follow-up durations, specifically using research cohorts (which are designed particularly for health research purposes), are necessary to gain a better understanding of the MetS-dementia relationship.

Ascertainment of MetS

Although most studies identified in this review adopted similar criteria to define MetS, there are still some important nuances and considerations that are worth noting. While the majority of studies state that they followed the established NCEP-ATP III criteria for defining MetS, in some instances, the exact definitions specified were not fully adhered to, likely due to lack of data availability. These differences could have contributed to the varied findings, but it is often difficult to tell since most studies were also relatively small and underpowered to detect associations. For instance, two studies used body mass index estimates instead of the required waist circumference measurements outlined in the established MetS criteria (such as in NCEP-ATP III), and this alteration could possibly explain the lack of an association observed in these studies, but investigations leveraging larger samples are warranted.[203,211] Moreover, two studies

used solely the International Classification of Diseases (ICD) diagnostic codes to capture specific MetS components such as 'high triglycerides' (hyperlipidaemia diagnosis), 'high blood pressure' (hypertension diagnosis) or 'high blood glucose' (diabetes diagnosis)[204,211], and one study used self-reported diagnosis data[207] instead of incorporating biological or blood readings for defining these components – as specified in the established MetS criteria. Additionally, one study did not capture medication usage, which is required to define specific components (as per established MetS criteria).[207] For instance, 'high blood pressure' can be captured through systolic and diastolic blood pressure readings but may also be captured through a participant's medication history of 'antihypertensive use/treatment'. Despite these differences, the results across these aforementioned studies are relatively consistent. Nevertheless, deviations from the MetS criteria could result in inappropriate capture of its specific components, leading to misclassification of study participants. This limitation is difficult to mitigate, as it is likely a function of inherent data restrictions outside of what researchers can control. Nevertheless, study authors do acknowledge these limitations in their work, and some authors attempt to address these through the use of appropriate proxy measures (with appropriate evidence and justifications for doing so) in cases where the original criteria specified in established MetS definitions could not be met, while others have also conducted sensitivity analyses in smaller cohorts of their dataset where all of the necessary variables were available to achieve compliance with established MetS definitions.[206,207,211]

Confounder Adjustment

Another important consideration to note is that the level of confounder adjustment differed across studies identified in this review. While most studies adjusted for age and sex, other important confounders that are particularly relevant in the context of understanding the

relationship between MetS and risk of dementia[17,226] were not included in several studies, such as: education, socioeconomic status, ethnicity, lifestyle and behavioural variables (such as physical activity and smoking status), and *APOE*-ε4 carrier status. Interestingly, while just four out of the ten studies received a 'weak' (three)[203,204,206] or 'moderate' (one)[209] quality rating for confounder adjustments, these studies also happened to contribute the largest sample sizes (with the largest being a medical records cohort) and the greatest number of dementia cases among those identified in the review. Therefore, differences in confounder adjustments may have contributed to the high heterogeneity evident across study findings for each dementia outcome.

Strengths and Limitations

To date (at the time of conducting this work), this is the most comprehensive review of prospective studies examining the relationship between MetS and risk of incident dementia and key subtypes. The inclusion criteria for MetS as an exposure allowed for inclusion of a broad range of exposure definitions, which accommodates the minor variations that exist in previously established MetS definitions, but is also restrictive enough to ensure studies with too many deviations are not included. For example, during screening, one paper was identified whose exposure definition included all the necessary MetS components that were in compliance with established MetS criteria, but also incorporated c-reactive protein, which is not in the established criteria, and thus it was excluded from this review.[227] Another strength of this work is that the systematic review incorporated several outcome measures including: all-cause dementia, and key dementia subtypes (Alzheimer's disease, vascular dementia, Lewy Body dementia, and other dementias). This allowed an understanding of the state of evidence surrounding the relationship of MetS with a broad range of dementia outcomes, each of which are known to have varying pathological and aetiological underpinnings in the context of different health conditions and risk

factors.[228] This review also has several limitations. First, only studies published in English were included, which could limit the generalisability of the findings. Second, findings from other sources, such as pre-prints or grey literature were not included. Third, while a broad set of MetS criteria and dementia outcomes were captured, the minor inconsistences in both exposure and outcome definitions adopted within studies may still contribute to the heterogeneity observed in the findings, and thus, may limit the overall comparability between included studies.

Conclusion

In conclusion, this systematic review provides a comprehensive understanding of the evidence surrounding the relationship between MetS and the risk of developing dementia. The current body of prospective evidence remains mixed, which is most likely due to inherent methodological limitations within studies (as discussed earlier). Moreover, few studies reported on how the relationship between MetS and dementia may vary based on key population characteristics that might further explain associations (i.e., factors such as age, sex, duration of MetS, genetic predisposition, number of MetS components, and follow-up length). Given this uncertainty, larger and more comprehensive prospective cohort studies – which include detailed patient data for ample confounder adjustment, a large sample size, long follow-up, and different kinds of subgroup/secondary analyses – are necessary to fully elucidate the nature of the relationship between MetS and the risk of developing dementia. Insights gained from this Chapter helped to inform and lay the foundation for the analyses presented in later Chapters.

As mentioned previously, this systematic review was initially conducted in early 2022. At the time of conception, there were plans to conduct a meta-analysis as well. However, due to the limited number of identified studies in this review and the subsequently planned prospective

analyses conducted in this DPhil thesis (UK Biobank - Objective 2, and EPIC-Norfolk - Objective 3), a decision was made to pause the remainder of the work (i.e., meta-analysis) at the time. This decision provided the opportunity to incorporate into the meta-analysis: 1) the two prospective cohort study findings from this thesis; and 2) any additional emerging studies published in the research literature (for which weekly search alerts were set up after the initial search date). Findings from the prospective studies conducted as part of this thesis are presented in Chapters 3 and 4, respectively.[213,229] After conducting these two prospective cohort studies, the remaining scope of work (i.e., an update of this systematic review and subsequent meta-analysis) was re-visited in mid-2024, for which detailed findings are presented later in Chapter 5.

CHAPTER 3

Investigating the Association Between Metabolic Syndrome and Incident Dementia in the UK Biobank

CHAPTER SUMMARY

The review from the previous Chapter highlighted that the association between MetS and incident dementia remains inconclusive, likely due to methodological factors such as a small study population and short follow-up among existing published studies. The aim of this Chapter was to investigate the association between MetS and the risk of developing incident dementia in the UK Biobank, a large-scale population-based prospective cohort study of 0.5 million individuals aged 40-69 years recruited between 2006-2010 with over 15 years of follow-up. This Chapter also further examined how these associations vary according to follow-up length, number of MetS components present, and genetic risk for dementia.

The main exposure in this study was MetS status at baseline, defined as the presence of at least three of the following (based on the 2009 Harmonized Criteria): elevated waist circumference, elevated triglycerides, elevated blood pressure, elevated glycated haemoglobin A1c (HbA1c) levels, and reduced HDL cholesterol. The main outcome was incident all-cause dementia, which was identified using hospital inpatient and death registry records. Cox proportional-hazards models were used to investigate the association between MetS and incident all-cause dementia, adjusting for several key sociodemographic, lifestyle and genetic factors.

The analysis identified 176,249 dementia-free adults aged ≥60 years at baseline, among which 73,510 (41.7%) had MetS. Over 15 years of follow-up (median: 12.3), 5,255 participants developed dementia. MetS was associated with a 12% increased risk of developing incident all-cause dementia (HR, 1.12, 95% CI: 1.06, 1.18), compared to no MetS. Associations remained consistent when restricting to longer follow-up intervals of >5-10 years (HR, 1.17, 95% CI: 1.07, 1.27) and >10 years (HR, 1.22, 95% CI: 1.12, 1.32). In terms of the number of MetS components,

only the presence of four (HR, 1.19, 95% CI: 1.03, 1.38) or five (HR, 1.50, 95% CI: 1.28, 1.76) components were significantly associated with an increased risk of developing incident dementia, compared to having zero components. There was a statistically significant interaction ($p < 0.001$) between MetS and *APOE*-ε4. Specifically, MetS was associated with an increased risk of dementia in *APOE*-ε4 non-carriers (HR, 1.26, 95%CI: 1.16, 1.37) but not in *APOE*-ε4 carriers (HR, 1.02, 95%CI: 0.94, 1.10). No statistically significant interaction was found when examining associations between MetS and non-*APOE* dementia polygenic risk score (PRS) (*P*-value for interaction: 0.42) and risk of incident dementia.

In conclusion, this study found that MetS was associated with an increased risk of developing incident all-cause dementia. Dementia risk varied according to follow-up length, number of MetS components present, and genetic factors (specifically *APOE*-ε4 carrier status). These findings provide strong evidence suggesting that MetS is a risk factor for dementia. However, future research using large samples with diverse populations is necessary to confirm these associations and their overall generalisability.

Parts of the material presented in this Chapter were published in *Alzheimer's and Dementia*, under the title "Association between metabolic syndrome and risk of incident dementia in UK Biobank" (Qureshi et al., 2023): https://doi.org/10.1002/alz.13439. This work was also presented at several scientific conferences and featured in several news outlets worldwide (see section **"DPhil Publications, Recognitions and Awards"** for further details).

BACKGROUND

The systematic review presented in Chapter 2 identified several studies that have previously investigated the association between MetS and dementia risk. Findings from this review indicate that MetS could represent a novel risk factor for dementia, but the relationship still remains unclear due to the large variability among existing published studies on this topic. In line with the findings from Chapter 2, a previous (2019) meta-analysis of six longitudinal studies found no statistically significant pooled association between MetS and risk of incident all-cause dementia (HR: 1.12, 95% CI: 0.94, 1.33).[70] As further evidenced in Chapter 2, the lack of clarity on these associations may stem from the fact that the majority of existing published studies on this topic consist of small sample sizes (i.e. < 8,000 participants[203-205,207-211,229]) and/or short follow-up periods (i.e. <5 years[203,205-210]). The latter aspect is particularly important to address because, as stated in earlier Chapters, dementia has a long prodromal phase prior to a clinical diagnosis, and reverse causation is a particular limitation of studies with short follow-up.

Previous studies have also demonstrated that the associations between individual MetS components (e.g., elevated blood glucose, elevated blood pressure or elevated waist circumference) and cognitive dysfunction and/or dementia may differ by genetic risk for dementia.[215-218,230] However, whether genetic predisposition to dementia modifies any observed associations between MetS and risk for dementia, in the context of current knowledge (based on Chapter 2), has not been previously investigated thoroughly. Moreover, previous evidence indicates that, individually, each component of MetS, has been consistently associated with an

increased risk of developing dementia.[17] However, the combined contribution of these components (i.e., MetS) in this relationship is not yet fully understood.

Therefore, to address these limitations, the study conducted in this Chapter sought to investigate the association between MetS and the risk of developing incident dementia in a population-based cohort of more than 175,000 participants with over 15 years of follow-up from the UK Biobank. The study in this Chapter also examines whether *APOE*-ε4 genotype, as well as a non-*APOE* PRS for dementia, interacts with MetS to modify the risk of developing dementia. The role of MetS components in relation to dementia risk is also briefly explored.

METHODS

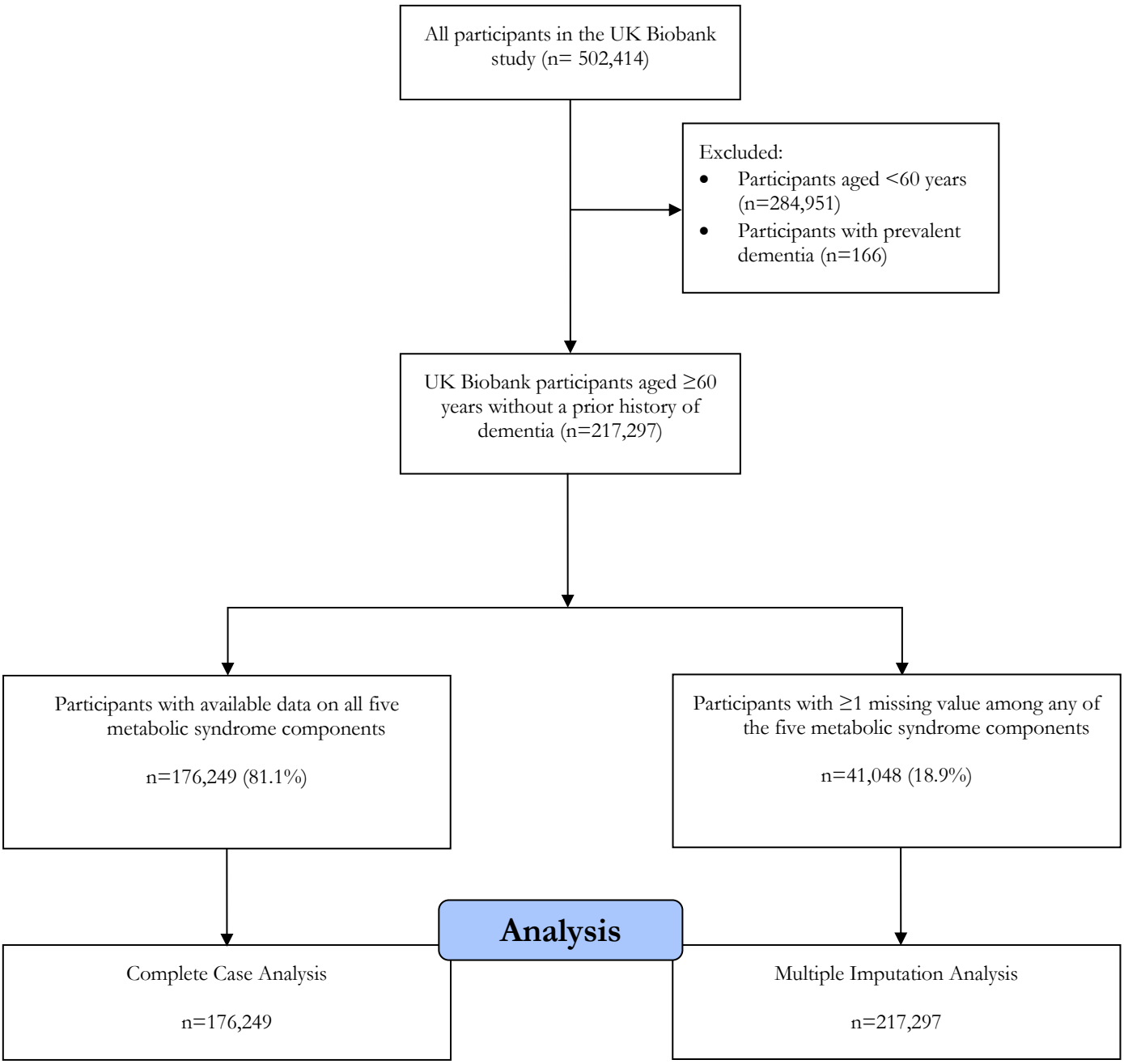
Study Population

This study presented here used data from the UK Biobank, which is a large-scale population-based prospective cohort study of more than half a million participants aged 40-69 years who were recruited between 2006-2010 across various regions in the United Kingdom.[231] Participants attended baseline assessment centres across England, Scotland and Wales, where they provided electronically signed consent. At baseline, participants provided information on sociodemographic, lifestyle, environmental and health-related factors collected through a touch-screen questionnaire and a nurse-led verbal interview, underwent various physical examinations, and provided biological samples. Medication use was also ascertained during the nurse-led verbal interview. All participants were followed up for health conditions through linkage to national and electronic health-related datasets.[232] UK Biobank received ethical approval from the National Health Service (NHS) North West Centre for Research Ethics Committee (Ref: 11/NW/0382). Further information regarding the UK Biobank cohort can be found at: https://www.ukbiobank.ac.uk/

The main analysis in this Chapter was restricted to participants aged ≥60 years at baseline to ensure the study population consisted of individuals who were at risk of developing late-onset dementia. This age restriction was applied because the proportion of individuals aged <60 who developed dementia was small, likely due to the relatively short mean follow-up duration available in this study (at the time of study: <12 years) and the fact that dementia diagnoses typically occur after age 65, with the average age of diagnosis occurring at age ~80+ years.[233]

Therefore, focusing on a population aged 60 and older helped to capture a more at-risk population in the context of this study cohort. Participants were also excluded from the study if they had prevalent self-reported or diagnosed dementia. Further details regarding cohort creation are provided in **Figure 3.1**.

Figure 3.1: Cohort flow diagram



Metabolic Syndrome

MetS was defined using the 2009 Harmonized Criteria proposed by the IDF and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI).[26] While there are several different criteria available to define MetS, the 2009 Harmonized Criteria was chosen as it was based on the most recent recommendations gathered from a consensus meeting between several major healthcare organisations who sought to unify the existing criteria for MetS into a single, cohesive definition (described further in Chapter 1).[26]

The presence of at least three of the following five components constituted a MetS diagnosis: (1) elevated waist circumference: ≥ 102 cm in males and ≥ 88 cm in females); (2) elevated triglycerides (≥ 150 mg/dL or 1.7 mmol/L); (3) elevated blood pressure (≥130 mmHg systolic blood pressure and/or ≥85 mmHg diastolic blood pressure) or antihypertensive medication use; (4) elevated fasting blood glucose (≥100 mg/dL or ≥5.6 mmol/L) or drug treatment for elevated blood glucose; and (5) reduced HDL cholesterol (<40 mg/dL or 1.0 mmol/L in males; <50 mg/dL or 1.3 mmol/L in females) or lipid-modifying medications.

Data on circulating glucose levels were obtained predominantly from non-fasting blood samples, which are more likely to be affected by recent food intake (as compared to fasting samples), which can lead to high variability in glucose measurements. Therefore, HbA1c was used as a proxy measure of glucose, based on the recommendations of the American Diabetes Association, with a cut point of HbA1c ≥5.7% (39 mmol/mol) to represent hyperglycaemia.[234] The use of proxy measures (in lieu of the originally defined MetS components) have also been

adopted in previous literature. For instance, in a recent UK Biobank study adopting the NCEP-ATP III guidelines to define MetS, the authors found that participant data on fasting glucose levels – one of the components used to define MetS – was very low (4.3%).[235] Thus, the authors instead used HbA1c – a variable with more complete participant data – as a proxy measure for fasting glucose levels. Several previous studies have also adopted proxy measures to define other MetS components, particularly when the precise measures were not available to fully comply with established MetS definitions.[236-238]

Additionally, lipid-modifying medications are known to have multiple effects on the lipid profile (including HDL cholesterol and triglycerides).[239] Thus, to prevent double counting, lipid-modifying medications were assigned to the reduced HDL cholesterol group for the analysis. Medication usage was captured using Anatomical Therapeutic Chemical (ATC) codes, which was informed by a thorough literature review of previous studies that used ATC codes to capture medication use in their definitions of MetS[240-250], and with expert clinical input.

Participants were categorised into two groups: (1) No MetS (reference group), and (2) MetS. Complete information regarding the variables and medication codes used to capture and define MetS components are available in **Appendix 3.1** and **Appendix 3.2**.

Dementia

Incident all-cause dementia was chosen as the main outcome due to challenges in reliably distinguishing subtypes and because many dementia cases present with mixed pathology

(discussed previously in Chapter 1). Cases of incident all-cause dementia were identified using hospital inpatient admissions and death registry records. Inpatient admission records were available from the Hospital Episode Statistics for England, the Scottish Morbidity Record for Scotland, and the Patient Episode Database for Wales. Death registry records were available from the National Health Service (NHS) England for England and Wales, and the Information and Statistics Division for Scotland. Primary and secondary hospital diagnoses and causes of death were recorded using the ICD-10 coding system. The ICD codes used to ascertain dementia were selected and validated by the UK Biobank outcome adjudication group. A full list of these codes are provided in **Appendix 3.3**.[251]

Covariates and Effect Modifiers

In this study, several covariates were included, consisting of sociodemographic, lifestyle, and genetic factors which have been previously associated with dementia or MetS, and considered here to be potential confounders in determining the relationship between the exposure and outcome.[17,226] Age (in years) at baseline was calculated based on the date of birth and the date of attending an assessment centre. The Townsend deprivation index was used as a proxy for material socio-economic deprivation and was assigned to each study participant using their residential postal code at baseline, and was categorised into fifths (1-5: least deprived to most deprived).[252] Sex ('male', 'female') was captured using NHS records and/or self-reported data from the touchscreen questionnaire. Ethnicity ('white', 'non-white'), education level ('primary', 'secondary', 'post-secondary non-tertiary', 'tertiary'), household income in British Pound Sterling (GBP; less than 18,000', '18,000-30,999', '31,000-51,999', '52,000-100,000',

'greater than 100,000'), smoking status ('never', 'previous', 'current'), and alcohol intake ('never', 'former drinker', 'special occasions only', '1-3 times per month', '1-2 times per week', '3-4 times per week', 'daily or almost daily', 'prefer not to answer') were captured from the touchscreen questionnaire. Physical activity level ('low' – metabolic equivalent of task (MET) minutes ≤1200, 'high' – MET >1200) was derived from the touch-screen questionnaire items which were adapted to the validated short International Physical Activity Questionnaire [253]; time spent conducting vigorous, moderate, and walking activity was weighted by the amount of energy expended which enabled capture of total MET minutes per week.

APOE-ε4 carrier status ('ε4 non-carrier', 'ε4 carrier') was derived using the rs429358 and rs7412 single nucleotide polymorphisms (SNP), which were directly genotyped on the UK Biobank arrays.[254] Non-*APOE* dementia PRS was used in secondary analyses to assess interactions. This measure was based on a 39-SNP score (available on the Polygenic Score Catalog online as PGS001775) and was derived based on previously published methods[255] that used a range of publicly available genome-wide association study summary statistics for late-onset Alzheimer's disease.[256-258] Weights for the score were computed in the International Genomics of Alzheimer's Project.[257,258] PLINK 2[259] with hard call threshold 0.1 was used in order to make sure that none of the SNPs were in linkage disequilibrium with the *APOE* SNPs ($R^2 <$ 0.3). One SNP had minor allele frequency <0.005, and was therefore excluded. The final score was made up of 38 SNPs, where all SNPs had imputation information >0.9 and no SNPs were ambiguous. The dementia PRS was split into quintiles, and further categorised into 'low' (quintile

1), 'intermediate' (quintiles 2-4), and 'high' (quintile 5) groups, with a higher PRS indicating a greater dementia risk.

Statistical Analysis

Descriptive statistics were used to compare baseline characteristics between participants with and without MetS; mean and SD were calculated for normally distributed variables, and median and IQR for skewed variables. Multivariable Cox proportional-hazards models using follow-up time as the underlying time scale were used to estimate the association between MetS and incident all-cause dementia. Follow-up time (in years) was calculated from the baseline assessment date until the date of first incident dementia diagnosis, date of death, date of loss to follow-up, or end of follow-up, whichever occurred first. End of complete follow-up was based on the availability of electronic health record data in the UK Biobank, which was censored on September 30, 2021 for England; July 31, 2021 for Scotland; and February 28, 2018 for Wales. The proportional hazards assumption was visually examined using scaled Schoenfeld residuals, with no variables violating the assumption. Only participants with complete data on all five individual MetS components were included in the main analysis (see **Figure 3.1** for details regarding cohort creation). The main analysis was adjusted for age, sex, ethnicity, education, Townsend deprivation index, household income, smoking status, weekly alcohol intake, physical activity level, and *APOE*-ε4 carrier status. Participants with any missing covariate data, or who responded with "prefer not to answer/do not know" were assigned as a separate category for each categorical variable.

To investigate the potential for reverse causation, the analysis was stratified according to the follow-up length available for each participant: 1) ≤ 5 years, 2) >5 to 10 years, and 3) ≥10 years.

In order to better understand the influence of each confounder on the relationship between MetS and risk of incident all-cause dementia, the effect of individual and sequential adjustment of each included covariate was investigated. In individual adjustment, models were first adjusted for age and sex, followed by further addition of each covariate into the model separately. In sequential adjustment, models were again adjusted for age and sex, followed by inclusion of the additional remaining covariates into the model in a stepwise manner.

The interaction between MetS and genetic predisposition to dementia was also investigated. This involved entering MetS × *APOE*-ε4 carrier status ('not a carrier', 'ε4 carrier') and MetS × non-*APOE* dementia PRS ('low', 'intermediate', 'high') interaction terms separately into the main model. Effect estimates within each strata of genetic risk were obtained for MetS versus no MetS.

To investigate possible joint associations of MetS and genetic predisposition to dementia, a 4-level categorical variable was derived containing each combination of MetS and *APOE*-ε4 carrier status; a 6-level categorical variable was also derived containing each combination of MetS and non-*APOE* dementia PRS categories. The main analysis was repeated with these variables entered into separate models. This approach provides a comprehensive

understanding of how these individual genetic factors may synergistically influence dementia risk by MetS status.

The interaction between MetS and sex ('Female', 'Male') was also examined due to prior evidence of effect modification.[260,261] Furthermore, stratified analyses were conducted to investigate effect modification by age groups (<60 years, 60 to <65 years, and 65+ years).

The association between individual MetS components and dementia risk was also examined, as well as the association between the number of MetS components (defined as a categorical variable on a scale from 0-5, with zero as the reference group) and dementia risk. The relationship between all sixteen possible combinations of MetS components and incident dementia was also investigated.

In the analyses presented in this Chapter, lipid-modifying medications were assigned to the reduced HDL cholesterol group. To explore whether this decision impacted the findings, the effect of assigning these medications to the elevated triglycerides group instead of reduced HDL cholesterol was also examined.

Several sensitivity analyses were also performed to examine the robustness of the findings, including repeating the main analysis with: (1) the use of age as the underlying time scale; (2) exclusion of participants with shorter follow-up time to avoid potential differential bias; (3) accounting for death as a competing risk; (4) additional adjustment for cardiovascular disease

('yes', 'no') – defined as a diagnosis of stroke, coronary heart disease, or heart failure captured from the nurse-led verbal interview – (which may be a confounder or on the causal pathway)[26]; (5) using the NCEP-ATP III definition for MetS [37], which is a commonly used alternative definition for the condition; and (6) using multiple imputation to investigate the potential impact of missing data. Briefly, the Multiple Imputation by Chained Equations (MICE) package (in RStudio) was used to impute data on missing values for individual MetS components and key covariates. Specifically, missing data were imputed for the following MetS components: waist circumference, triglycerides, blood pressure, HbA1c, and HDL cholesterol. The covariates included in the imputation model were age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity and *APOE*-ε4 carrier status. The imputed MetS component values were then used to define the binary MetS variable (as per the 2009 Harmonized Criteria) in each imputed dataset. Estimates from each dataset were used to produce a pooled estimate, following the rules outlined by Rubin.[262,263]

All p-values were two sided, with statistical significance set at $p < 0.05$. All analyses were performed using RStudio version 4.2.2.

RESULTS

Cohort Characteristics

Among 502,414 participants recruited into the UK Biobank, the following were excluded: 284,951 participants aged <60 years, 166 with prevalent dementia, and 41,048 with missing data on ≥1 MetS component. Baseline characteristics of participants with missing data on MetS components were highly similar to those with complete data (**Appendix 3.4**). The final analytical sample consisted of 176,249 participants, of whom 41.7% had prevalent MetS. Participants' characteristics according to incident dementia status are presented in **Appendix 3.5**.

Baseline characteristics of the study participants are provided in **Table 3.1**. Compared to participants without MetS, those with MetS were more likely to be older, male, of non-white ethnicity, have lower educational qualifications, reside in more socioeconomically deprived areas, have lower household income levels, be current or previous smokers, be less physically active, and *APOE*-ε4 carriers. Among those with MetS, 52.8% had three, 33.2% had four, and 14.0% had five MetS components; the most prevalent component being elevated blood pressure (96.2%), followed by elevated triglycerides (73.5%), reduced HDL cholesterol (71.9%), elevated waist circumference (69.8%), and elevated HbA1c (49.8%). Over 2,088,296 person-years of follow-up (median [IQR]: 12.3 [11.5-13.1] years), 5,255 cases of incident all-cause dementia were identified (see **Figure 3.2** for a Kaplan-Meier plot by MetS status).

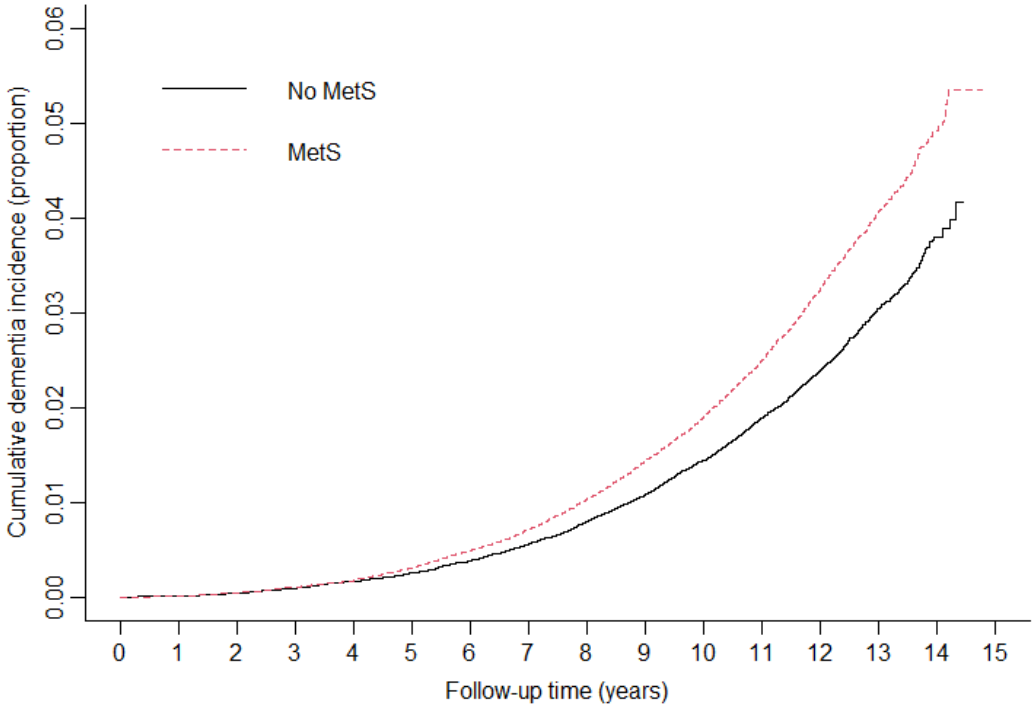
Table 3.1: Baseline characteristics by MetS status

Characteristic		No MetS (N=102739)	MetS (N=73510)	Overall (N=176249)
Follow-up length	Mean (SD)	12.0 (2.0)	11.7 (2.4)	11.8 (2.2)
Age (years)	Mean (SD)	64.0 (2.8)	64.4 (2.9)	64.1 (2.9)
Sex	Female	56323 (54.8%)	35729 (48.6%)	92052 (52.2%)
	Male	46416 (45.2%)	37781 (51.4%)	84197 (47.8%)
Ethnicity	White	100305 (97.6%)	70369 (95.7%)	170674 (96.8%)
	Non-White	1987 (1.9%)	2777 (3.8%)	4764 (2.7%)
	Missing	447 (0.5%)	364 (0.5%)	811 (0.5%)
Education level	Primary	23907 (23.3%)	23318 (31.7%)	47225 (26.8%)
	Secondary	48010 (46.7%)	29675 (40.4%)	77685 (44.1%)
	Post-secondary non-tertiary	11261 (11.0%)	7661 (10.4%)	18922 (10.7%)
	Tertiary	18329 (17.8%)	11692 (15.9%)	30021 (17.0%)
	Missing	1232 (1.2%)	1164 (1.6%)	2396 (1.4%)
Townsend deprivation index, quintiles	1 (least deprived)	22162 (21.6%)	13059 (17.8%)	35221 (20.0%)
	2	21438 (20.9%)	13782 (18.7%)	35220 (20.0%)
	3	20989 (20.4%)	14231 (19.4%)	35220 (20.0%)
	4	20182 (19.6%)	15038 (20.5%)	35220 (20.0%)
	5 (most deprived)	17882 (17.4%)	17338 (23.6%)	35220 (20.0%)
	Missing	86 (0.1%)	62 (0.1%)	148 (0.1%)
Household income (in GBP)	Less than 18,000	25097 (24.4%)	23588 (32.1%)	48685 (27.6%)
	18,000 to 30,999	27809 (27.1%)	18821 (25.6%)	46630 (26.5%)
	31,000 to 51,999	18982 (18.5%)	10954 (14.9%)	29936 (17.0%)
	52,000 to 100,000	9589 (9.3%)	4848 (6.6%)	14437 (8.2%)
	Greater than 100,000	2351 (2.3%)	1058 (1.4%)	3409 (1.9%)
	Missing	18911 (18.4%)	14241 (19.4%)	33152 (18.8%)
Smoking status	Never	54640 (53.2%)	32645 (44.4%)	87285 (49.5%)
	Previous	40038 (39.0%)	33354 (45.4%)	73392 (41.6%)
	Current	7563 (7.4%)	6945 (9.4%)	14508 (8.2%)
	Missing	498 (0.5%)	566 (0.8%)	1064 (0.6%)
Alcohol intake	Never	4038 (3.9%)	4392 (6.0%)	8430 (4.8%)
	Former drinker	3176 (3.1%)	3466 (4.7%)	6642 (3.8%)
	Special occasions only	10253 (10.0%)	11030 (15.0%)	21283 (12.1%)
	1-3 times per month	9377 (9.1%)	8024 (10.9%)	17401 (9.9%)
	1-2 times per week	24086 (23.4%)	17992 (24.5%)	42078 (23.9%)
	3-4 times per week	24691 (24.0%)	14204 (19.3%)	38895 (22.1%)
	Daily or almost daily	26978 (26.3%)	14227 (19.4%)	41205 (23.4%)
	Prefer not to answer	77 (0.1%)	91 (0.1%)	168 (0.1%)
	Missing	63 (0.1%)	84 (0.1%)	147 (0.1%)
Physical activity level	Low (MET minutes ≤ 1200)	24873 (24.2%)	22992 (31.3%)	47865 (27.2%)
	High (MET minutes > 1200)	57557 (56.0%)	33502 (45.6%)	91059 (51.7%)
	Missing	20309 (19.8%)	17016 (23.1%)	37325 (21.2%)
***APOE*-ε4 carrier status**	Non-carrier	73825 (71.9%)	51909 (70.6%)	125734 (71.3%)
	Carrier	25686 (25.0%)	19219 (26.1%)	44905 (25.5%)
	Missing	3228 (3.1%)	2382 (3.2%)	5610 (3.2%)
Elevated waist circumference	Present	14731 (14.3%)	51275 (69.8%)	66006 (37.5%)
Elevated triglycerides	Present	23094 (22.5%)	54002 (73.5%)	77096 (43.7%)
Elevated blood pressure*	Present	77127 (75.1%)	70692 (96.2%)	147819 (83.9%)
Elevated HbA1c*	Present	7895 (7.7%)	36636 (49.8%)	44531 (25.3%)
Reduced HDL-cholesterol*	Present	15791 (15.4%)	52888 (71.9%)	68679 (39.0%)

Abbreviations: MetS = Metabolic Syndrome, APOE = Apolipoprotein, SD = standard deviation, MET = metabolic equivalent of task, GBP = British pound sterling, HbA1c = hemoglobin A1c, HDL = high density lipoprotein. Percentages do not add up to 100 due to rounding.

*Includes medication use

Figure 3.2: Cumulative unadjusted dementia incidence by MetS status



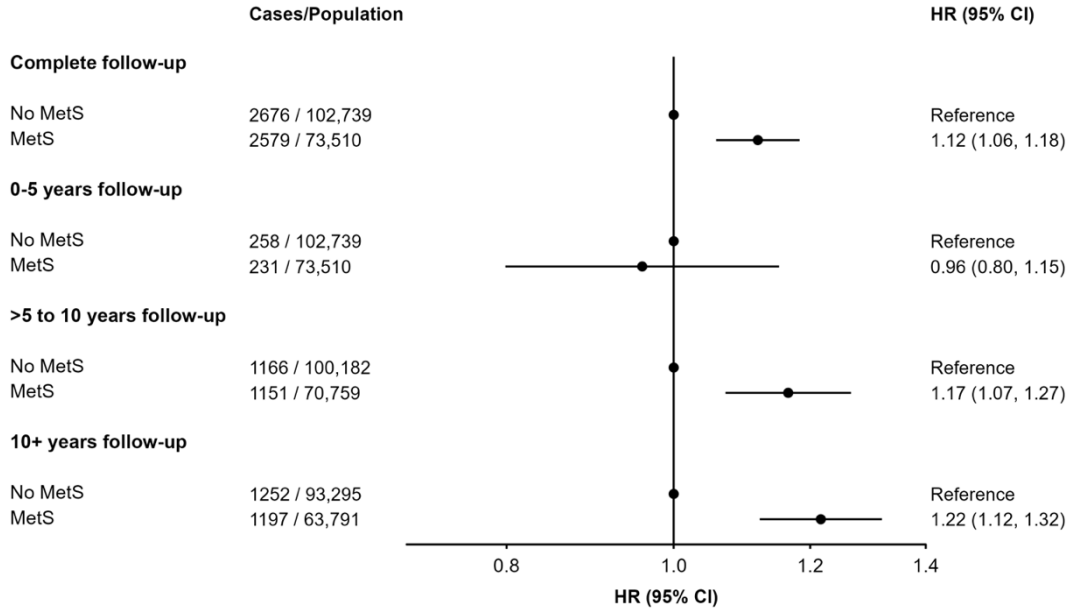
Abbreviations: MetS = Metabolic Syndrome

MetS and Risk for All-Cause Dementia

Compared to participants with no MetS, those with MetS had an increased risk of incident all-cause dementia (fully adjusted HR, 1.12, 95% CI: 1.06, 1.18; **Figure 3.3**). The association remained similar when restricting to those with >5-10 years (HR, 1.17, 95% CI: 1.07, 1.27) and >10 years of follow-up (HR, 1.22, 95% CI: 1.12, 1.32), but was null for those with ≤5 years of follow-up (HR, 0.96, 95% CI: 0.80, 1.15). The effect of individual and sequential adjustment of covariates are shown in **Appendix 3.6**. After adjusting for age and sex (HR, 1.29, 95% CI: 1.22, 1.36), household income had the largest attenuating effect (HR, 1.23. 95%CI: 1.17, 1.30) on the associations. In sensitivity analyses, results remained similar after 1) using age as a

time scale, 2) excluding participants from Wales, 3) accounting for death as a competing risk, 4) using the NCEP-ATP III definition for MetS, and 5) performing multiple imputation for missing exposure and covariate data (**Appendix 3.7**). While additional adjustment for cardiovascular disease did not change the direction of the association between MetS and dementia, the relationship was slightly attenuated (HR, 1.05, 95% CI: 1.01, 1.13).

Figure 3.3: Cox proportional hazards models investigating the association between MetS and incident dementia by different follow-up periods



Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, Ref. = Reference group, IQR = Interquartile Range
Mean, Median (IQR) follow-up length in years: 1) 0 to 5 years: 4.9, 5.0 (5.0, 5.0); 2) >5 to 10 years: 9.8, 10.0 (10.0, 10.0); 3) 10+ years: 12.5, 12.5 (11.9, 13.2).
Mean age of participants in years: 1) 0 to 5 years: 64.1; 2) >5 to 10 years: 64.1; 3) 10+ years: 64.0 years.
Model adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity, APOE-ε4 carrier status

MetS-Dementia: Age and Sex

Age-stratified analyses demonstrated that the strength of the association between MetS and dementia was slightly greater in those aged <65 years compared to older participants, but the direction of the associations were the same across age groups (but attenuated in older ages) (**Table 3.2**).

Table 3.2: Cox proportional hazards models investigating the association between MetS and incident dementia among different age groups

Age Grouping	Cases/Population	HR (95%CI)
Inclusion of All Participants Aged ≥50 Years		
No MetS	3073 / 196,298	Ref.
MetS	2860 / 114,719	1.13 (1.07, 1.19)
Age-Stratification		
<60 Years		
No MetS	397 / 93,559	Ref.
MetS	281 / 41,209	1.22 (1.04, 1.43)
60 to <65 Years		
No MetS	801 / 38,277	Ref.
MetS	1781 / 42,512	1.19 (1.08, 1.32)
≥65 Years		
No MetS	1781 / 42,512	Ref.
MetS	1778 / 35,233	1.08 (1.01, 1.16)

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, , Ref. = Reference group, PRS = Polygenic risk score, APOE = Apolipoprotein E, MetS = Metabolic syndrome

Models adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity, APOE-e4 carrier status.

The interaction between MetS and sex and risk of incident dementia was not statistically significant (*P*-value for interaction: 0.33; **Table 3.3**).

Table 3.3: Cox proportional hazards models investigating the association between MetS and incident dementia according to sex

Sex	Cases/Population	HR (95%CI)
Female		
No MetS	1337 / 56,323	Ref.
MetS	1145 / 35,729	1.08 (1.01, 1.17)
Male		
No MetS	1339 / 46, 416	Ref.
MetS	1434 / 37,781	1.16 (1.07, 1.25)

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, , Ref. = Reference group, APOE = Apolipoprotein E, MetS = Metabolic syndrome

Model**s** adjusted for age, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity, APOE-ε4 carrier status. P-value for overall interaction between MetS and sex: 0.33.

MetS-Dementia: Genetic Predisposition

There was statistical evidence of an interaction between MetS and *APOE*-ε4 genotype (*P*-value for interaction: <0.001) on the risk of incident dementia (**Table 3.4**). MetS was associated with a significant increased dementia risk in *APOE*-ε4 non-carriers (HR, 1.26, 95% CI: 1.16, 1.37) but not in *APOE*-ε4 carriers (HR, 1.02, 95% CI: 0.94, 1.10). However, despite higher relative risks in non-carriers, the absolute incidence of dementia was higher in *APOE*-ε4 carriers (**Figure 3.4**). Specifically, among non-carriers, the 12-year cumulative dementia incidence was 2.3% (95% CI: 2.20, 2.40) for those with MetS and 1.4% (95% CI: 1.30, 1.50) for those without MetS. In comparison, among *APOE*-ε4 carriers, the corresponding incidence was 6.5% (95% CI: 6.2, 6.9) for those with MetS and 5.1% (95% CI: 4.8, 5.4) for those without MetS. Therefore, the risk difference was higher for *APOE*-ε4 carriers (1.4%) than non-carriers (0.9%).

No statistically significant interaction was found between MetS and non-*APOE* dementia PRS (*P*-value for interaction: 0.42) and risk of incident dementia (**Table 3.4**).

Table 3.4: Cox proportional-hazards models investigating the association between MetS and incident dementia by genetic predisposition

Genetic Factor	Cases/Population	HR (95%CI)
(A) APOE-ε4 Carrier Status		
Non-carrier		
No MetS	1152 / 73,825	1 (Ref.)
MetS	1230 / 51,909	1.26 (1.16, 1.37)
Carrier		
No MetS	1424 / 25,686	1 (Ref.)
MetS	1261 / 19,219	1.02 (0.94, 1.10)
(B) Non-APOE Dementia PRS		
Low		
No MetS	297 / 16,759	1 (Ref.)
MetS	337 / 12,255	1.19 (1.02, 1.40)
Intermediate		
No MetS	1272 / 50,852	1 (Ref.)
MetS	1225 / 36,188	1.12 (1.04, 1.22)
High		
No MetS	594 / 17,159	1 (Ref.)
MetS	557 / 11,854	1.13 (1.01, 1.28)

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, , Ref. = Reference group, PRS = Polygenic risk score, APOE = Apolipoprotein E, MetS = Metabolic syndrome

A) Model adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity. Excluded: 5,610 with missing information on APOE-ε4 carrier status. P-value for overall interaction between MetS and APOE-ε4: <0.001

B) Model adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity, APOE-ε4 carrier status. Excluded: 31,182 with missing information on non-APOE dementia PRS. P-value for overall interaction between MetS and non-APOE dementia PRS: 0.42

Figure 3.4: 12-year risk of incident dementia by MetS status and genetic predisposition for dementia

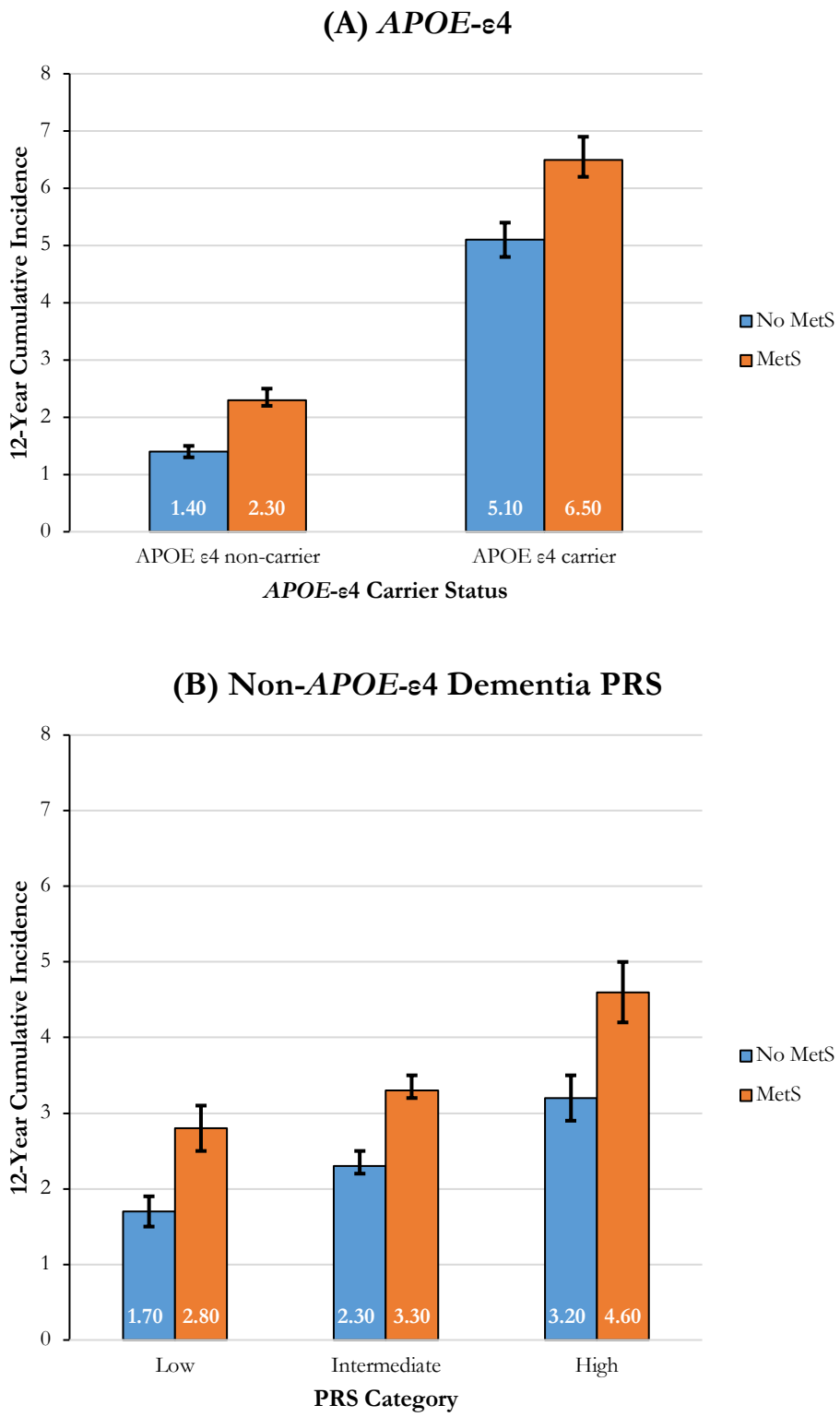


Table 3.5 presents results from models investigating the joint associations of MetS with: A) *APOE*-ε4 carrier status and B) non-*APOE* dementia PRS. This analysis revealed that, for *APOE*-ε4 carriers, the risk for developing incident dementia was similar whether they did or did not have MetS (*APOE*-ε4 carriers without MetS: HR, 3.70, 95% CI: 3.42, 4.02; *APOE*-ε4 carriers with MetS: HR, 3.71, 95% CI: 3.43, 4.01). In contrast, for non-*APOE* dementia PRS, the risk of dementia increased with a higher PRS and with the presence of MetS**.**

Table 3.5: Joint associations of A) MetS and *APOE*-ε4 carrier status and B) MetS and non-*APOE* Dementia PRS for risk of incident dementia

Genetic Factor	Cases/Population	HR (95%CI)	12-Year Cumulative Incidence (95%CI)
***APOE* ε4**			
APOE ε4 - / MetS -	1152 / 73,825	1 (Ref.)	1.40 (1.30, 1.50)
APOE ε4 - / MetS +	1230 / 51,909	1.28 (1.18, 1.39)	2.30 (2.20, 2.40)
APOE ε4 + / MetS -	1424 / 25,686	3.70 (3.42, 4.02)	5.10 (4.80, 5.40)
APOE ε4 + / MetS +	1261 / 19,219	3.71 (3.43, 4.01)	6.50 (6.20, 6.90)
Non-*APOE* Dementia PRS			
Low PRS / MetS -	297 / 16,759	1 (Ref.)	1.70 (1.50, 1.90)
Low PRS / MetS +	337 / 12,255	1.29 (1.10, 1.51)	2.80 (2.50, 3.10)
Intermediate PRS / MetS -	1272 / 50,852	1.42 (1.25, 1.61)	2.30 (2.20, 2.50)
Intermediate PRS / MetS +	1225 / 36,188	1.60 (1.41, 1.82)	3.30 (3.20, 3.50)
High PRS / MetS -	594 / 17,159	1.98 (1.72, 2.28)	3.20 (2.90, 3.50)
High PRS / MetS +	557 / 11,854	2.30 (2.00, 2.65)	4.60 (4.20, 5.00)

HR = Hazard Ratio, CI = Confidence Interval, , Ref. = Reference group, PRS = Polygenic risk score, APOE = Apolipoprotein, MetS = Metabolic syndrome

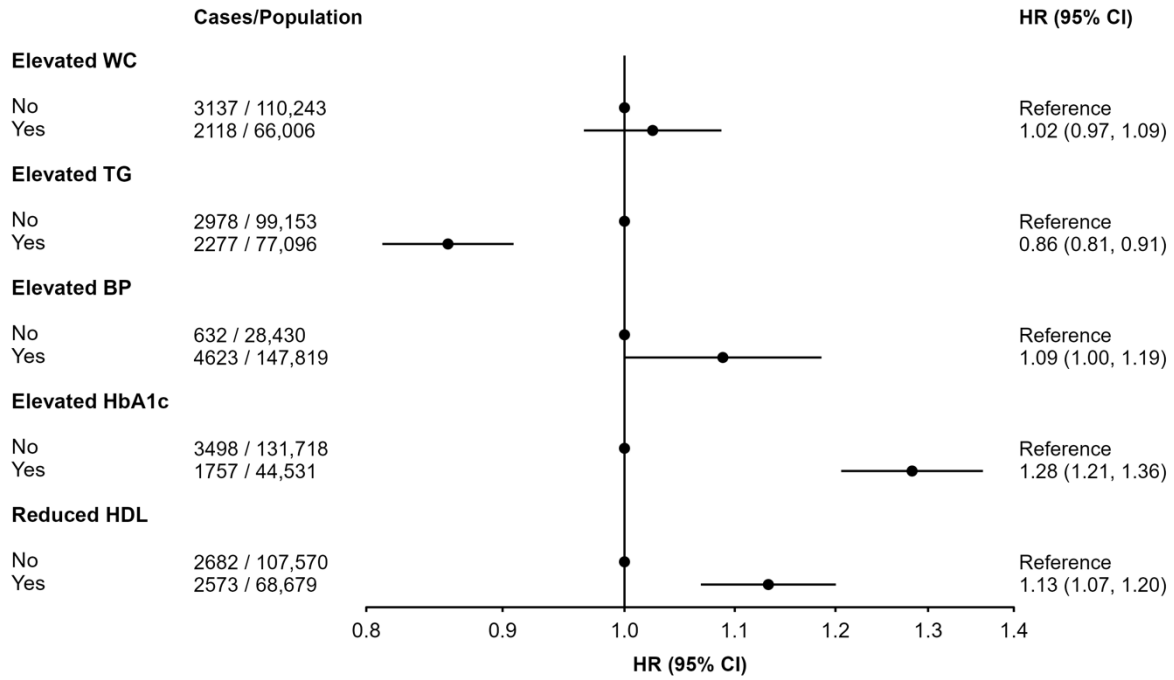
A) Model adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity. Excluded: 5,610 with missing information on APOE ε4 carrier status. P-value for overall interaction between MetS and APOE ε4: <0.001

B) Model adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity, APOE ε4 carrier status. Excluded: 31,182 with missing information on non-APOE dementia PRS. P-value for overall interaction between MetS and non-APOE dementia PRS: 0.42

Individual MetS Components and Dementia Risk

In analyses investigating individual MetS components, elevated HbA1c (HR, 1.28, 95% CI: 1.21, 1.36), reduced HDL cholesterol (HR, 1.13, 95% CI: 1.07, 1.20), and elevated blood pressure (HR, 1.09, 95% CI: 1.00, 1.19) were all associated with an increased risk of dementia (**Figure 3.5**). Conversely, elevated triglycerides were associated with a lower risk (HR, 0.86, 95% CI: 0.81, 1.91), while there was no association between elevated waist circumference and incident dementia. The findings were similar when assigning the use of lipid-modifying medications to the elevated triglycerides group instead of the reduced HDL cholesterol group (elevated triglycerides: HR, 0.80, 95% CI: 0.74, 0.86; reduced HDL cholesterol: HR, 1.16, 95% CI: 1.07, 1.25). Associations also remained similar when restricting to participants with >5-10 years and >10 years of follow-up (see **Appendix 3.8** for more details).

Figure 3.5: Cox proportional-hazards model investigating the association between individual MetS components and incident dementia

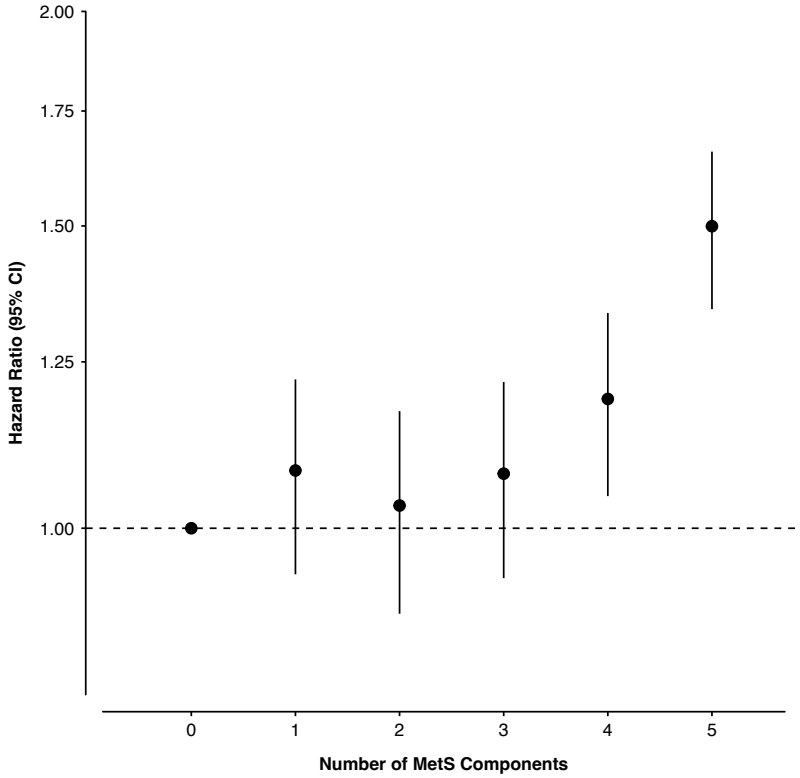


Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, Ref. = Reference group, WC = Waist Circumference, TG = Triglycerides, BP = Blood Pressure, HbA1c = Glycated Hemoglobin A1c, HDL = High-density Lipoprotein
All individual components entered into one model
Model adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity, APOE-ε4 carrier status

Number of MetS Components and Dementia Risk

Compared to participants with no MetS components, only the presence of four (HR, 1.19, 95% CI: 1.03, 1.38) or five (HR, 1.50, 95% CI: 1.28, 1.76) components was significantly associated with an increased risk of developing dementia (**Figure 3.6**). These associations remained similar when changing the reference category from zero MetS components only, to zero to two MetS components. Moreover, the findings generally remained similar regardless of the different combination of four MetS components present (see **Appendix 3.9**), as well as when restricting to >5-10 years and >10 years of follow-up (see **Appendix 3.10**).

Figure 3.6: Cox proportional-hazards model investigating the association between the number of MetS components present and incident dementia



Cases / Population:	237 / 11,765	1127 / 43,310	1312 / 47,664	1207 / 38,820	884 / 24,417	488 / 10,273
HR (95%CI):	1 (Ref.)	1.08 (0.94, 1.24)	1.03 (0.90, 1.18)	1.08 (0.93, 1.24)	1.19 (1.03, 1.38)	1.50 (1.28, 1.76)

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, Ref. = Reference group
Model adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity, APOE-ε4 carrier status

DISCUSSION

This Chapter presents findings from a population-based cohort study of more than 175,000 individuals aged ≥60 years, demonstrating that MetS was associated with a 12% increased risk of developing dementia over 15 years of follow-up. Associations also remained similar when restricting to dementia cases diagnosed after longer follow-up periods. Stronger associations were observed in those with four or five MetS components (regardless of what the components were) and in those with a low genetic risk for dementia based on *APOE*-ε4 carrier status.

At the time of conducting this study, only two comparable research studies found a significant positive association with incident all-cause dementia. A record linkage study in South Korea of 4M+ individuals aged ≥40 years reported a 12% increased risk of all-cause dementia over a mean follow-up of 4.9 years[206], while a Taiwanese study reported that worsened MetS (i.e., those who did not have MetS at the first time point, but developed it at the second time point over a 5-year period) was associated with a two-fold increased risk of all-cause dementia in those aged ≥65 years over approximately 10 years of follow-up.[204] In contrast, other studies have reported no association between MetS and risk of dementia and its subtypes.[203,205,207-211] These discrepant findings may be attributed to reverse causation bias resulting from short follow-up periods in the majority of studies (i.e., <5 years). This phenomenon has also been documented previously; for example, Floud et al. observed that low body mass index was associated with an increased dementia risk during the first decade of follow-up. However, this association considerably weakened and approached null after 15 years, indicating that these findings were substantially distorted by the effects of reverse causality.[264] In the current study, the long follow-

up duration (up to 15 years) makes the results less susceptible to reverse causation bias. Specifically, the finding that there was no association during the early years of follow-up suggest that reverse causation is unlikely to be a major issue. If reverse causation was a major source of bias, then it is likely that the observed associations would weaken over longer follow-up periods.

Results from this study also show a greater relative risk of dementia among *APOE*-ε4 non-carriers with MetS. These findings are consistent with a study that found MetS to be associated with greater cognitive decline in non-carriers.[265] A previous study found that ε4 non-carriers with dementia had reduced insulin sensitivity – as reflected by lower insulin-mediated glucose disposal rates – which may make these individuals more vulnerable to the adverse effects of hyperinsulinemia inherent in MetS.[266] Another possible interpretation provided for this finding is that the pathological mechanisms behind the development of dementia may have already been accumulated and exerted earlier on among *APOE*-ε4 carriers than non-carriers, contributing to the higher background risk evident among them. In contrast, among *APOE*-ε4 non-carriers, other physiological dysregulations (i.e., the vascular and metabolic damages inherent in MetS) may be necessary to initiate the cascade of events that result in cognitive deterioration which eventually progress to dementia.[267,268] Thus, genetic and other non-MetS related risk factors may be the primary drivers for dementia development among *APOE*-ε4 carriers, with MetS-related risk factors having a much greater influence among *APOE*-ε4 non-carriers at risk of dementia.

Some previous studies have shown a higher risk of mortality among *APOE*-ε4 carriers[269-272], and thus, it is possible that this 'competing risk' may contribute to the observed lack of an association between MetS and dementia among this group (due to carriers dying before the onset of dementia). However, in this study sample, *APOE*-ε4 carrier status was strongly associated with dementia risk, and from the perspective of the current analysis, the observation of a higher relative risk in ε4 non-carriers could be due to the greater absolute background risk of dementia among ε4 carriers (as shown in **Figure 3.4**). In turn, this could have led to the attenuated relative risk of dementia seen in ε4 carriers. This interpretation is further supported by the observation that the absolute risk differences between those with and without MetS were greater among *APOE*-ε4 carriers (1.4%) versus in non-carriers (0.9%). Nevertheless, a better understanding of this relationship is needed, with a particular need to include *APOE*-ε4 non-carriers in future research – a group that is often overlooked in preventative research trials aimed at dementia risk reduction.

In this study, elevated HbA1c, elevated blood pressure, and reduced HDL cholesterol were associated with an increased risk of dementia, which is consistent with previous research.[273-275] Moreover, the finding of a lack of an association between elevated waist circumference and dementia in participants aged ≥60 at baseline is consistent with previous work showing this MetS component was linked to a higher risk of late-onset dementia when measured at the age of 50 years, but not after 60.[23] Conversely, this study also showed an inverse association between elevated triglycerides and dementia, which also remained similar after assigning lipid-modifying medication use to this group. Previous studies have shown elevated triglycerides to be associated

with an increased dementia risk at mid-life but a reduced risk at late-life, indicating a differential impact of triglycerides across the lifespan.[21,276] In contrast, this study showed that there was an inverse association between elevated triglycerides and dementia which may be due to reverse causation, as previous evidence indicates that dementia may lead to changes in metabolism and diet which ultimately results in lower triglyceride levels among those affected.[277,278] However, supplementary analyses revealed that this result remained consistent across different follow-up durations, and thus, reverse causation is unlikely to have materially affected this association. Another explanation for this finding could be attributed to more aggressive treatment among individuals with elevated triglycerides, which could have ultimately reduced their dementia risk. Therefore, those presenting with elevated triglycerides (and deemed to be at high risk for dementia) may now have low levels due to aggressive treatment, leading to the misleading conclusion that low triglycerides are linked to a greater dementia risk. Nevertheless, the possibility that this relationship may reflect a true biological association cannot be ruled out, and further research exploring the underlying mechanisms is warranted.

Additionally, previous research shows an increased risk of dementia with an increasing number of MetS components, starting with a notably elevated risk evident among those with just one component.[229,279] In contrast, findings from this work show that risk is only significantly elevated among those with four or five MetS components. One of the assumptions often criticised is that each possible MetS grouping contributes equally and uniformly to the risk of developing dementia and other conditions.[280] However, the findings presented in this study suggests that there may be a subset of those with MetS – specifically, those with four or five

components – who could significantly benefit from early treatment and prevention strategies aimed at reducing their dementia risk.

To date, there is limited evidence on the potential impact of varying combinations of MetS components on dementia risk.[281] In the study presented in this Chapter, it was found that only some MetS combinations were associated with dementia risk. Notably, the combination of reduced HDL cholesterol, elevated blood pressure and elevated triglycerides was associated with a significantly reduced risk of dementia. Taken together, these results suggest that risk for dementia may vary substantially according to which MetS components are present, further highlighting the importance of investigating the contribution of different MetS combinations in future studies that particularly have large enough samples to examine such associations sufficiently and appropriately.

Strengths and Limitations

The current study has several notable strengths. These include leveraging a large study population with extensive phenotypic and genotypic data collection and a long follow-up period, which enabled a robust investigation of the association between MetS and risk for dementia.[231] The present study also has several limitations. First, this study used hospital inpatient admissions and death records to ascertain incident dementia cases, which likely underestimates the number of cases captured from other sources, such as primary care or memory clinics.[251,282] However, previous work has demonstrated high validity for the methods used to ascertain dementia in this study.[251,283] Second, this study did not investigate the association between MetS and dementia

subtypes (e.g., Alzheimer's or vascular dementia) since the available medical record data have low accuracy for identifying subtypes.[251] Third, HbA1c was used as a proxy for fasting glucose (due to low number of fasting samples), which differs from the 2009 Harmonized Criteria for MetS; however, the American Diabetes Association recommendations support using this measure as an appropriate proxy for glucose values.[234] Fourth, this study may be susceptible to confounding by indication, as using medications – which have been previously associated with reduced risk of dementia[284] – to define specific MetS components could underestimate the true association between MetS and dementia risk. Fourth, the UK Biobank cohort is known to be healthier than the general population and consists of low ethnic diversity (i.e., a predominantly White population)[232]; thus, further investigation of these associations in other cohorts or populations with different ethnicities is warranted. Finally, given the observational design of this study, residual confounding and other non-causal explanations remain.

Conclusion

The findings presented in this Chapter highlight that MetS was associated with an increased risk of developing dementia. Risk for dementia also varied according to follow-up length, number of MetS components present, and genetic risk for dementia (specifically *APOE*-ε4 carrier status). These findings provide strong evidence that MetS may be a risk factor for dementia. However, future research in other cohorts is necessary to confirm these associations.

Furthermore, what still remains unknown is whether the impact of MetS on risk for dementia varies based on its presence or absence across different life stages.[17,229] While there is

already existing evidence of age-specific associations between individual components of MetS and dementia risk, the role of age in the context of MetS (as a whole) and dementia is not clear.[17,229] While the study presented in this Chapter attempted to investigate such age-based trends, it was limited by the relatively narrow age range in the cohort. Understanding age-based associations across different life stages could provide insights regarding potentially critical periods where risk for dementia may be particularly elevated. Additionally, the present study in this Chapter only examined MetS at one time point. Thus, the impact of time or length of exposure to MetS on dementia risk remains limited; a better understanding of these relationships can help quantify the potential cumulative or chronic effects of MetS on dementia risk, and this information can further help identify which populations may benefit most from targeted treatments or interventions.[17,204,206,229]

Addressing these existing knowledge gaps are important next steps in understanding the role of MetS as a potential target for dementia prevention strategies. The next Chapter addresses some of these key questions, hoping to provide further clarification and insights regarding the relationship between MetS and risk of dementia.

CHAPTER 4

Association of Metabolic Syndrome and Risk Incident Dementia in EPIC-Norfolk: Understanding the Role of Age and Exposure Duration

CHAPTER SUMMARY

Findings from the previous Chapter suggest that MetS may be a risk factor for the development of dementia. However, the impact of mid-life versus late-life MetS and the duration living with MetS on dementia risk remains underexplored. Therefore, the objective of the study presented in this Chapter was to investigate whether the association between MetS and risk of dementia differs across mid-life versus late-life, and to explore how the duration of MetS influences this risk. Here, findings were presented from a prospective cohort study using data from EPIC-Norfolk. With its wide baseline age range, repeat assessments on the same participants and long follow-up to capture incident dementia, EPIC-Norfolk presented a unique opportunity to address previously unanswered questions.

In full cohort analyses, a total of 20,150 dementia-free adults aged 50-79 years who attended baseline assessments were included. Subsequently, to evaluate the association between duration/trajectory of MetS and risk for dementia, group-based trajectory analysis was performed on 12,756 participants who attended ≥2 health assessments over 20 years. Similar to Chapter 3, MetS was defined as the presence of three or more of the following five components (based on the 2009 Harmonized Criteria): elevated waist circumference, elevated triglycerides, elevated blood pressure, elevated HbA1c, or reduced HDL cholesterol. The main outcome was incident all-cause dementia, which was ascertained using hospital inpatient records, death certificates, and mental healthcare records.

The mean (SD) age of participants was 62.6 (7.5) years, and 54% were female. Over 25 years of follow-up (mean 18.8 [SD 6.3]), 2,653 participants developed dementia. In the full sample, MetS was associated with an increased risk of dementia (HR, 1.11, 95% CI: 1.01-1.21).

These associations remained similar in mid-life (age 50-59 years: HR, 1.12, 95% CI: 0.87-1.43; age 60-69 years: HR, 1.21, 95% CI: 1.05-1.39), but were attenuated in late-life (age 70-79 years: HR, 0.96, 95% CI: 0.81-1.14). A linear trend was observed between the number of MetS components and dementia risk in those aged 60-69 years (P trend=0.004), but not in other age groups. In trajectory analysis, a prolonged duration/trajectory of MetS (i.e., a group predominantly consisting of those who persistently had MetS across multiple time points) was associated with a 26% increased risk of developing dementia (HR, 1.26, 95% CI: 1.13-1.40) when compared to those with consistently low MetS. No association was found for increasing MetS (HR, 1.01, 95% CI: 0.88-1.17).

In conclusion, findings from this Chapter revealed that mid-life MetS was associated with an increased risk of developing dementia, but not in late-life. A prolonged duration of MetS was also associated with an elevated risk for dementia. These findings provide insights regarding critical periods of dementia risk in the context of MetS, and highlight the importance of considering age and duration of exposure to MetS when devising dementia prevention strategies.

Parts of the material presented in this Chapter have been accepted for publication in *The Lancet Healthy Longevity* (currently in-press) under the title "Role of age and exposure duration in the association between metabolic syndrome and risk of incident dementia: a prospective cohort study" (Qureshi et al., 2024): https://doi.org/10.1016/j.lanhl.2024.100652. This work was also presented at several scientific conferences (see section **"DPhil Publications, Recognitions and Awards"** for further details).

BACKGROUND

Findings from the previous Chapter provide important insights regarding the association between MetS and dementia, suggesting MetS as a risk factor for the development of incident dementia. These findings, in conjunction with the learnings gained from the systematic review (in Chapter 2), also further shed light on the remaining knowledge gaps in the understanding of these associations; particularly those which may be relevant to informing strategies aimed at preventing or delaying the onset of dementia in individuals living with MetS. Strategies to prevent or delay dementia by targeting modifiable risk factors, such as those in MetS, have become top priority, and this has been emphasised in recent dementia risk reduction guidelines issued by the WHO and in a previous report by the Lancet Commission.[17,18,285] MetS is of particular interest in this regard, as it has been shown that the condition can often be effectively managed through actionable lifestyle changes, making it a promising target for dementia prevention strategies.[286]

In order to effectively design preventative strategies, it is essential to understand who to target and when. This approach is particularly relevant for dementia, where risk factors might have different impacts across different stages of the life course.[17,18] As highlighted in Chapter 1, this includes components of MetS – such as obesity and high blood pressure – where exposure to these factors in mid-life is consistently associated with increased risk for dementia, while late-life exposure is typically associated with reduced risk. The latter observations are unlikely to be causal, and rather explained by reverse causation bias, whereby prodromal dementia results in weight loss and lower blood pressure.[17,77] Repeat assessments of exposures over time can provide key insights into these relationships, and clarify whether dementia risk differs based on both

timing of exposure, and exposure duration. Addressing these questions can also help understand whether there is a critical period in life where dementia risk is particularly elevated, which could open a potential window of opportunity to mitigate this risk. While recent research has identified MetS as a potential risk factor for dementia, an understanding of how age at exposure to MetS and duration living with MetS influence this risk remains limited.[70,229,287]

These key knowledge gaps are addressed in this Chapter using population-based data from the EPIC-Norfolk cohort study. Notably, the EPIC-Norfolk cohort includes a sample of participants with a wide baseline age range, repeat assessment data on participants, and long-follow up to capture incident dementia cases; these traits within the cohort present a unique opportunity to address previously underexplored questions in this research area.

Thus, the objectives of the study presented here in this Chapter were to first, investigate the association between the presence of MetS at different life stages and risk of incident dementia in 20,150 participants (full cohort analysis). Second, this study then explores the association between the duration/trajectory of living with MetS and subsequent risk for incident dementia in a subset of 12,756 participants with repeat assessments available (trajectory cohort analysis).

METHODS

Study Population

EPIC-Norfolk is a large population-based prospective cohort study of women and men aged 39-79 years recruited between 1993-1997.[288,289] A total of 25,639 participants underwent a baseline health assessment at recruitment (known as 'health checks' to participants) which included questionnaires on sociodemographic, lifestyle, environmental and health-related factors, including medical history and medication use, physical examinations and collection of biological samples. Between 1998-2000, a total of 15,786 participants attended a second health check. Following this, a third health check was conducted between 2004-2011 where a total of 8,623 participants attended. While additional health checks were performed after this date, comprehensive biological samples were only collected during the first three health checks. Further information regarding the EPIC-Norfolk cohort can be found at: https://www.epic-norfolk.org.uk/

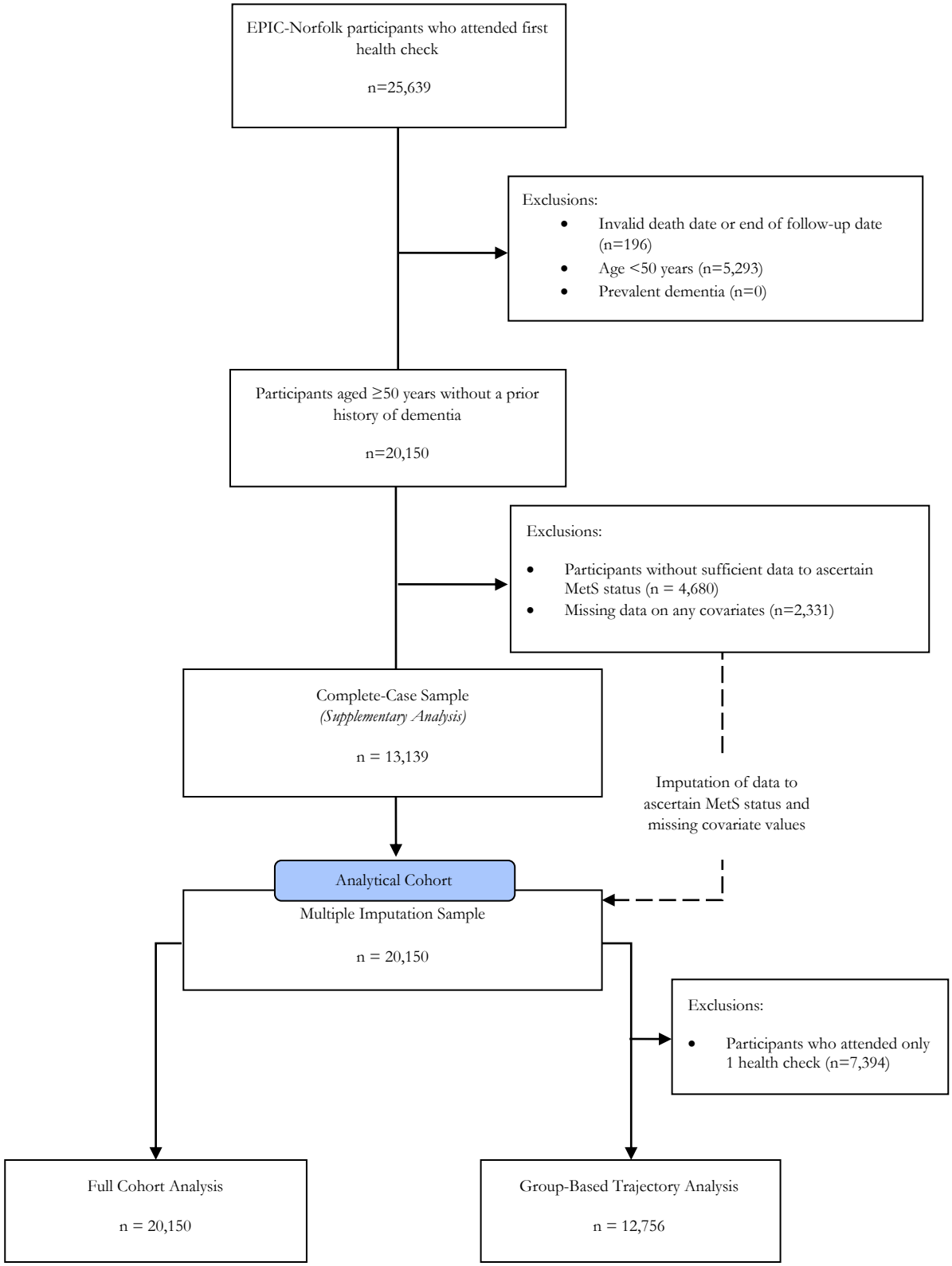
Approval to access EPIC-Norfolk data involved completing a data request form which required the submission of a research proposal outlining the objectives of the study and a detailed list of the variables being requested. Variable selection was informed by the online data dictionary available at https://www.epic-norfolk.org.uk/cgi-bin/dictionary, and by key collaborating members of the study team at Cambridge University (Dr Robert Luben and Dr Shabina Hayat).

Informed consent was obtained from all participants included in the study. The EPIC-Norfolk study was approved by the Norfolk Local Research Ethics Committee (05/Q0101/191) and East Norfolk and Waveney NHS Research Governance Committee (2005EC07L). EPIC-Norfolk has also received approval for follow-up through record linkage (REC Ref 98CN01).

For this study, the sample was restricted to participants aged ≥ 50 years at baseline (i.e., the first health check) to include those at risk of developing late-onset dementia over the 25-year follow-up period. Specifically, the following exclusions were applied to the initial EPIC-Norfolk sample (n = 25,639): (1) participants with an invalid death date or end of follow-up date (n = 196); (2) participants aged <50 years (n = 5,293); and participants with prevalent self-reported or diagnosed dementia (n = 0).

A total of 20,150 participants were included in the full cohort analysis. Subsequently, group-based trajectory analysis was performed using data from a subset of the total sample, consisting of 12,756 participants who attended ≥2 health assessments during the study period. Further details regarding the process of cohort creation are provided in **Figure 4.1**.

Figure 4.1: Cohort flow diagram



Abbreviations: EPIC = European Prospective Investigation into Cancer; MetS = Metabolic syndrome

Metabolic Syndrome

As per previously described methods (outlined in Chapter 3), MetS was defined using the 2009 Harmonized Criteria.[26] **Appendix 4.1** details information regarding the EPIC-Norfolk variables used to define each of the MetS components used in this analysis to derive binary MetS status (yes vs. no).

Dementia

Dementia cases were identified using Hospital Episode Statistics, death certificates, and mental healthcare datasets which captured information on participants in contact with mental health services and memory clinics.[290] All dementia diagnoses were recorded using the ICD-10 coding system. **Appendix 4.2** details ICD codes used to identify all-cause dementia.

Covariates

Similar to Chapter 3, covariates included sociodemographic, lifestyle, and health-related factors identified as potential confounders in the relationship between MetS and dementia risk.[17,226] The following measures were captured using self-reported data from baseline health and lifestyle questionnaires: age (in years) at baseline derived using the date of birth and the date of attending the baseline assessment, sex ('female', 'male'), education ('no qualifications', 'lower secondary' [i.e., CSE/O-Level/GCSE or equivalent], 'upper secondary [i.e., AS/A-Level or equivalent], and 'higher education or other equivalent professional qualification'), smoking status ('current', 'former', 'never') and alcohol intake frequency ('current', 'former', 'never'). Socioeconomic status (categorised in fifths, 1-5: least deprived to most deprived) was derived

using the Townsend deprivation index, which combines information on unemployment, overcrowding, non-car ownership and non-home ownership.[252,291] Physical activity ('inactive', 'moderately inactive', 'moderately active', 'active') was derived using a four-level physical activity index derived from the EPIC-validated short physical activity questionnaire which was designed to assess combined work and leisure activity.[292] More specifically, the physical activity categories were defined as: inactive (a sedentary job and no recreational activity); moderately inactive (a sedentary job with <0.5 hours recreational activity per day or a standing job with no recreational activity); moderately active (a sedentary job with 0.5 to 1 hours of recreational activity per day, or a standing job with <0.5 hours of recreational activity per day, or a physical job with no recreational activity); and active (a sedentary job with >1 hour of recreational activity per day, or a standing job with >0.5 hours of recreational activity per day, or a physical job with at least some recreational activity, or a heavy manual job).

APOE-ε4 carrier status ('ε4 non-carrier', 'ε4 carrier') was derived using rs429358 and rs7412 SNPs, which were directly genotyped. DNA for genotyping was extracted from blood (9 mL) collected in EDTA tubes at the second health check. For participants that did not provide blood samples at the second health check, DNA for genotyping was extracted from remnant buffy coats collected at baseline.[288,289] *APOE* genotype was assessed using Pyrosequencing, as described in previous methods elsewhere.[293]

Statistical Analysis

Descriptive statistics were used to compare baseline characteristics between participants with and without MetS. Cox proportional-hazards models with age as the underlying timescale were used to estimate the association between MetS and incident dementia among the following age groups: all ages (50-79 years; n = 20,150), early mid-life (50-59 years; n = 8,085), late mid-life (60-69 years; n = 7,940), and late-life (70-79 years; n = 4,125). Follow-up time was calculated as age at baseline until age at first incident dementia diagnosis, age at death, age lost to follow-up, or age at end of follow-up, whichever occurred first. End of follow-up was based on the availability of electronic health record data, which was censored on March 31st, 2019. The proportional-hazards assumption was visually examined using scaled Schoenfeld residuals, with no variables violating the assumption. Following similar methods outlined in Chapter 3, multiple imputation by chained equations was used to impute values for participants with insufficient data on the individual components used to ascertain MetS status or for those who had missing values for any of the covariates of interest. All analyses were adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake frequency, physical activity, and *APOE*-ε4 carrier status.

Secondary analyses included investigating the association between the number of MetS components (categorical: 0-5, reference group: 0) and dementia risk across different ages, as well as associations between the individual MetS components and dementia.

To investigate whether associations varied by follow-up length, stratified analyses were conducted by restricting to participants with follow-up periods of ≤ 10 year, 10 to <15 years, and 15+ years. The interaction between MetS and sex ('female', 'male') was also examined due to prior evidence of effect modification in association with dementia risk.[294,295] A supplementary analysis was also performed using a complete-case sample, an additional sensitivity analysis was conducted to account for death as a competing risk.

Group-based trajectory modelling was used to identify trajectories of MetS duration.[296] This approach is a specialised form of finite mixture modelling used to identify clusters of individuals following similar patterns or trajectories over time.[296-299] The group-based trajectory analysis was restricted to participants who attended ≥2 health checks (n = 12,756). The mean time of attendance was 3.7 years between the baseline and the second health check, 9.5 years between the second and third health check, and 13.0 years between baseline and the third health check. The best-fitting number of trajectories were estimated by assessing the Bayesian Information Criterion (BIC), where lower values generally indicate better model fit, and by ensuring high classification accuracy: as indicated by (1) average posterior probabilities of ≥ 0.7, (2) sufficient class sizes, and (3) ensuring the number of classes identified were both meaningful and clinically interpretable.[296-299] To facilitate interpretability, labels were assigned to trajectories based on a visual depiction of their graphical patterns over time.

The identified trajectories of MetS duration were then used in Cox proportional-hazards models to assess associations with incident dementia risk. To assess the robustness of findings,

a sensitivity analysis was conducted to examine associations of MetS duration trajectories with risk for dementia among participants who attended all 3 health checks. To investigate the impact of unequal time intervals between different health checks, group-based trajectory analyses were repeated using MetS trajectory models that accounted for non-discrete time differences.

All p-values were two-sided, with statistical significance set at $p<0.05$. All analyses were performed using RStudio v4.2.2. Trajectory modelling was conducted using R-package 'lcmm'.

RESULTS

Cohort Characteristics

The mean (SD) age of participants was 62.6 (7.5) years, 54% were female, and 99.7% were of White ethnicity. Among 20,150 participants identified in the study, 7,019 (34.8%) had MetS at baseline. Compared to participants without MetS, those with MetS were more likely to be older, male, have lower educational qualifications, reside in more socioeconomically deprived areas, former smokers and less physically active (**Table 4.1**).

Among those with MetS, the most common component was elevated blood pressure (88%), followed by elevated triglycerides (87%), elevated waist circumference (61%), elevated HbA1c (54%), and reduced HDL cholesterol (52%). Over 25 years of follow-up (mean [SD] = 18.8 [6.3]), 2,653 cases (13.2%) of incident all-cause dementia were identified (**Appendix 4.3**). Participants with missing data (i.e., insufficient data to ascertain MetS status) were highly similar to those with complete data (**Appendix 4.4**).

Table 4.1: Baseline characteristics by MetS status

Characteristic	No MetS (N= 13,131)[a]	MetS (N= 7,019)[a]	Overall (N = 20,150)[a]
Age	61.6 (7.5)	64.3 (7.2)	62.6 (7.5)
Sex			
Male	5,939 (45%)	3,354 (48%)	9,293 (46%)
Female	7,192 (55%)	3,665 (52%)	10,857 (54%)
Education level			
No qualifications	4,919 (37%)	3,324 (47%)	8,243 (41%)
Lower secondary	1,343 (10%)	582 (8.3%)	1,925 (9.6%)
Upper secondary	5,230 (40%)	2,520 (36%)	7,750 (38%)
Higher education or equivalent	1,639 (12%)	593 (8.4%)	2,232 (11%)
Socioeconomic status			
1 (least deprived)	2,845 (22%)	1,305 (19%)	4,150 (21%)
2	2,691 (20%)	1,323 (19%)	4,014 (20%)
3	2,579 (20%)	1,378 (20%)	3,957 (20%)
4	2,535 (19%)	1,480 (21%)	4,015 (20%)
5 (most deprived)	2,481 (19%)	1,533 (22%)	4,014 (20%)
Smoking status			
Current	1,381 (11%)	795 (11%)	2,176 (11%)
Former	5,568 (42%)	3,379 (48%)	8,947 (44%)
Never	6,182 (47%)	2,845 (41%)	9,027 (45%)
Physical activity level			
Inactive	3,892 (30%)	2,981 (42%)	6,873 (34%)
Moderately inactive	3,792 (29%)	1,900 (27%)	5,692 (28%)
Moderately active	3,014 (23%)	1,265 (18%)	4,279 (21%)
Active	2,433 (19%)	873 (12%)	3,306 (16%)
Alcohol intake frequency			
Current	11,393 (87%)	5,674 (81%)	17,067 (85%)
Former	1,121 (8.5%)	876 (12%)	1,997 (9.9%)
Never	617 (4.7%)	469 (6.7%)	1,086 (5.4%)
***APOE*-ε4 carrier**	3,670 (28%)	2,048 (29%)	5,718 (28%)
Dementia at follow-up	1,599 (12%)	1,054 (15%)	2,653 (13%)
MetS Components			
Elevated WC	1,378 (10%)	4,312 (61%)	5,690 (28%)
Elevated TG	3,682 (28%)	6,138 (87%)	9,820 (49%)
Elevated BP	7,929 (60%)	6,164 (88%)	14,093 (70%)
Elevated HbA1c	1,945 (15%)	3,805 (54%)	5,750 (29%)
Reduced HDL	1,084 (8.3%)	3,646 (52%)	4,730 (23%)

Abbreviations: MetS = Metabolic syndrome, APOE = Apolipoprotein E, WC = Waist circumference, TG = Triglycerides, BP = Blood pressure, HbA1c = Glycated Haemoglobin A1c, HDL = High-density lipoprotein.

[a]Mean (SD); n (%).

Impact of MetS on Dementia Risk: Full Cohort

In the full cohort (all ages: 50-79 years), MetS was associated with an increased risk of developing dementia (HR, 1.11, 95% CI: 1.01-1.21, **Figure 4.2**). Results remained similar when repeating the analysis in a complete-case sample (**Appendix 4.5**). Associations remained significant when restricting to those with ≥15 years of follow-up (HR, 1.16, 95%CI: 1.03-1.30), but were null during shorter follow-up (**Appendix 4.6**).

There was no statistical evidence of an interaction between MetS and sex with risk of dementia *(P* for interaction = 0.28, **Table 4.2**).

Table 4.2: Association between MetS and incident all-cause dementia according to sex

Sex	Cases/Population	HR (95%CI)
Female		
No MetS	955 / 7,192	Ref.
MetS	661 / 3,665	1.14 (1.01, 1.28)
Male		
No MetS	644 / 5,939	Ref.
MetS	393 / 3,354	1.06 (0.93, 1.21)

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, MetS = Metabolic syndrome, Ref. = Reference Group
Models adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake frequency, physical activity, APOE-ε4 carrier status.

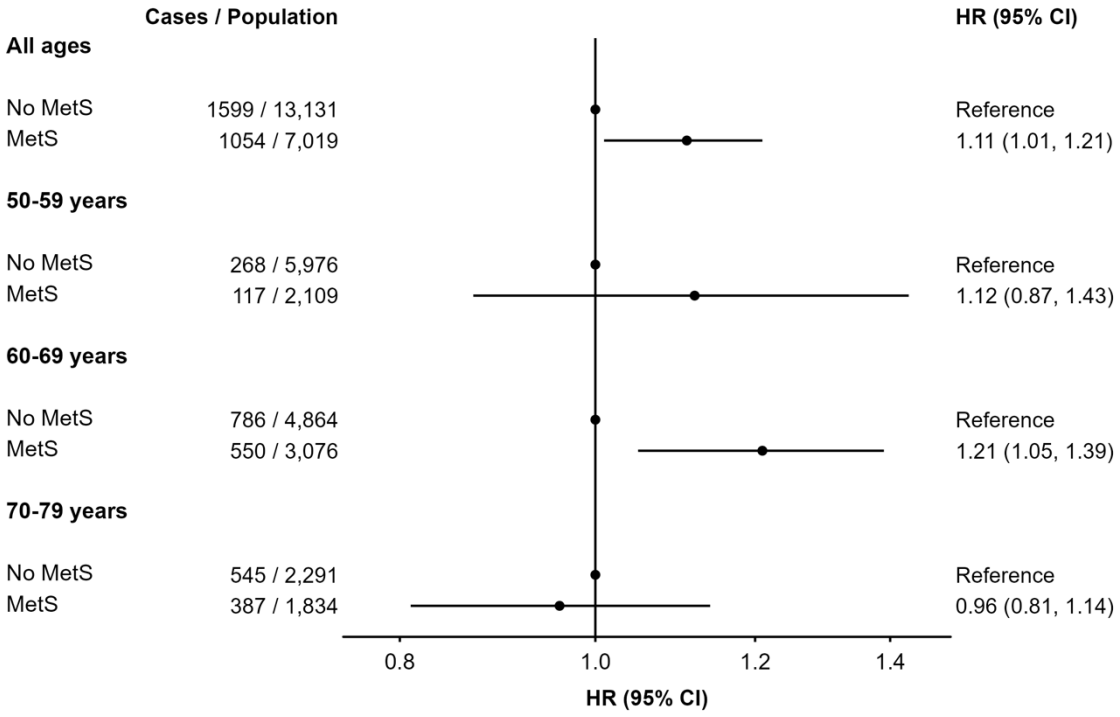
P-value for overall interaction between MetS and sex: 0.28

Impact of MetS on Dementia Risk: Age-Specific Analyses

In age-specific analyses, MetS in late mid-life (i.e., age 60-69 years) was significantly associated with a 21% increased risk of developing dementia (HR, 1.21, 95%CI: 1.05-1.39). A similar trend was observed for those with early mid-life MetS (i.e., age 50-59 years), although

this association did not reach statistical significance (HR, 1.12, 95% CI: 0.87-1.43). No association was observed for those with late-life MetS (i.e., age 70-79 years; HR, 0.96, 95% CI: 0.81-1.14). Results remained similar in sensitivity analyses accounting for death as a competing risk (**Appendix 4.7**).

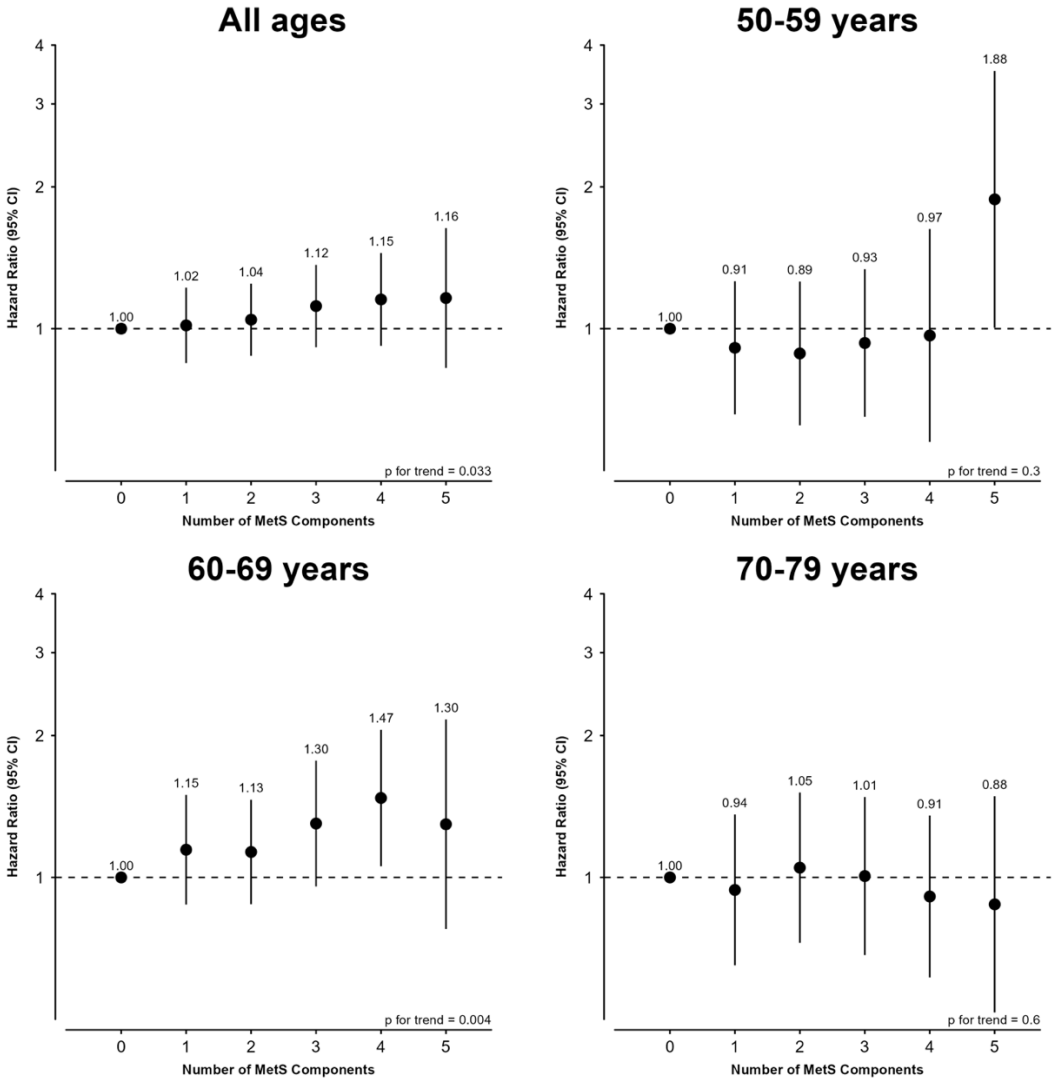
Figure 4.2: Association between MetS and incident all-cause dementia according to different ages



Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, MetS = Metabolic syndrome
Models adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake frequency, physical activity, APOE-ε4 carrier status.
All ages: Mean (SD) age: 62.6 (7.5) years; Mean (SD) follow-up: 18.8 (6.3) years.
50-59 years: Mean (SD) age: 54.8 (2.9) years; Mean (SD) follow-up: 21.7 (4.4) years.
60-69 years: Mean (SD) age: 64.9 (2.9) years; Mean (SD) follow-up: 18.6 (6.2) years.
70-79 years: Mean (SD) age: 73.1 (1.9) years; Mean (SD) follow-up: 13.7 (6.5) years.

An increasing number of MetS components was significantly associated with greater dementia risk in the full cohort (*P* for trend = 0.033, **Figure 4.3**). Similar trends were observed among those with MetS at late mid-life (*P* for trend = 0.004), but not in those with MetS at early mid-life (*P* for trend = 0.3) or late-life (*P* for trend = 0.6). Detailed results for Figure 4.3 are provided in **Appendix 4.8**.

Figure 4.3: Association between number of MetS components and incident all-cause dementia according to different ages

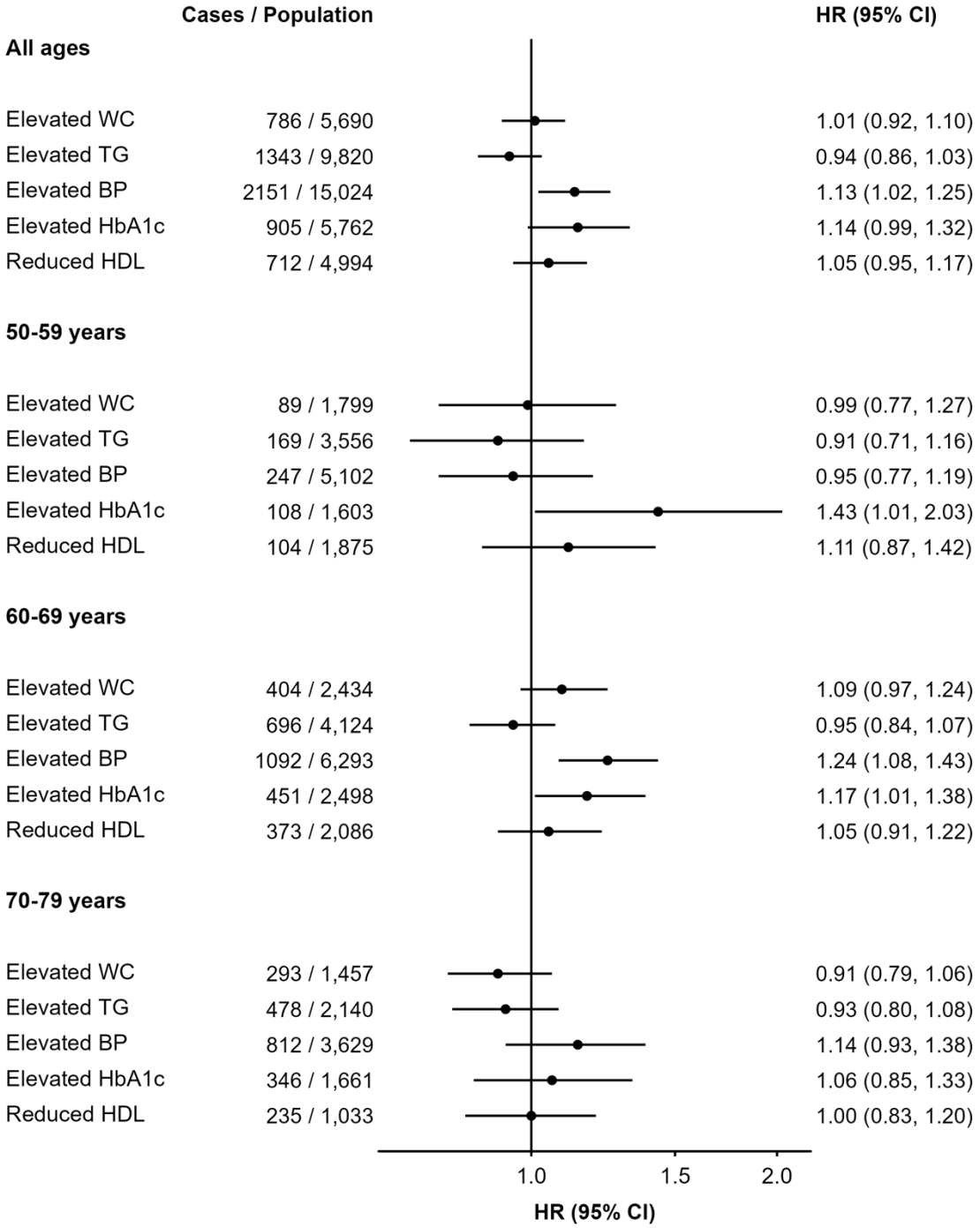


Abbreviations: MetS = Metabolic syndrome, CI = Confidence Interval

Models adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake frequency, physical activity, APOE-ε4 carrier status.

Examining individual components, only elevated blood pressure was significantly associated with an increased risk for dementia in the full cohort (HR, 1.13, 95% CI: 1.02-1.25, **Figure 4.4**). Among individuals with early mid-life MetS, only elevated HbA1c was significantly associated with increased dementia risk (HR, 1.43, 95% CI: 1.01-2.03). In those with late mid-life MetS, both elevated blood pressure (HR, 1.24, 95% CI: 1.08-1.43) and elevated HbA1c (HR, 1.17, 95% CI: 1.01-1.38) were significantly associated with heightened dementia risk. No significant associations for individual MetS components and risk of dementia were observed for those with late-life MetS.

Figure 4.4: Association between individual MetS Components and incident all-cause dementia according to different ages



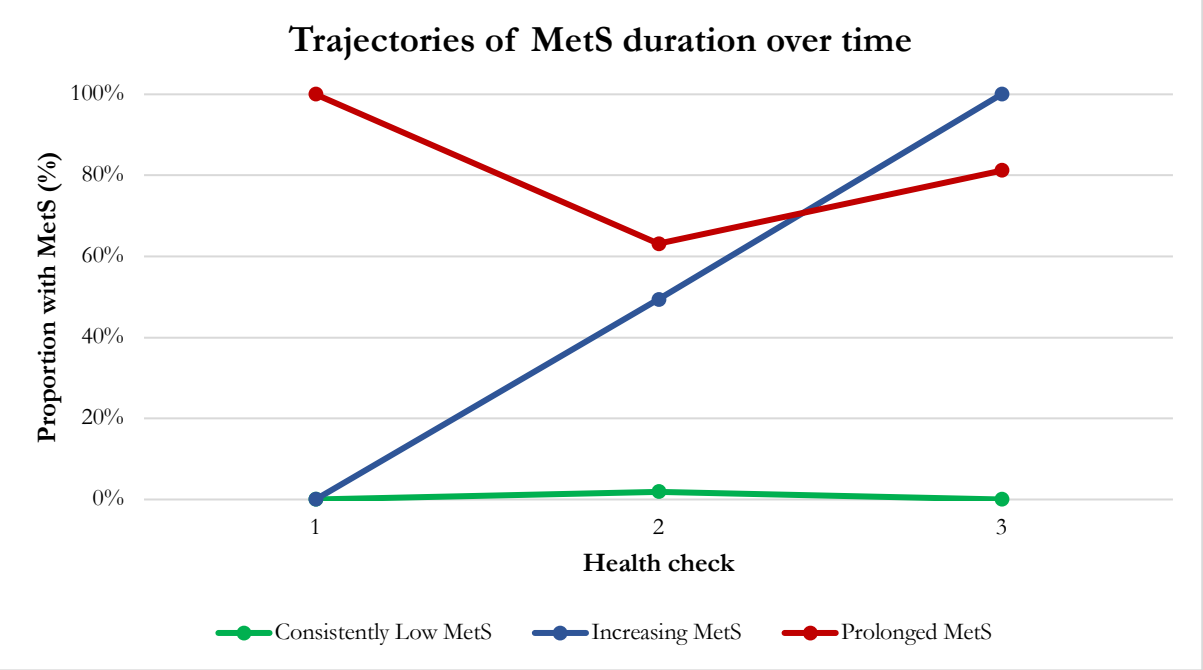
Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, , WC = Waist circumference, TG = Triglycerides, BP = Blood pressure, HbA1c = Glycated haemoglobin A1c, HDL = High-density Lipoprotein

All components entered into one model. Model adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake, physical activity, APOE-ε4 carrier status.

Impact of MetS Trajectories on Dementia Risk

Group-based trajectory modelling identified three distinct trajectories of MetS duration, which were labelled as: "consistently low", "increasing", and "prolonged" duration of MetS comprising of 41.6%, 22.2% and 36.2% participants, respectively. The "consistently low" group predominantly consisted of participants without MetS who maintained this status over time. The "increasing" group started with a low proportion of MetS cases, which progressively increased as these participants developed and often sustained MetS over time. The "prolonged" group mainly consisted of participants with persistent MetS over time. Model fit statistics and a visual depiction of identified trajectories are provided in **Appendix 4.9** and **Figure 4.5**, respectively. Both statistical fit and overall interpretability of trajectories were key considerations during model selection. Although a 4-class model had a slightly lower BIC value, a 3-class model was chosen due to its clearer and more clinically interpretable groupings.

Figure 4.5: Visual depiction of trajectories of MetS duration



Abbreviations: MetS = Metabolic syndrome
N = 12,756 (excluding those who attended only 1 health check out of 3)

Findings from trajectory modelling revealed that participants with a prolonged duration of MetS had a 26% increased risk of developing dementia (HR, 1.26, 95% CI: 1.13-1.40) when compared to those with consistently low MetS (**Table 4.3**). No association was observed for those following an increasing MetS trajectory (HR, 1.01, 95% CI: 0.88-1.17).

Table 4.3: Association between trajectories of MetS duration and incident all-cause dementia

	Cases / Population	HR (95% CI)	p-value
Trajectories of MetS Duration[a]			
Consistently Low MetS	662 / 5,311	Ref.	
Increasing MetS	274 / 2,831	1.01 (0.88, 1.17)	0.9
Prolonged MetS	674 / 4,614	1.26 (1.13, 1.40)	**<0.001**

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, MetS = Metabolic syndrome, Ref. = Reference Group
Model adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake frequency, physical activity, APOE-ε4 carrier status.
a: Using data from those who attended ≥2 health checks (N= 12,756)

Results remained similar in sensitivity analyses restricting the sample to participants who attended all three health checks (**Table 4.4**), and when accounting for non-discrete time intervals between health checks (**Appendix 4.10**).

Table 4.4: Association between trajectories of MetS duration and incident all-cause dementia among participants who attended all 3 health checks

	Cases / Population	HR (95% CI)	p-value
Trajectories of MetS duration (data: attended all 3 health checks, N = 4,914)			
Consistently Low MetS	160 / 1,912	Ref.	
Increasing MetS	134 / 1,668	0.98 (0.78, 1.24)	0.9
Prolonged MetS	135 / 1,334	1.24 (0.98, 1.57)	0.068

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, MetS = Metabolic syndrome, Ref. = Reference Group
Models adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake frequency, physical activity, APOE-ε4 carrier status

DISCUSSION

This Chapter presents insights from a population-based analysis of more than 20,000 individuals aged 50-79 years with over 25 years of follow-up. Several of the findings presented in this Chapter are consistent with those of the UK Biobank study (presented previously in Chapter 3); specifically, these include the findings indicating that MetS was associated with a significantly increased risk of developing dementia and that the strength of this association was consistent when restricting to longer follow-up periods. However, in the study presented in this Chapter, further additional analyses by age revealed similar associations among adults with MetS in mid-life, but not in late-life. Moreover, individuals with a prolonged duration of exposure to MetS (which was assessed over a period of 20 years) were more likely to develop dementia than those with consistently low MetS, while no association was observed for those with newly developed MetS (i.e., "increasing"). Taken together, these findings provide important insights regarding critical periods of dementia risk in those with MetS, and highlight the importance of not only considering the presence or absence of MetS, but also duration of exposure to MetS.

In this study, MetS was associated with an 11% increased risk of dementia, which is in line with UK Biobank findings from Chapter 3 and studies in the broader published literature from USA, Europe and Asia.[70,287] However, few studies have examined age-specific risk in this context. A recent study of 7,265 British civil servants found no significant relationship between MetS and incident dementia when measuring MetS status in the same participants at different ages of 40-59, 60-69, and 70-84 years.[229]; however, the findings from this work may have been hampered due to study traits such as a narrow baseline age range (40-59 years) and short follow-

up, particularly in the oldest age group (mean: 5.7 years). This short follow-up duration in the older age group (i.e., late-life) was due to the baseline age range being confined to mid-life; in other words, the analysis for late-life participants was based on a subsample of mid-life participants from baseline who reached these older ages in the subsequent assessments, thus, resulting in short follow-up among this group (and potentially resulting in selection bias). In contrast, the study presented here in this Chapter included a cohort of participants with a wide baseline age range spanning those at mid-life and late-life (50-79 years) and a long follow-up, even among the oldest age group (mean follow-up in oldest age group: 13.7 years). This design is a key strength of this work, as it allowed for a similar follow-up length across groups at different life stages (with any observed shorter follow-up durations in late-life participants likely being due to higher mortality in this group rather than resulting from a study design specific issue). Notably, in this Chapter, it was shown that having MetS in mid-life was associated with an elevated risk for developing dementia, but not in late-life. This finding is consistent with previous research indicating that specific dementia risk factors, including elevated blood pressure and obesity (both of which are components of MetS), are linked to increased dementia risk at mid-life but not late-life.[17] The stronger association observed in mid-life, as opposed to late-life, could be due to increased susceptibility of the brain to the adverse effects of MetS during this potentially critical age window, resulting from a combination of heightened metabolic insults and simultaneous onset of negative age-related brain changes during this period.[300] However, survival bias among the older age group remains a concern, as participants in this group may be representative of healthier individuals who are less susceptible to the adverse effects of MetS.[300] Moreover, although following a similar positive trend when compared to findings from the full

sample, the lack of a significant association in early mid-life (i.e., age 50-59 years) – which could possibly due to low statistical power in this group – may warrant further investigation in cohorts with larger samples and slightly longer follow-up during this period.

Analyses presented in this Chapter also revealed that a prolonged duration/trajectory of MetS was associated with a 26% increased risk of developing dementia, while no association was observed for those following an increasing MetS trajectory. These results highlight the importance of considering not only the presence or absence of MetS, but also the duration and trajectory of MetS when devising dementia prevention strategies. Previous studies have investigated the association between longitudinal MetS status and dementia, but using a multi-level categorical variable to represent various combinations of MetS presence or absence, and over short time periods.[204,206,211] One study measured MetS status twice over 2 years and found that both persistent and non-persistent MetS was associated with an increased risk for dementia.[206] However, another study measuring MetS status twice over 5 years found that only non-persistent MetS was associated with an increased risk for dementia.[204] Assessment of MetS duration/trajectories over many years is limited, hindering insights regarding longitudinal patterns of MetS and their impact across different life stages. In contrast, the study presented in this Chapter employed group-based trajectory modelling to assess the impact of duration of exposure to MetS over a 20-year period, providing a comprehensive understanding of the diverse patterns of MetS presence vs. absence and their implications for dementia risk.

Strengths and Limitations

Strengths of the study presented here in this Chapter include the use of a relatively large study population with a wide baseline age range which allowed examination of age-specific risks over a long follow-up period. Moreover, access to repeat assessments allowed examination of the impact of exposure duration rather than being limited to just one time point. The present study also has several limitations, some of which are similar to the previous study in Chapter 3. First, EPIC-Norfolk mainly consists of White participants, and thus, exploring the impact of age and duration of exposure to MetS in more diverse groups is warranted.[301] Second, participants were randomly recruited from general practices, making it likely that only individuals who were physically and cognitively capable attended baseline and follow-up assessments, potentially introducing healthy-volunteer bias.[289] Sample attrition across health checks has been previously noted in EPIC-Norfolk, with participants attending subsequent health assessments often being younger and healthier than those not attending, contributing to healthy-volunteer and survival bias.[289] The selective drop-out of individuals could have led to an underrepresentation of individuals with physical/cognitive impairments, particularly in the older age group (70-79 years); as a result, our findings in this group may underestimate the true magnitude of the association between MetS and dementia. Despite these trends, the cohort still represents a diverse population with a wide socioeconomic distribution, age distribution among women and men, and captures a range of lifestyle factors.[289] Moreover, results of our study remained consistent even after accounting for death as a competing risk. Third, the study in this Chapter did not investigate associations of MetS with different dementia subtypes (i.e., Alzheimer's or vascular dementia), since medical records data have low accuracy for identifying subtypes.[290,302] However,

validation studies show that these records are reliable for ascertaining all-cause dementia.[251,282] Fourth, HbA1c was used as a proxy measure for fasting glucose (due to the limited number of fasting samples available); while this differs from the Harmonized Criteria for MetS, the American Diabetes Association guidelines support use of HbA1c as an appropriate proxy measure for glucose values.[234] Finally, given the observational design of this study, residual confounding remains and causality cannot be inferred. Whilst observational studies should be cautious about inferring causality, this work does, however, address several aspects of causality as outlined in the Bradford-Hill criteria,[303] including i) Specificity: by demonstrating a distinct association between MetS and increased dementia risk, independent of other factors; ii) Temporality: by showing significant associations between baseline MetS and increased dementia risk over a 25-year follow-up, and demonstrating that these associations remained significant in analyses restricting to participants with long follow-up periods; and iii) Biological Gradient: as evidenced through a significant dose-response relationship observed between an increasing number of MetS components and elevated dementia risk.

Conclusion

In summary, findings from this Chapter show that MetS was associated with an increased risk of developing dementia, confirming previously observed trends from the study presented in Chapter 3. Additional insights (unique to this particular study) revealed that the presence of MetS in mid-life, but not late-life, was linked to a heighted dementia risk. Moreover, a prolonged duration of living with MetS was also associated with a substantially elevated risk for dementia. Taken together, these findings provide important insights regarding critical periods of dementia

risk in those with MetS, and highlight that age and duration of exposure to MetS may be key factors to consider when devising strategies to prevent or reduce the risk of dementia.

Chapter 3 introduced evidence from the UK Biobank cohort, revealing a significant association between MetS and an increased risk for developing dementia among more than 175,000 participants. In comparison, the findings in the current Chapter (using EPIC-Norfolk data) not only confirm the associations seen in the UK Biobank, but also build further on this by elucidating the impact of age and duration of exposure to MetS on dementia risk. Insights from these two studies are especially valuable given the limitations evident in previously published literature on this topic, where the conclusions that can be gathered were hampered by study traits such as small sample sizes, short follow-up periods, and inadequate adjustment of relevant confounders.

In contrast, the two large-scale population-based prospective cohort studies presented in this DPhil thesis (Chapter 3 and 4) provide robust and consistent evidence regarding the link between MetS and dementia risk, with key strengths including relatively large study samples, a long follow-up duration, and comprehensive confounder adjustments. These studies lay the foundation for the next Chapter, in which these thesis findings are integrated and synthesised in conjunction with the broader published literature on this topic, specifically through performing an updated systematic review and meta-analysis of prospective studies on the association of MetS and risk of incident dementia.

CHAPTER 5

Updated Systematic Review and Meta-Analysis of Prospective Studies on the Relationship Between Metabolic Syndrome and Incident Dementia

CHAPTER SUMMARY

The contents of this Chapter builds on the work presented in Chapters 2-4. The objectives of this Chapter were to update the previous systematic review (from Chapter 2) and subsequently perform a meta-analysis of relevant studies that were identified. Specifically, the updated review and meta-analysis incorporated results from the two prospective studies conducted in Chapters 3-4, as well as any additional literature published since the previous search (updated up to February 2024). The previous systematic review identified 10 eligible studies and the updated review presented here includes an additional 4 eligible studies. Subsequently, meta-analyses of relevant studies were conducted to examine the pooled associations between MetS and the risk of developing: incident all-cause dementia, incident Alzheimer's disease, and incident vascular dementia.

Random-effects models were used to estimate pooled Hazard Ratios (pHR) and 95% CIs. Risk of bias was assessed using the EPHPP Quality Assessment Tool for Quantitative Studies.[212]

For the updated systematic review, a total of 14 studies met the eligibility criteria (out of N=4,719 studies, among which 954 were screened as part of the update) which included 4,345,741 participants who were initially free of dementia. A total of 10 studies were eligible for the meta-analysis involving MetS and the outcome of all-cause dementia, while 5 studies were eligible for the meta-analysis of Alzheimer's disease and vascular dementia (respectively). Pooled estimates indicated that, compared to participants with no MetS, those with MetS had a significantly greater risk of developing incident all-cause dementia (27,708 cases; pHR, 1.12, 95% CI: 1.08-1.15, I^2 = 12.0%). However, no significant association was observed between MetS and

risk of incident Alzheimer's disease (14,890 cases; pHR, 0.91, 95% CI: 0.72-1.15, I^2 = 41.0%) or vascular dementia (2,642 cases; pHR, 1.40, 95% CI: 0.96-2.06, I^2 = 59.0%), although the direction of association was positive for the latter outcome. Moreover, the direction and strength of these associations remained relatively similar in several subgroup analyses. Meta-regression analyses of the relationship between MetS and incident all-cause dementia was also performed, which revealed that associations potentially differed based on: the age of participants included among identified studies, and the criteria used to ascertain MetS.

In conclusion, findings from this updated systematic review and meta-analysis suggest that MetS is a significant independent risk factor for the development of all-cause dementia. However, further large-scale studies with long follow-up are needed to fully understand the influence of MetS on dementia risk, and particularly its impact on specific dementia subtypes.

BACKGROUND

Chapter 2 of this thesis presented findings from a systematic review on the relationship between MetS and the risk of developing dementia (including key subtypes). The review revealed that the understanding of the relationship between MetS and dementia remains largely inconclusive. This knowledge gap then prompted a further investigation of these associations, for which two separate large-scale population-based cohort studies on this topic were conducted and presented as a part of this thesis (in Chapters 3-4).

The aim of this specific Chapter was to update the previous systematic review in order to integrate the new insights generated from thesis Chapters 3-4, and identify any additional studies published in the literature since the last search. Furthermore, using these updated results, meta-analyses were conducted to examine the pooled associations of MetS with incident all-cause dementia, incident Alzheimer's disease, and incident vascular dementia. Insights into these associations using the latest available data can aid in the understanding of the link between MetS and dementia, and investigating the impact on different subtypes can help clarify whether the relationship may be driven primarily by neurodegenerative factors, vascular contributions, or other mechanisms.

METHODS

Updated Systematic Review

An updated search of the literature was performed to identify additional articles published after the initial search date (February 9, 2022). The updated search was conducted on February 19, 2024, using the same methods described previously (refer to Chapter 2 for further details regarding the systematic review methodology).

Meta-Analysis

Given the heterogeneity between the identified studies, the data was pooled using random effects meta-analysis models.[304] Outcomes that were captured include: 1) incident all-cause dementia; 2) incident Alzheimer's disease; and 3) incident vascular dementia. Statistical heterogeneity was assessed using Cochran's Chi-squared test (Chi^2; $p<0.05$ indicated significant heterogeneity) and the I-squared statistic (I^2; a value of <25%, 25% to 75% and >75% were classified as low, moderate and high heterogeneity, respectively).[305] The original data were reported as HR and 95% CIs, while one study reported results as odds ratios (ORs) and 95% CIs. Where studies reported multiple models assessing the associations of interest, only the fully-adjusted model was included in the meta-analysis. For consistency and appropriate comparison, meta-analyses were performed using only studies reporting HR and 95% CI values, and only studies that adopted similar definitions to define the main exposure (i.e., binary MetS variable). Those adopting other exposure definitions (e.g., categorical MetS status measured over multiple time points) that were not comparable to other studies were therefore excluded. Studies that could not be included in the meta-analyses due to important differences in the exposure, outcome or statistical methods were synthesised narratively.

Subgroup Analyses

Several subgroup analyses were performed to examine the association of MetS and dementia by: 1) the age at recruitment; 2) the MetS criteria adopted; 3) ethnicity; and 4) risk of bias ratings.

Meta-Regression Analysis

Univariate meta-regression models were used to investigate the effects of potential moderators in the relationship between MetS and dementia risk. Meta-regression models were fit by regressing pooled HRs of dementia risk on the following factors: (1) publication year; (2) mean/median follow-up duration (in years); (3) mean/median age at baseline (in years); (4) use of MetS criteria: NCEP-ATP III (yes vs. no); (5) proportion of female participants (%); (6) adjustment for *APOE*-ε4 carrier status (yes vs. no); and (7) ethnicity of the study cohort (predominantly White vs. predominantly non-White).

Recommendations state that at least ten or more effect estimates are required to appropriately conduct a meta-regression analysis.[306] Due to the number of eligible studies available, the meta-regression analysis was only performed for the outcome of all-cause dementia. Moreover, an adjusted p-value was calculated based on the permutation test. Briefly, performing a permutation test in meta-regression analyses serves as a method to control for multiple testing and provides a more robust assessment to evaluate significance.[307-309] This non-parametric method is particularly useful when traditional p-value calculations may not completely capture the intricacies of the data under study, particularly in instances where data might be limited by a small sample of studies (as is the case in this work) where there is potential for overfitting. By randomly rearranging the data and recalculating the test statistic multiple

times, the permutation test generates a distribution of the test statistic under the null hypothesis, enabling a more accurate estimation regarding the significance of the findings. This also helps reduce the potential for Type-I error.[307-309] The permutation test also makes less statistical assumptions regarding the distribution of the data under study, and while it may be require more computational resources, it generally leads to more accurate estimations than conducting traditional statistical tests, potentially helping to avoid spurious findings.[307-309]

Publication Bias

Publication bias is important to assess given that the results of any meta-analysis may be biased due to the probability of a study being published based on the presence of a significant finding (also known as the "winner's curse" or "file-drawer effect").[310] Therefore, publication bias was assessed using funnel plots and Egger's statistic where appropriate (i.e., recommendation: at least ten studies are required for obtaining an accurate Egger's statistic results).[311,312] It should be noted that performing these tests when the number of studies included in the meta-analysis is small (i.e., n <10) could result in low power to detect a real publication bias.[311,312] Therefore, Egger's test was only conducted for the outcome of incident all-cause dementia, which had a sufficient number of studies as per previous recommendations and guidelines.

All meta-analyses presented in this Chapter were conducted in RStudio v4.2.2, using the "metagen" function available in the "meta" package.[313]

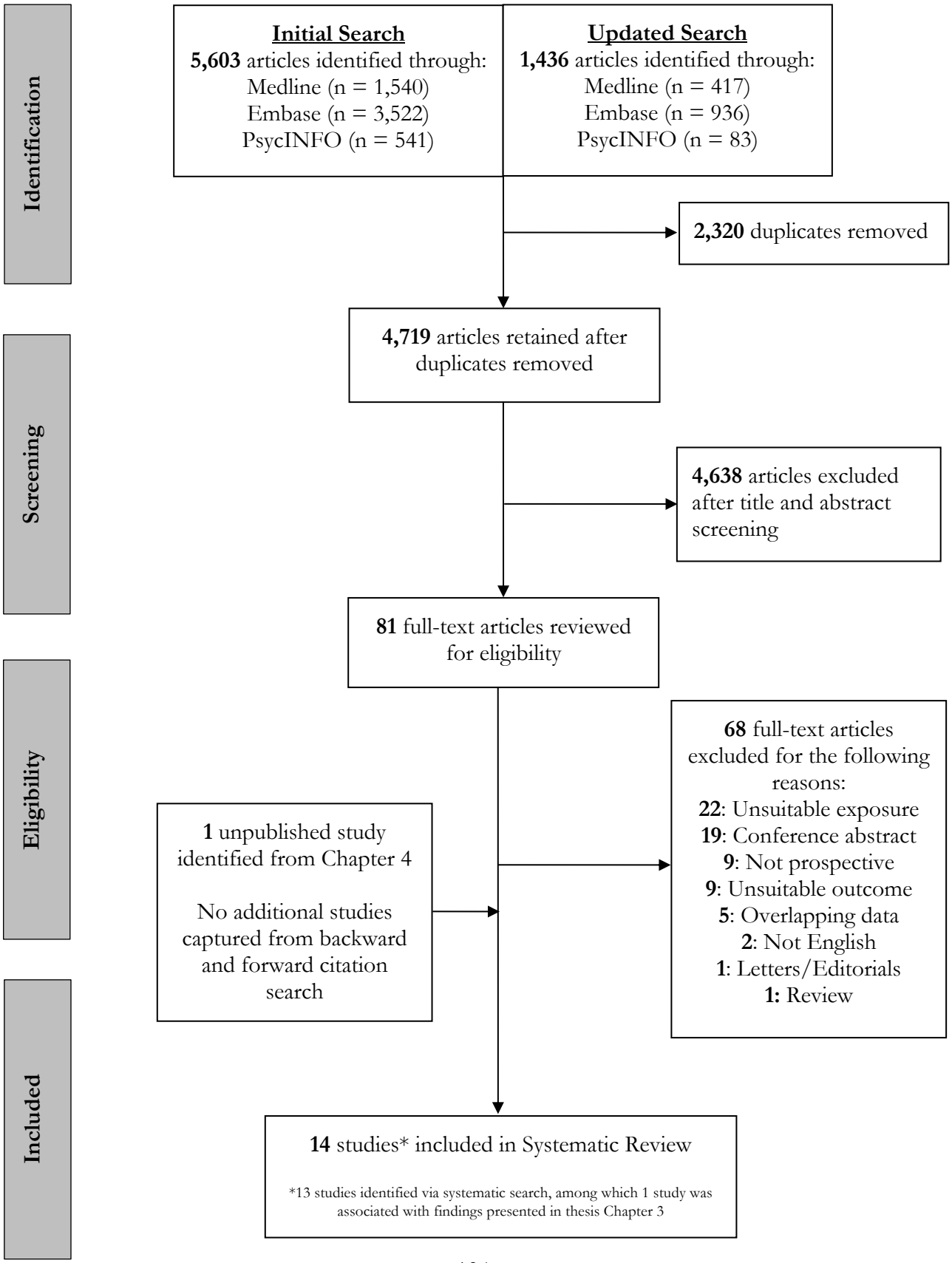
RESULTS

Updated Systematic Review

In Chapter 2, a total of 3,765 articles were screened after conducting the initial systematic search. The updated search presented in this Chapter yielded an additional 954 articles for screening, among which a total of 16 full-text articles were reviewed independently by two reviewers (DQ and EK). After full-text review, 13 articles were excluded. This resulted in a total of three newly identified eligible studies for the updated systematic review[229,287,314] including UK Biobank findings[287] presented in Chapter 3 of this thesis. The study findings from the EPIC-Norfolk study (from Chapter 4; currently unpublished) were also included in this update as this work met all of the eligibility criteria of the review. Therefore, a total of 4 newly identified studies were additionally included as part of the update, while 10 separate studies were previously identified from the initial search outlined in Chapter 2. This resulted in a total of 14 eligible studies for the updated systematic review presented here, which included 4,345,741 participants who were initially free of dementia. No additional studies were identified via backward and forward citation searches. See **Figure 5.1** below for further details regarding the flow chart for study selection and exclusion for this updated systematic review.

Corresponding authors of two studies[229,314] were contacted, among which both responded to provide clarification or additional data.

Figure 5.1: Flow chart of study selection and exclusion after updated search



The characteristics of the newly identified studies are provided in **Table 5.1** and **Table 5.2**. Three studies were conducted using data from the United Kingdom[229,287,315], and one was conducted using data from participants in Australia and the United States.[314] All newly identified studies used data from population-based research cohorts. Three of the studies adopted the 2009 Harmonized Criteria to ascertain MetS[229,287,315], while one study used the 2018 American College of Cardiology/American Heart Association (ACC/AHA) Task Force Guideline for MetS.[314] The prevalence of MetS ranged between 31.7%[229] to 41.7%[287] (one study did not report this information[314]). Only all-cause dementia was included as an outcome in all newly identified studies, which was ascertained using medical records in three studies[229,287,315], and through adjudication using the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) in one study.[314] Analytic sample sizes varied among the newly identified studies, ranging from a sample of 6,660 participants[229] to 176,249 participants.[287] Notably, the newly identified studies had considerably larger samples than the previously identified studies from the initial systematic search (presented in Chapter 2).

Among the newly identified studies, the mean baseline age was ~65 years in three studies[229,287,315], and ~75 years in one study.[314] The proportion of females included across these studies was around >50% for three studies[287,314,315], while one study included only 29.3% female participants.[229] Some variation was noted in the follow-up length, with one study reporting a median of 4.7 years follow-up (mean not reported)[314], while the three other studies had considerably longer follow-up lengths ranging between a mean of 10.9 to 18.8 years.[229,287,315] All models adjusted for age, sex/gender, education, smoking status, and alcohol intake. However, of note, only two studies (specifically those identified from this thesis, in Chapters 3-4) included adjustment for *APOE*-ε4 carrier status.[287,315]

Table 5.2 describes the main results of these newly identified studies in the context of the relationship between MetS and the risk of developing incident all-cause dementia. Two studies found that MetS was associated with a significantly increased risk of incident all-cause dementia.[287,315] The other two studies reported no significant association[229,314], although the association was in a similar direction (i.e., positive association) in one of these studies.[229]

Table 5.1: Characteristics of the additional four studies identified in the updated systematic review

Study author, publication year	Region (data source)	Race/Ethnicity	Study design	Setting	Analytic sample size	% Female	Mean baseline age in years (SD)	Mean follow-up length in years (SD)	Exposure: MetS criteria	Outcomes Reported	Outcome Assessment
Machado-Fragua et al., 2022[229]	UK (Whitehall II)	Age <60: White: 90.1% Non-white: 9.9% Age 60-69: White:91.6% Non-white: 8.4% Age ≥70: White: 90.3% Non-white: 9.7%	Research Cohort	Community	Age <60: N = 7,265 Age 60-69: N = 6,660 Age ≥70: N = 3,608	Age <60: 30.5% Age 60-69: 29.3% Age ≥70: 29.4%	Age <60: 55.1 (2.9) Age 60-69: 65.0 (1.5) Age ≥70: 73.9 (1.9)	Age <60: 19.6 (5.9) Age 60-69: 10.9 (5.8) Age ≥70: 5.7 (3.2)	Harmonized Criteria	All-cause dementia	Medical records, ICD-10: F00-F03, F05.1, G30, G31
Qureshi et al., 2023[287]	UK (UK Biobank)	White: 96.8% Non-white: 2.7% Missing: 0.5%	Research Cohort	Community	N = 176,249	52.2%	64.1 (2.9)	11.8 (2.2)	Harmonized Criteria	All-cause dementia	Medical records, ICD-9: 331.0, 290.4, 331.1, 290.2, 290.3, 291.2, 294.1, 331.2, 331.5; ICD-10: F00, F00.0, F00.1, F00.2, F00.9, G30, G30.0, G30.1, G30.8, G30.9, F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, I67.3, F02.0, G31.0, A81.0, F02, F02.1, F02.2, F02.3, F02.4, F02.8, F03, F05.1, F10.6, G31.1, G31.8
Qureshi et al., 2024[315]	UK (EPIC-Norfolk)	White: 99.7% Non-white: 0.3%	Research Cohort	Community	N = 20,150	54.0%	62.6 (7.5)	18.8 (6.3)	Harmonized Criteria	All-cause dementia	Medical records, ICD-10: F00, G30, F00.0, G30.0, F00.1, G30.1, F00.2, G30.8, F00.9, G30.9, F01, F01.0, F01.1, F01.2, F01.8, F01.9, F02, F02.0, F02.1, F02.2, F02.3, F02.8, G31.0, G31.8, F03, F05.1, F10.7
Ekram et al., 2023[314]	Australia & USA (ASPREE trial)	White: 91.2%$# Non-white: 8.8%$#	Research Cohort	Community	N = 16,965	56.3%$#	75.1 (4.5)$#	4.7 (3.6-5.7)§§ &	ACC/AHA 2018 Guideline	All-cause dementia	Adjudicated based on DSM-IV

MetS: Metabolic syndrome, NCEP-ATP III: National Cholesterol Education Program - Adult Treatment Panel III, AHA/NHLBI: American Heart Association and the National Heart, Lung, and Blood Institute, IDF: International Diabetes Foundation, DSM: Diagnostic and Statistical Manual of Mental Disorders, NR: Not reported, ICD-9: International Classification of Diseases, Ninth Revision, ICD-10: International Classification of Diseases, Tenth Revision CDR: Clinical Dementia Rating, SD: Standard deviation, EPIC: European Prospective Investigation into Cancer, ASPREE: ASPirin in Reducing Events in the Elderly, ACC/AHA: American College of Cardiology/American Heart Association Task Force Guideline

§§: Median (Interquartile Range), $#: Among primary sample of 18,264 participants, &: Additional information provided by the authors

Table 5.2: Newly identified studies reporting outcome of all-cause dementia

Study author, publication year	Number and % of MetS cases	Number and % of incident all-cause dementia	Effect estimate (95% CI)	Confounder adjustments
Machado-Fragua et al., 2022[229]	Age <60: 1,302 (17.9%) Age 60-69: 2,111 (31.7%) Age ≥70: 1,787 (49.5%)	Age <60: 393 (5.4%) Age 60-69: 417 (6.3%) Age ≥70: 264 (7.3%)	Age <60: HR: 1.23 (0.96 - 1.57) p = 0.098& Age 60-69: HR: 1.14 (0.91 - 1.42) p = 0.247& Age ≥70: HR: 1.10 (0.86 - 1.40) p = 0.495&	Age, sex, education, ethnicity, birth cohort, smoking, alcohol intake, fruit and vegetable intake, physical activity
Qureshi et al., 2023[287]	73,510 (41.7%)	5,255 (3.0%)	HR: 1.12 (1.06 - 1.18) p < 0.0001&	Age, sex, ethnicity, education, Townsend deprivation index score, household income, smoking, alcohol intake, physical activity, APOE-ε4 carrier status.
Qureshi et al., 2024[315]	7,019 (34.8%)	2,653 (13.2%)	HR: 1.11 (1.01-1.21) p < 0.0001&	Age, sex, Townsend deprivation index, education, smoking status, alcohol intake frequency, physical activity, and APOE-ε4 carrier status
Ekram et al., 2023[314]	NR	524 (3.1%)	SHR: 0.96 (0.74 - 1.26)$$ p = NR	Age, gender, ethnicity, education, smoking, alcohol intake, chronic kidney disease, depression, previous cancer history

MetS: Metabolic syndrome, HR: Hazard Ratio, CI: Confidence Interval, APOE: Apolipoprotein E, NR: Not Reported, SHR: Sub-distribution Hazard Ratio

&: Additional information provided by the authors, $$: based on a subset of non-frail participants in a sample of 16,965 participants

Risk of Bias

The methodology regarding risk of bias assessment has been previously described in Chapter 2. Among the 14 studies that were identified in this updated systematic review, a total of three studies were rated as 'strong' quality[205,210,315], nine as 'moderate'[203,207-209,211,213,229,287,314] and 'two' as weak[204,206] (**Table 5.3**). Studies that were deemed to have a moderate rating were subject to selection bias (n=7)[207-209,213,229,287,314], lack of sufficient confounder adjustment (n=1)[203] or were subject to potential attrition (n=1).[211] Studies that were deemed to have a weak rating did not describe the validity and reliability of data collection methods (n=2) or exhibited a lack of sufficient confounder adjustment (n=2).[204,206]

Table 5.3: Quality assessment (risk of bias) ratings for all studies included in the updated systematic review

Study Author, Publication Year	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawals and Drop-outs	Global Rating
Creavin et al., 2012[211]	STRONG	MODERATE	STRONG	MODERATE	STRONG	WEAK	MODERATE
Ekram et al., 2023[314]	WEAK	MODERATE	STRONG	STRONG	STRONG	STRONG	MODERATE
Exalto et al., 2015[203]	MODERATE	MODERATE	WEAK	MODERATE	STRONG	STRONG	MODERATE
Fan et al., 2017[204]	MODERATE	MODERATE	WEAK	MODERATE	WEAK	STRONG	WEAK
Forti et al., 2010[205]	MODERATE	MODERATE	STRONG	MODERATE	STRONG	MODERATE	STRONG
Lee et al., 2020[206]	MODERATE	MODERATE	WEAK	MODERATE	WEAK	MODERATE	WEAK
Machado-Fragua et al., 2022[229]	WEAK	MODERATE	STRONG	MODERATE	STRONG	STRONG	MODERATE
Muller et al., 2007[207]	WEAK	MODERATE	STRONG	MODERATE	STRONG	STRONG	MODERATE
Ng et al., 2016[208]	WEAK	MODERATE	STRONG	MODERATE	STRONG	STRONG	MODERATE
Peng et al., 2018[213]	WEAK	MODERATE	STRONG	MODERATE	STRONG	STRONG	MODERATE
Qureshi et al., 2023 (UK Biobank)[287]	WEAK	MODERATE	STRONG	MODERATE	STRONG	STRONG	MODERATE
Qureshi et al., 2024 (EPIC-Norfolk)[315]	STRONG	MODERATE	STRONG	MODERATE	STRONG	STRONG	STRONG
Raffaitin et al., 2009[209]	WEAK	MODERATE	MODERATE	MODERATE	STRONG	STRONG	MODERATE
Solfrizzi et al., 2010[210]	STRONG	MODERATE	STRONG	MODERATE	STRONG	MODERATE	STRONG

Meta-Analysis

Of the 14 studies identified in the updated systematic review, a total of 13 studies investigated the association between MetS and the risk of developing incident all-cause dementia.[203-211,229,287,314,315] Five studies investigated the association of MetS with the risk of incident Alzheimer's disease and vascular dementia, respectively.[205-207,209,210] One of these 13 studies reported two separate effect estimates corresponding to completely different and non-overlapping populations that were analysed separately (i.e., individuals aged <75 and those aged ≥75) – this justified the inclusion of both of these estimates in the meta-analysis.[205] Moreover, three of the 13 studies were excluded from the meta-analyses as the exposure definition or reported effect estimates were not directly comparable with other studies.[204,211,314]

MetS and All-Cause Dementia

The meta-analysis of the association between MetS and incident all-cause dementia consisted of eleven effect estimates from ten studies[203,205-210,229,287,315] (**Figure 5.2 – A**). The analysis indicated a significantly greater risk of incident all-cause dementia in those with MetS compared to those without MetS (4,307,830 participants, 27,708 cases; pHR, 1.12, 95% CI: 1.08-1.15, I^2 = 12.0%).

The association between MetS and incident all-cause dementia remained consistent in subgroup analyses (see **Appendices 5.1-5.6**) restricted to: (1) studies reporting results for those aged 65+ years (pHR, 1.08, 95% CI: 1.00-1.16, I^2 = 15.0%); (2) studies that ascertained MetS using the 2009 Harmonized Criteria (pHR, 1.12, 95% CI: 1.11-1.14, I^2 = 0.0%); (3) studies consisting of predominantly White populations (pHR, 1.11, 95% CI: 1.06-1.16, I^2 = 0.0%); and (4) studies rated as 'strong' or 'moderate' (i.e., excluding studies with a 'weak' global rating) based on risk of bias assessments (pHR, 1.09, 95% CI: 1.02-1.17, I^2 = 17.0%). In contrast, no

significant pooled association was evident in subgroup analyses restricted to studies using the NCEP-ATP III criteria to ascertain MetS (pHR, 0.91, 95% CI: 0.70-1.18, I^2 = 32.0%), and studies consisting of predominantly non-White populations (pHR, 1.03, 95% CI: 0.80-1.33, I^2 = 57.0%).

MetS and Alzheimer's Disease

Five cohort studies investigated the association between MetS and incident Alzheimer's disease.[205-207,209,210] The meta-analysis, which consisted of six effect estimates from five studies (**Figure 5.2 – B**), revealed no significant association between MetS and risk of incident Alzheimer's disease (4,109,436 participants, 14,890 cases; pHR, 0.91, 95% CI: 0.72-1.15, I^2 = 41.0%).

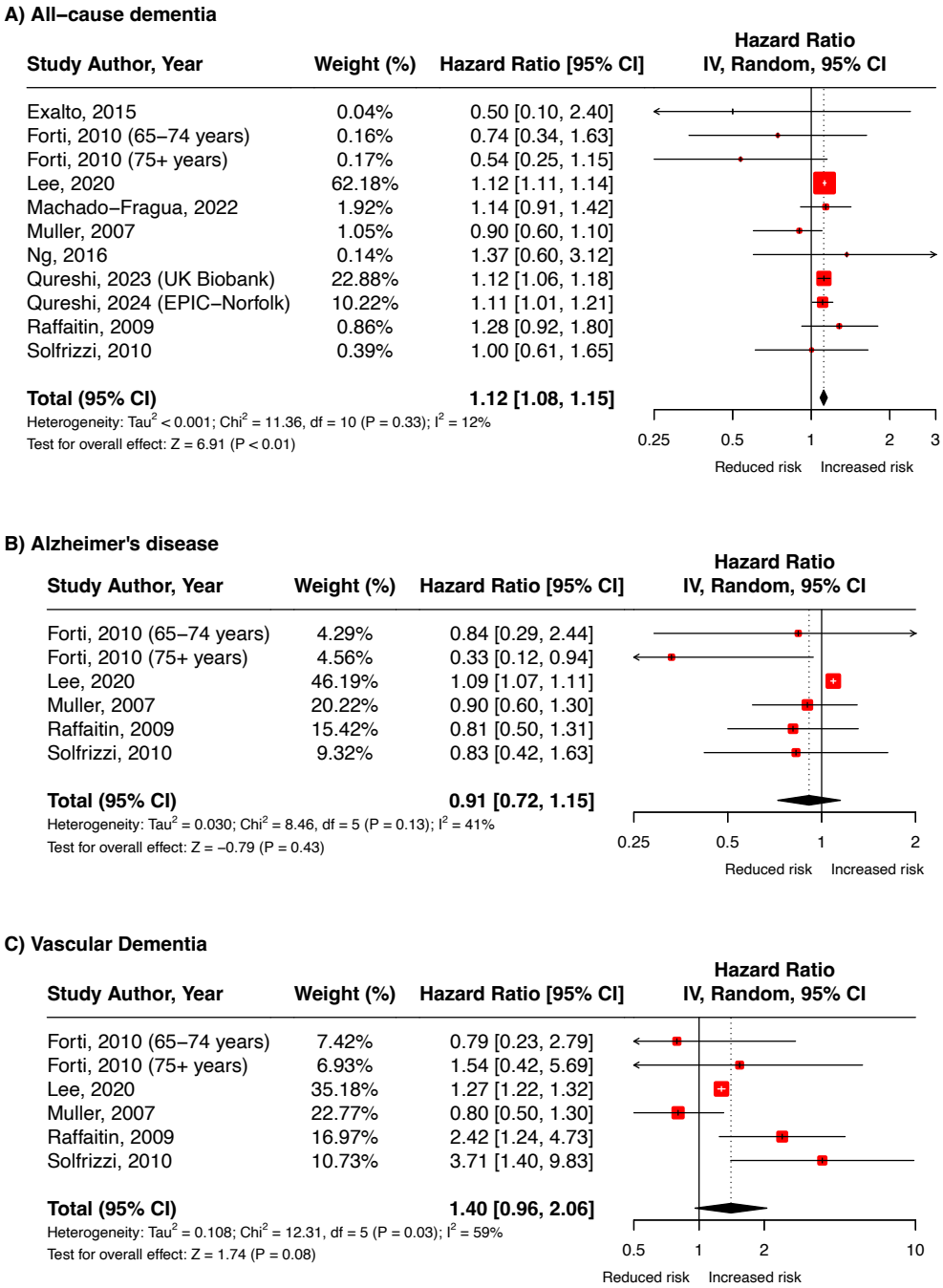
These results remained similar in subgroup analyses (see **Appendices 5.1-5.6**) restricted to: (1) studies reporting results for those aged 65+ years (pHR, 0.85, 95% CI: 0.65-1.11, I^2 = 0.0%), (2) studies that ascertained MetS using the NCEP-ATP III criteria (pHR, 0.80, 95% CI: 0.62-1.04, I^2 = 0.0%); (3) studies consisting of predominantly White populations (pHR, 0.74, 95% CI: 0.52-1.05, I^2 = 0.0%); and (4) studies rated as 'strong' or 'moderate' (i.e., excluding studies with a 'weak' global rating) based on risk of bias assessments (pHR, 0.80, 95% CI: 0.62-1.04, I^2 = 0.0%). While subgroup analyses restricted to studies consisting of predominantly non-White populations showed no significant association of MetS and incident Alzheimer's disease, the direction of the association differed from the other results presented in this context (pHR, 1.08, 95% CI: 0.97-1.19, I^2 = 0.0%); however, only two studies were included in this particular subgroup analysis, thereby limiting the conclusions that can be drawn from this specific analysis.

MetS and Vascular Dementia

Five cohort studies investigated the association between MetS and incident vascular dementia.[205-207,209,210] The meta-analysis, which consisted of six effect estimates from these five studies (**Figure 5.2 – C**), indicated no statistically significant association between MetS and risk of incident vascular dementia (4,109,436 participants, 2,642 cases; pHR, 1.40, 95% CI: 0.96-2.06, I^2 = 59.0%). Despite a lack of statistical significance, the pooled estimate suggests an increased risk of vascular dementia associated with MetS. The high heterogeneity indicates substantial variability among studies included within this specific meta-analysis, potentially contributing to the non-significant findings observed here.

These results remained similar in subgroup analyses (see **Appendices 5.1-5.6**) restricted to: (1) studies reporting results for those aged 65+ years (pHR, 1.55, 95% CI: 0.71-3.39, I^2 = 75.0%); (2) studies that ascertained MetS using the NCEP-ATP III criteria (pHR, 1.54, 95% CI: 0.79-3.00, I^2 = 67.0%); and (3) studies rated as 'strong' or 'moderate' (i.e., excluding studies with a 'weak' global rating) based on risk of bias assessments (pHR, 1.54, 95% CI: 0.79-3.00, I^2 = 67.0%). While the direction of the association remained similar when restricting to studies consisting of predominantly non-White populations, the strength of the association was considerably weaker (pHR, 1.08, 95% CI: 0.71-1.65, I^2 = 71.0%, $P_{Heterogeneity}$ = 0.06) when compared with studies consisting of predominantly White populations (pHR, 2.08, 95% CI: 1.18-3.67, I^2 = 25.0%, $P_{Heterogeneity}$ = 0.26). Greater heterogeneity was also observed across studies consisting of predominantly non-White populations as compared to those consisting of predominantly White populations.

Figure 5.2: Meta-analysis of the hazard ratios of the association between MetS and risk of developing incident A) All-cause dementia; B) Alzheimer's disease; C) Vascular dementia



Abbreviations: CI = Confidence Interval; df = Degrees of Freedom

Meta-Regression Findings

Table 5.4 displays results from univariate meta-regression analyses investigating potential effect modification in the association between MetS and the risk of incident all-cause dementia based on various study-level characteristics.[203,205-210,229,287,315] The meta-regression analyses showed little evidence of effect modification based on the year of publication (adjusted p = 0.249), mean/median follow-up duration (adjusted p = 0.646), proportion of female participants among studies (adjusted p = 0.116), adjustment for *APOE*-ε4 carrier status (adjusted p = 0.225), and ethnicity (predominantly White vs. predominantly non-White; adjusted p = 0.570). However, there was some evidence for effect modification based on mean/median baseline age of participants included in the identified studies (adjusted p = 0.043), and studies using the NCEP-ATP III criteria to ascertain MetS (adjusted p = 0.019). Specifically, a negative association was observed for both age (Est: -0.003) and the use of the NCEP-ATP III criteria (Est: -0.145) in relation to the outcome of all-cause dementia. However, it is worth noting that few studies (N = 11) were included in the meta-regression analysis, and thus, these results should be interpreted with caution. Moreover, since only one study received a 'weak' quality assessment rating[206], meta-regression was not performed for the characteristic of "study quality/risk of bias assessment". However, a sensitivity analysis excluding this weak study revealed similar findings to the main meta-regression results.

Table 5.4: Univariable meta-regression models to assess the influence of various study-level factors among articles investigating the association between MetS and risk of incident all-cause dementia (eligible results N = 11)

Study characteristic	Estimate	95% CI	Q (m)	p value	Adjusted p*
Publication year	0.004	-0.007 - 0.014	0.425	0.514	0.249
Mean/median follow-up (in years)	-0.001	-0.006 - 0.004	0.117	0.732	0.646
Mean/median age at baseline (in years)	-0.003	-0.008 - 0.002	1.036	0.309	0.043
Used NCEP-ATP III MetS criteria (yes vs. no)	-0.145	-0.336 - 0.046	2.212	0.137	0.019
% female sex	-0.002	-0.007 - 0.003	0.644	0.422	0.116
Adjusted for APOE-e4 carrier status (yes vs. no)	-0.017	-0.064 - 0.030	0.500	0.480	0.225
Ethnicity (predominantly White vs. not)	-0.011	-0.057 - 0.036	0.197	0.657	0.570

Abbreviations: NCEP-ATP III = National Cholesterol Education Program – Adult Treatment Panel III; Q (m) = Q for moderators; MetS = Metabolic Syndrome; APOE = Apolipoprotein E

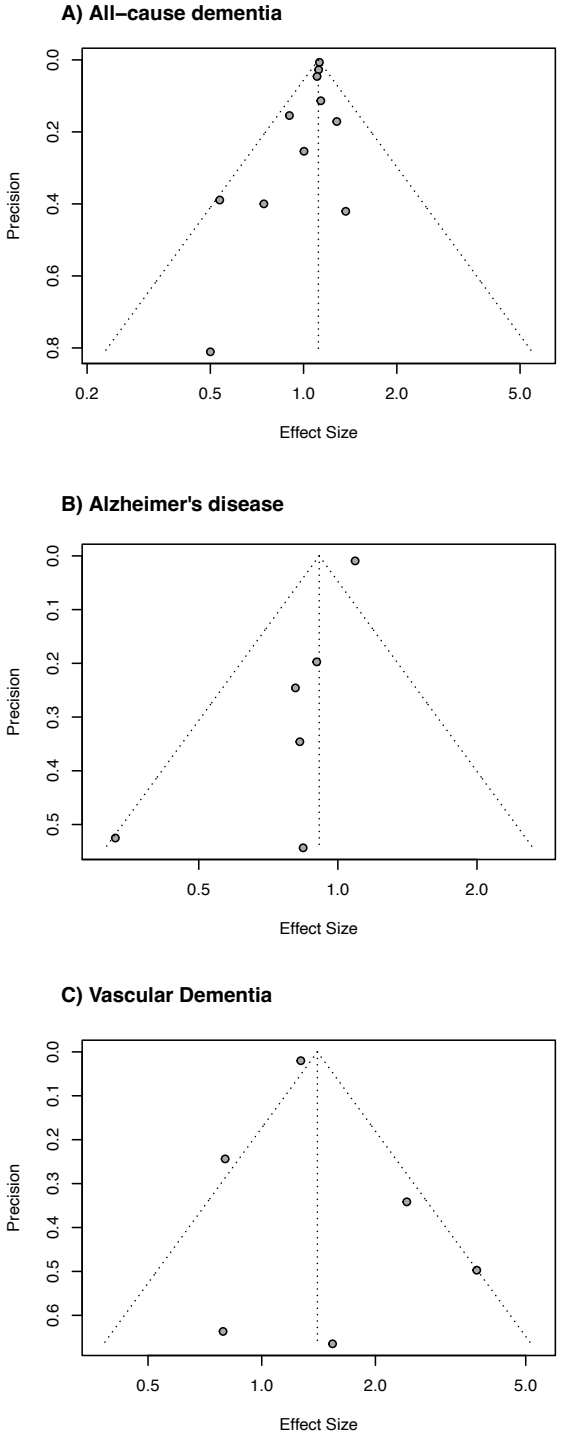
*Using permutation test

Publication Bias

Figure 5.3 presents the funnel plots for studies investigating the association of MetS with the three dementia outcomes of interest: A) incident all-cause dementia; B) incident Alzheimer's disease; and C) incident vascular dementia. Upon visual inspection of these funnel plots, it was evident that the plots for the outcomes of all-cause dementia and vascular dementia appear to be relatively symmetrical, indicating a low likelihood of publication bias among studies investigating MetS in relation to these two outcomes. In contrast, it was noted that the funnel plot for the outcome of Alzheimer's disease appeared to show asymmetry, potentially suggesting the presence of publication bias among results investigating the association of MetS with this outcome. However, given the limited number of studies included in these analyses, results should be interpreted with caution.

The Egger's tests for publication bias was also conducted, specifically for studies investigating the association between MetS and incident all-cause dementia (see **Appendix 5.7**). The results suggested a low likelihood of publication bias for this outcome, as indicated by a non-significant p-value ($p = 0.078$). Due to the limited number of studies (i.e., $n < 10$), Egger's test was not calculated for the outcomes of incident Alzheimer's disease and incident vascular dementia.

Figure 5.3: Funnel plot of studies investigating the association of MetS and risk of incident A) All-cause dementia; B) Alzheimer's disease; and C) Vascular dementia



Precision = Standard Error; Effect Sizes = Hazard Ratios

DISCUSSION

Results from this updated systematic review and meta-analysis revealed that MetS was associated with a significantly increased risk of developing incident all-cause dementia. However, no significant association was observed for incident Alzheimer's disease. Moreover, the pooled estimate for the association between MetS and vascular dementia was also non-significant, but notably, the association followed a similar direction when compared to the results for all-cause dementia and was considerably stronger in magnitude (all-cause dementia pHR: 1.12 vs. vascular dementia pHR: 1.40). Overall, these findings confirm the importance of MetS as a potential risk factor for incident all-cause dementia, however, its impact on specific subtypes of dementia still remains unclear. Given that the majority of studies assessing dementia subtypes in this context were published more than a decade ago with few number of dementia cases (as compared to all-cause dementia), further investigation of these relationships is warranted.

Few comparable meta-analyses have been conducted on this topic, as noted earlier in this thesis. A systematic review and meta-analysis conducted by Atti et al., in 2019 investigated the association of MetS with incident all-cause dementia, Alzheimer's disease, and vascular dementia.[70] The authors included only six studies in their meta-analysis of MetS and incident all-cause dementia, and found no statistically significant association (pHR, 1.12, 95% CI: 0.94-1.33, I^2 = 28.0%)[70]; however, the observed effect was remarkably consistent with, and followed the same direction as, the findings presented in Chapter 3 (UK Biobank, HR: 1.12), Chapter 4 (EPIC-Norfolk, HR: 1.11), and now here in Chapter 5 (pooled meta-analysis, HR: 1.12). Furthermore, the authors included only four studies in their meta-analysis of the association between MetS with incident Alzheimer's disease and vascular dementia, finding no significant association with Alzheimer's disease (pHR, 0.84, 95% CI: 0.66-1.08, I^2 = 0.0%). However, MetS

was associated with a statistically significant increased risk of developing vascular dementia (pHR, 1.37, 95% CI: 1.01-1.86, I^2 = 62.0%).[70] Moreover, a 2021 meta-analysis conducted by Zuin et al., investigated the association of MetS with incident Alzheimer's disease, and similarly found no significant association among four prospective studies (pHR, 0.80, 95% CI: 0.61-1.06, I^2 = 8.03%).[71] While informative, it is difficult to draw conclusions from these previous meta-analyses for several reasons: 1) they included studies with overlapping data; 2) they included a smaller number of studies overall; 3) they excluded eligible effect estimates from identified studies (e.g., study conducted by Ng et al.,[208] presented relevant findings in supplementary analyses that were not captured in previous authors' meta-analyses); and 4) they included studies with MetS exposure variables that were not directly comparable to other studies – for instance, Fan et al.,[204] examined binary MetS status which was categorised across multiple time points, which was not directly comparable to effect estimates of other studies that examined binary MetS status at only one time point. In contrast, the meta-analysis presented in this Chapter includes a much larger sample size (and greater number of dementia cases), incorporating data from more than 4 million participants to investigate the pooled associations of MetS with outcomes of incident all-cause dementia, Alzheimer's disease, and vascular dementia. The results here illustrate that MetS was associated with a significantly increased risk of developing incident all-cause dementia. Notably, the precision of this pooled estimate for all-cause dementia was also considerably higher (as observed from the narrower CI values) than those presented in previous reviews which showed non-significant results. The pooled association of MetS on Alzheimer's disease and vascular dementia were similar to previous findings (in terms strength and direction), but it is important to note that data used in these analyses mostly came from studies published more than a decade ago, and captured few number of dementia cases (compared to analyses of all-cause dementia). Overall, the study findings presented in this updated systematic review and

meta-analysis provide better clarity regarding the association of MetS and the risk of developing dementia. Specifically, the work presented in this Chapter incorporates more recently conducted studies that are more robust, with large sample sizes and long follow-up lengths, which helps to more accurately measure the association between MetS and dementia risk.

Subgroup meta-analyses presented in this Chapter also provide valuable insights regarding potential factors that may be driving some of the differences observed in the relationship between MetS and the risk of developing dementia. The relationship of MetS and all-cause dementia remained consistent in several subgroup analyses restricting to participants aged 65+ years, using different MetS criteria, restricting to studies with predominantly White populations, and after excluding studies with weak quality assessment ratings. However, no significant association was observed for any of the dementia outcomes when restricting to studies consisting of predominantly non-White populations (but it is important to note that only a small number of studies were included in these specific analyses; three for the outcome of all-cause dementia, and two for Alzheimer's disease and vascular dementia, respectively). In subgroup analyses restricted to studies of predominantly White populations, similar trends were observed when compared to findings from the main analysis; however, the association between MetS and incident vascular dementia was notably stronger for the analysis of predominantly White populations (as compared to non-White populations), possibly indicating ethnic differences in these relationships, but this requires further investigation in larger studies with diverse samples. Moreover, significant associations were observed when examining studies that used the 2009 Harmonized Criteria to define MetS, but not for those that used the NCEP-ATP III criteria; this finding suggests that some of the variation evident across studies may be influenced by differences in the MetS criteria adopted across studies (perhaps due to differences

in cut-offs for high blood glucose, or inclusion vs. exclusion of ethnic-specific cut-offs for waist circumference). Further clarity on these relationships is necessary through the use of more uniform standards for defining MetS in the context of studies assessing dementia risk.

Findings from this Chapter suggest that there may be distinct associations between MetS and different dementia subtypes. Although neither association reached statistical significance, the pooled HR for incident Alzheimer's disease was 0.91 (95% CI: 0.72-1.15), suggesting a potential negative or null association, while the pooled HR for vascular dementia was 1.40 (95% CI: 0.96-2.06), suggesting a potential positive association. These differences may be due to chance, or they may reflect the distinct pathophysiological mechanisms at play in the association between MetS and the risk of developing these different dementia subtypes. Alzheimer's disease is known to be characterised by neurodegenerative changes within the brain, including amyloid depositions and neurofibrillary tangles, which are associated with cellular dysfunction and neuronal death.[316,317] While there is some evidence to suggest that the mechanisms involved in MetS – such as insulin resistance, hyperinsulinemia, or inflammation – may contribute to Alzheimer's disease pathology, there is stronger mechanistic evidence linking MetS to the development of vascular dementia, particularly due to the number of vascular-related components used to define a diagnosis of MetS.[316,317] More specifically, the pathogenesis of vascular dementia is primarily driven by vascular risk factors (such as those inherent in MetS) which lead to cerebrovascular disease and reduced blood flow to the brain that, in turn, leads to neurological injury and disruption of cognitive networks, eventually leading to the development of vascular dementia.[318,319] Unfortunately, poor accuracy for capturing different dementia subtypes in the UK Biobank and EPIC-Norfolk data[251,282,290] limited the ability to conduct such kinds of analyses of subtypes within the studies presented in thesis Chapters 3-4. While other

studies did investigate these associations, there was considerable heterogeneity in the effect sizes and lack of statistical significance noted in the findings. Therefore, further large-scale studies with diverse samples, long follow-up, and accurate outcome classification are needed to fully understand the impact of MetS on these different dementia subtypes.

This study also presented results from a meta-regression analysis, specifically for the association between MetS and incident all-cause dementia. Notably, the meta-regression revealed evidence that age of the study sample had a significant influence on the observed associations with the risk for developing incident all-cause dementia. Specifically, a negative association was observed, indicating that as age increases, the strength of the association between MetS and all-cause dementia slightly decreases. This suggests that a stronger link between MetS and risk for dementia was observed in studies of younger cohorts, and this partially supports the age-specific relationships presented and discussed previously in Chapter 4 of this thesis. Moreover, the meta-regression also showed that the use of the NCEP-ATP III criteria was associated with a slightly weaker reported association between MetS and all-cause dementia. This result implies that the choice of MetS criteria may influence the MetS-dementia relationship. Taken together, findings from these meta-regression models underscore the importance of considering age-specific differences as well as the importance of standardising methods to ascertain MetS when designing studies and interpreting data in context of the relationship between MetS and dementia risk. However, given the small number of studies, the findings here should be interpreted with caution, and the insights that can be drawn would benefit from further investigation through additional work.

Strengths and Limitations

To date, this is the largest and most comprehensive systematic review and meta-analysis of prospective studies investigating the relationship between MetS and incident dementia. Strengths and limitations of the systematic review have been previously discussed in detail within Chapter 2 of this thesis. Additional strengths related to the meta-analysis include: 1) inclusion of recent studies with much larger samples and longer follow-up lengths, allowing for capture of more robust estimates than those presented in previous meta-analyses; 2) inclusion of studies with relatively similar definitions of MetS that allowed for appropriate pooling of results; and 3) performance of several subgroup analyses and meta-regression analyses to help understand potential sources of heterogeneity across studies. However, the meta-analyses presented in this Chapter also have several limitations. First, despite inclusion of recent evidence on this topic, the overall number of studies included were still relatively small, which limit the interpretation and generalisability of the findings; this was especially the case when conducting subgroup analyses for the dementia subtypes of Alzheimer's disease and vascular dementia. Second, meta-regression analyses and Egger's test could not be conducted for the dementia subtypes of incident Alzheimer's disease and vascular dementia, again due to the limited the number of studies examining these outcomes. Third, there was some variability in the exposure and outcome definitions which may have contributed to the heterogeneity that could not be investigated further due to the limited number of studies included. Lastly, the reported estimates across studies may not reflect the true magnitude of the association between MetS and dementia due to the potential for reverse causation, selection bias, or potential exposure/outcome misclassification (some of these issues are discussed later in Chapter 7).[320]

Conclusion

In conclusion, this systematic review and meta-analysis summarises the most up-to-date evidence regarding the association between MetS and risk of developing dementia, including key dementia subtypes. The current analysis suggests that MetS is an independent risk factor for incident all-cause dementia. In regard to the dementia subtypes, current evidence points towards a potentially strong link between MetS and vascular dementia but not Alzheimer's disease, and these differences align well with the possible mechanisms that might explain their pathogenesis; however, further large-scale studies with long follow-up (and in diverse populations) are required to fully understand these relationships in order to draw much stronger conclusions about these relationships. Some of the potential underlying mechanisms at play are further investigated in the next Chapter, where associations of MetS with several neuroimaging and cognitive measures are examined using UK Biobank data.

CHAPTER 6

Examining the Association of Metabolic Syndrome with Neuroimaging and Cognitive Outcomes in the UK Biobank

CHAPTER SUMMARY

As identified and discussed in the previous Chapters, several observational studies have found an association between MetS and an increased risk for dementia. Other studies have also linked MetS to cognitive impairment.[321-323] Moreover, it has been suggested that MetS, as a whole, may be a better predictor of dementia pathology than each of its individual components alone.[324] The relationship between MetS and dementia may involve distinct pathways involving different aspects of brain health, characterised by early changes that appear in neuroimaging and tests of cognitive function. However, current research only provides indirect evidence about the association between MetS and dementia, and thus, the underlying neuropathological and cognitive associations implicated in this relationship remain unclear. Therefore, the aim of the study presented in this Chapter was to examine the association of MetS with neuroimaging and cognitive outcomes in dementia-free adults, offering insights into the impact of MetS on brain health prior to dementia onset.

In this study, a total of 37,395 dementia-free adults were identified from the UK Biobank. MetS was defined as ≥3 of the following components (based on the 2009 Harmonized Criteria): elevated waist circumference, triglycerides, blood pressure, HbA1c, or reduced HDL cholesterol. Multivariable-adjusted linear regression models were used to assess the association between MetS and several different structural neuroimaging outcomes and cognitive domains.

MetS was associated with lower total brain (Standardised Beta coefficient (β): -0.07, 95% CI: -0.09, -0.05), grey matter (β: -0.11, 95% CI: -0.13, -0.09) and hippocampal volumes (Left - β: -0.04, 95% CI: -0.06, -0.02; Right - β: -0.05, 95% CI: -0.07, 0.03), and greater white matter hyperintensity (WMH) volume (β: 0.09, 95% CI: 0.07, 0.11). MetS participants performed poorer

on cognitive tests of working memory (β: -0.10, 95% CI: -0.13, -0.07), verbal declarative memory (β: -0.08, 95% CI: -0.11, -0.05), processing speed (β: -0.07, 95% CI: -0.09, -0.04), verbal and numerical reasoning (β: -0.07, 95% CI: -0.10, -0.05), non-verbal reasoning (β: -0.03, 95% CI: -0.06, -0.01), and on tests of executive function, where higher scores indicated poorer performance (β: 0.06, 95% CI: 0.03, 0.09). An increasing number of MetS components were also associated with lower brain volumes, greater WMH volume, and poorer cognitive function across all domains that were assessed.

In conclusion, MetS was associated poorer brain health in dementia-free adults, characterised by lower brain volumes, greater vascular pathology, and poorer cognitive function. These findings provide important insights regarding how MetS is associated with early brain changes (as evident through neuroimaging and cognitive tests) even in those without dementia, and this information could help understand the previous differential associations observed between MetS and the various forms of dementia. Further research is necessary to understand whether reversal or improvement of MetS can improve brain health and reduce the risk of developing dementia.

Parts of the material presented in this Chapter were published in *Diabetes Care*, under the title "Association of metabolic syndrome with neuroimaging and cognitive outcomes in the UK Biobank" (Qureshi et al., 2024): https://doi.org/10.2337/dc24-0537. This work was also presented at several scientific conferences and featured in various news outlets (see section **"DPhil Publications, Recognitions and Awards"** for further details).

BACKGROUND

Previous studies, including those presented in this thesis (Chapters 3-4), have identified a significant association between MetS and an increased risk of developing dementia.[70,287] Building on this work by exploring links between MetS and preclinical or intermediate markers of dementia, such as early changes in structural neuroimaging and cognitive function, can enhance the understanding of the relationship between MetS and the risk for developing dementia. Maintaining both brain structure and cognitive abilities – hereafter collectively referred to as brain health – are crucial for healthy aging as loss of both are key indicators of progression towards dementia.[325] Evaluating neuroimaging and cognitive measures can also provide distinct insights regarding which aspects of brain health may be affected, such as atrophy, global or region-specific brain changes, vascular pathology, and different domains of cognitive function. Assessing different structural brain measures are important in this context: 1) examining total brain volume provides important insights about generalised atrophy in the brain[326]; 2) reductions observed in grey matter volume reflect neuronal loss (a hallmark of Alzheimer's disease)[327]; 3) loss of white matter volume can be indicative of disrupted neural connectivity which can result in cognitive impairment[328]; 4) reduced hippocampal volume can be a key indicator of memory loss[329,330]; and 5) examining WMH volume can help understand the potential involvement of vascular pathology.[331] Moreover, understanding associations with different cognitive domains is also crucial; changes in memory-specific domains are often evident in the initial stages of Alzheimer's disease, while impairments in processing speed, reasoning, and executive function have been observed in various forms of dementia, and have been shown to be particularly pronounced in the early stages of vascular dementia.[332,333] Therefore, studying these outcomes can help understand how the brain might be impacted before the potential onset of dementia occurs, and whether any changes are indicative of a specific type of dementia or pathology.

Different health conditions may influence these markers of brain health in distinct ways; some may exert a widespread effect, impacting multiple aspects of brain health, while others may exert a more localised effect.[334] Traditional cardiometabolic and vascular risk factors – such as diabetes, obesity, hypertension, and hyperlipidaemia – have been individually associated with poorer brain health.[335] However, it is well known that these individual risk factors are highly correlated with each other, often making it difficult to isolate their individual effects on overall brain health.[335] These relationships remain to be investigated in MetS (as a whole), which involves a clustering of different individual risk factors that more closely reflect real-world patient profiles rather than studying each individual risk factor solely in isolation.

In a 2021 meta-analysis of twelve studies (with sample sizes ranging from 50 to 7,000 participants), MetS was consistently associated with lower scores on global tests of cognition; however, its impact on individual domains of cognitive function was found to be mixed.[322] Moreover, while existing research has examined MetS in relation to either structural neuroimaging outcomes or cognition, few studies have examined these together[321,322,334,335], with most of the research in this area being focused on specific populations (e.g., MetS among schizophrenic patients).[336-338]

Given these knowledge gaps, the objective of the study presented in this Chapter was to investigate the association of MetS with several structural neuroimaging outcomes and domains of cognitive function in more than 37,000 participants from the UK Biobank. The impact of an increasing number of MetS components on these outcomes was also further explored.

METHODS

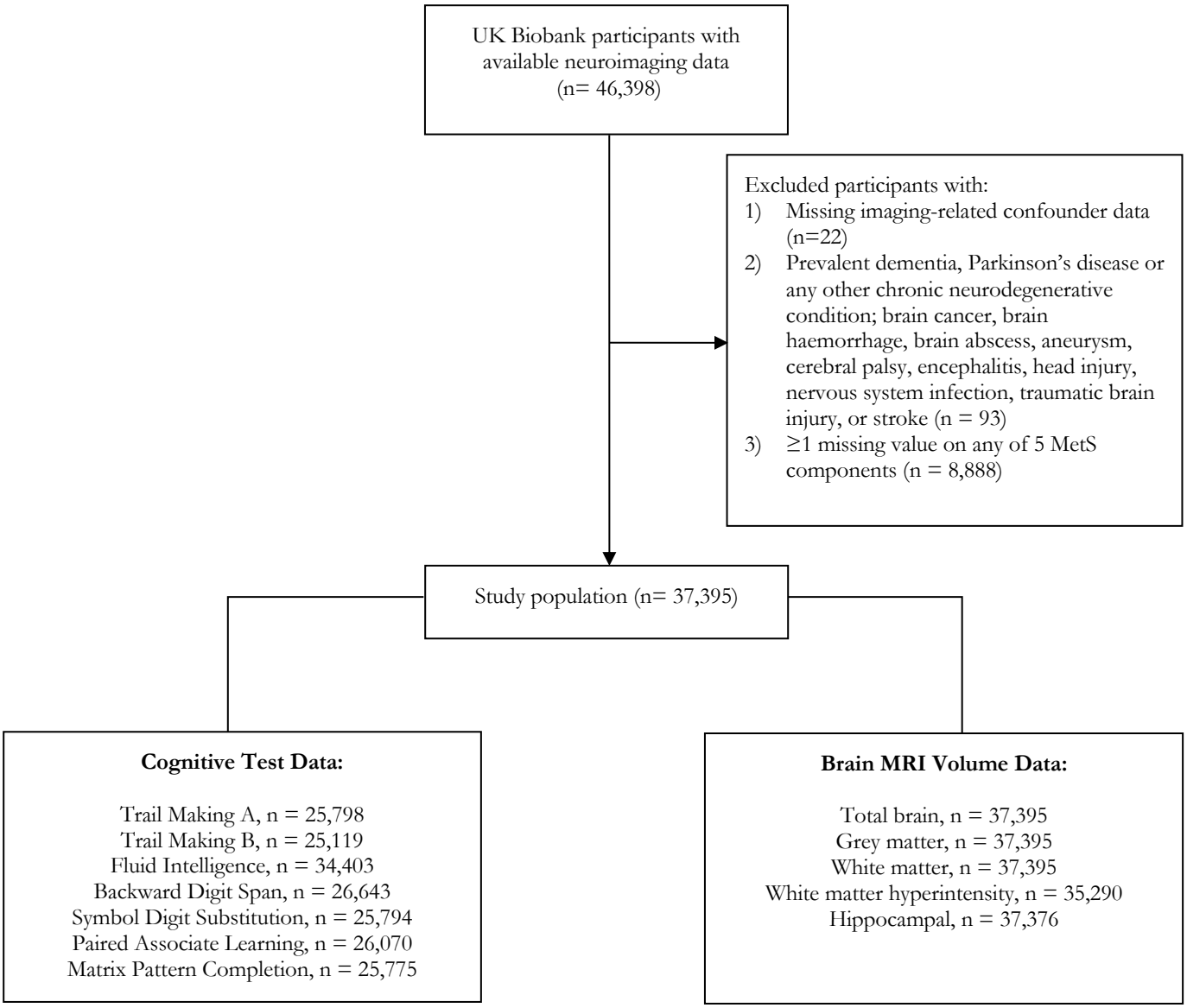
Data Source and Study Population

The study presented here was conducted using the UK Biobank, for which many of the details have been described previously in Chapter 3 and elsewhere.[231] At baseline (2006-2010), participants provided information on sociodemographic, lifestyle, environmental and health-related factors through a touch-screen questionnaire and a nurse-led verbal interview, underwent physical examinations, and provided blood samples to measure key biomarkers. Since 2014, participants have been re-invited to attend a follow-up imaging assessment to undergo brain, cardiac and abdominal MRI, dual-energy X-ray absorptiometry (DXA), and carotid ultrasound. During the imaging assessment, participants also underwent detailed cognitive tests of various cognitive domains and provided repeat measures of the baseline assessments (with the exception of key biomarker data, which was limited to baseline only). The imaging assessments were performed 9.27 ± 2.01 mean years after the study baseline. Using a standardised imaging protocol, participants were scanned across four imaging centres using Siemens Skyra 3T scanners (software VD13) with a standard 32-channel head coil.

At the time of data analysis, approximately 50,000 participants had undergone an imaging assessment. Participants were excluded from the study if they were missing data on imaging-related confounders (n = 22), or had prevalent self-reported or diagnosed dementia, Parkinson's disease or any other chronic neurodegenerative condition (such as motor neuron disease), brain cancer, brain haemorrhage, brain abscess, aneurysm, cerebral palsy, encephalitis, head injury, nervous system infection, traumatic brain injury, or stroke (n = 93). Furthermore, those with ≥1 missing value on any of the five MetS components (n = 8,888) were excluded in the main analysis. Missing values on MetS components and covariates were imputed in sensitivity analyses

(which is further described below). See **Figure 6.1** for additional details regarding the study cohort flow diagram. All participants provided electronically signed consent for their data to be used in health-related research.

Figure 6.1: Cohort flow diagram



Abbreviations: MetS = Metabolic syndrome; MRI = Magnetic Resonance Imaging

Metabolic Syndrome

MetS was defined at baseline using the 2009 Harmonized Criteria, for which details have been provided in the previous Chapters. MetS was ascertained using data solely from the baseline assessment since the key blood biomarker readings (i.e., triglycerides, HbA1c and HDL) were only collected at baseline assessments and not at the follow-up imaging assessment.

Participants were categorised into two groups: (1) No MetS (reference group), and (2) MetS. Complete information regarding the variables and medication codes used to define MetS components are available in **Appendix 6.1 and 6.2**.

Neuroimaging Measures

This study focused on examining volumetric assessments using structural brain MRI scans. These were captured using Imaging Derived Phenotypes (IDPs) that were derived from T1- and T2-weighted brain MRI scans using an image-processing automated pipeline developed by an external group in collaboration with the UK Biobank.[339] The purpose of the imaging processing pipeline was to help streamline the raw information from brain imaging by developing processed versions of the data in a form that is more meaningful for health research purposes.[340] The goal of these IDPs were to provide useful summary measures of the brain imaging data for broad research purposes by offering more objective quantifications of different aspects of brain structure and function.[340] For instance, T1-weighted structural images were processed through this pipeline in order to remove non-brain related aspects of the images, and to segment the imaging scans into various brain tissue types.[340] More specifically, these T1-weighted structural images provide strong contrast between different types of brain structures and tissue, including differentiation between grey and white matter, as well as segmenting

hippocampal volume with high precision.[340] Moreover, T1-/T2- weighted FLAIR (Fluid-Attenuated Inversion Recovery) structural images are particularly effective at identifying WMHs with contrast dominated by signal decay from interactions between water molecules (T2 relaxation times).[340]

IDPs were selected based on their relevance to markers of brain health in the context of cognitive decline and/or the development of dementia.[341] These included global grey matter, white matter, and total brain (sum of grey and white matter) volumes, which were segmented using FAST (FMRIB's [Functional Magnetic Resonance Imaging of the Brain] Automated Segmentation Tool[342]); hippocampal volume (left, right) using FIRST (FMRIB's Integrated Registration and Segmentation Tool[343]), and WMH volume from BIANCA (Brain Intensity AbNormality Classification Algorithm)[344], which uses both T1-weighted and T2-weighted data. In this study, white matter volume refers to the total volume of white matter in the brain. In contrast, WMHs refer areas of white matter that appear hyperintense (i.e., brighter) on brain MRI, which are often linked to aging, cognitive decline and dementia risk.[341] Outliers were defined as having a value greater than 8 times the median absolute deviation from the median of the data for any given IDP (N = 1,008) and were removed as per previous methods.[339] Full details regarding the neuroimaging variables used in this study are provided in **Appendix 6.3**.

Cognitive Tests

A total of twelve cognitive tests that were administered at the UK Biobank imaging assessment were initially considered for assessing cognition in this study.[345] The following five tests were removed: 1) the Reaction Time Test (which measures processing speed) was excluded because the cognitive domain it captures was more comprehensively assessed through the

Symbol-Digit Substitution Test – which is also known to be particularly sensitive to detecting changes related to cognitive impairment and dementia[346-348]; 2) the Picture Vocabulary Test (which measures crystallised memory) was excluded as previous work has shown that this assessment was not optimally calibrated for the UK population, resulting in ceiling effects which could compromise the accuracy of estimating domain-specific cognitive abilities here[349]; 3) the Prospective Memory Test (which measures prospective memory) was excluded because the main result for this assessment was provided as a categorical variable with limited information and insights that could be drawn (i.e., categories: completed vs. did not complete the test), making it susceptible to ceiling effects and unsuitable for comparison with all other tests that were continuous in nature (and subsequently standardised)[345]; 4) the Pairs Matching Test (which measures visual declarative memory), was excluded as previous studies have demonstrated that this assessment has very low test-retest reliability[345,350]; 5) the Tower Rearranging Test (which measures executive function), was also excluded due to its low test-retest reliability, which could potentially be due to the large number of participants reporting difficulty in understanding and interpreting the instructions of the task.[345,350]

Therefore, the present study included seven cognitive tests that examined different domains of cognitive function.[345] These tests included: the Trail-Making Tests (TMT) A and B (executive function), the Fluid Intelligence Test (verbal and numerical reasoning), the Backward Digit Span Task (working memory), the Symbol-Digit Substitution Test (complex processing speed), the Paired Associate Learning Task (verbal declarative memory), and the Matrix Pattern Completion Test (non-verbal reasoning).

Of note, higher scores indicate poorer cognitive performance for TMT (as it measures time taken to complete the test), whereas lower scores reflect poorer performance for all other tests. Individuals with TMT scores of ≤0 were removed from the analyses. Further details regarding the cognitive function variables used in this study are provided in **Appendix 6.3**, with brief descriptions of each test also presented below.

TMT Test A and B: The UK Biobank TMT test is a computerised version of the well-known Halstead-Reitan Trail Making Test.[345,351] The test measures executive function. It consists of two parts. In TMT Part A, participants were shown a screen with the numbers 1-25 that were randomly arranged, and then they were asked to touch the numbers in numerical order. In TMT Part B, participants were shown a screen with the numbers 1-13 and letters A-L which were arranged randomly. Participants were then asked to switch between touching the numbers in numerical order, and the letters in alphabetical order. If the incorrect number or letter was selected, a red screen would appear to indicate to the participant that they made a mistake, at which point they were required to touch the correct item in order to move on. The resulting score for the tests were measured as time (in deciseconds) taken to complete each test.[345]

Fluid Intelligence Test: The UK Biobank Fluid Intelligence Test consists of 13 multiple-choice questions, which were designed to assess verbal and numerical reasoning abilities.[345] Participants were presented with a question at the top of the screen, along with 3-5 options below. An example of a question assessing verbal reasoning would be the following: ["Bud is to flower as child is to"; Possible Answers: Grow, Develop, Improve, Adult, or Old]. In contrast, an example of a question assessing numerical reasoning would be the following: ["160…147…135…124…114… What comes next?"; Possible Answers: 106 / 105 / 104 / 103

/ 102). The resulting score for this test was measured as the number of questions answered correctly within a period of two minutes.[345]

Backward Digit Span Task: The Backward Digit Span Task was used to assess working memory.[345] Participants were asked to watch a video demonstration of the task before performing it themselves. During the task, participants were shown a two-digit number on their screen for a very brief period. This number then disappeared and then the participants were asked to enter the number in reverse order on a keypad displayed on the screen. The digit-sequence became subsequently longer with each correct round. If participants incorrectly recalled a digit-sequence, they were asked to recall a different sequence of the same digit length. The test terminated either when participants incorrectly recalled two trials of the same digit length, or if they correctly remembered a 12-digit number. The resulting score for this test was measured as the maximum number of digits correctly remembered in the reverse numerical order.[345]

Symbol-Digit Substitution Test: The Symbol-Digit Substitution Test was used to measure processing speed, and is similar to well-known tests such as the Wechsler Adult Intelligence Scale IV Coding Test[352] and the Symbol Digit Modalities Test.[353] During this test, participants were shown a key on a screen which paired several different symbols (presented in the top row) with numbers (presented in the bottom row). Underneath the key, participants were presented with a row of symbols, along with a blank row right below this, in which they had to enter the correct number (using a keypad on the screen) to pair with the specific symbol. The resulting score for this test was measured as the number of correct matches made within 1 minute.[345]

Paired Associate Learning Task: The UK Biobank Paired Associate Learning Task was used to measure verbal declarative memory.[345,354] In this test, participants were initially told that they would be shown a screen with different word pairs, and they had to try to remember as many of these pairs as possible. During the test, there was first a learning phase in which participants were shown a screen with 12 different pairs of word for 30 seconds. After this, they were then instructed to complete a different test (the Matrix Pattern Completion test, for which details are outlined below). Once this was completed, participants were then shown the first word of a pair (i.e., the target word) and were then asked to select, among four options, which word was paired with the target word. The task consisted of 10 questions. The resulting score for this test was measured as the number of questions that were correctly answered.[345]

Matrix Pattern Completion Test: The UK Biobank Matrix Pattern Completion Test was used to measure non-verbal reasoning abilities.[345] During this test, participants were shown a matrix design which had a piece missing in the lower right-hand corner. All of the designs had a logical structure which could be used to figure out what the missing piece looks like. Therefore, the participants were tasked with figuring out the patterns and rules of each design presented to them (15 items in total), and then select, from a list of 6-8 options, the correct missing piece. The resulting score was measured as the number of missing pieces that were correctly solved within 3 minutes.[345]

Covariates

Covariates included factors considered here to be potential confounders in determining the relationship between the exposure (MetS) and outcomes (neuroimaging outcomes and measures of cognitive function).[17,322,323,341]

Age in years was calculated as the interval between the date of birth and the date of attending an imaging assessment centre. The location of the imaging assessment centre ('Cheadle', 'Reading', 'Newcastle', 'Bristol') was defined as attendance at each respective imaging site. The Townsend deprivation index was used as a proxy for socio-economic deprivation and was assigned to each study participant using their residential postal code at baseline, and was categorised into fifths (1 to 5, defined as least deprived to most deprived).[252] Sex ('female', 'male') was defined using NHS records and/or self-reported data. Self-reported ethnicity ('White', 'Non-White'), education level ('primary', 'secondary', 'post-secondary non-tertiary', 'tertiary'), household income in GBP ('less than 18,000', '18,000-30,999', '31,000-51,999', '52,000-100,000', 'greater than 100,000'), smoking status ('never', 'previous', 'current'), and alcohol intake ('never', 'former drinker', 'infrequent' [i.e., special occasions only / 1-3 times per month], '1-2 times per week', '3-4 times per week', 'daily or almost daily') were measured on the touchscreen questionnaire. Physical activity level ('low' – MET minutes ≤1200, 'high' – MET >1200) was derived from touchscreen questionnaire items which were adapted to the validated short International Physical Activity Questionnaire[253]; time spent conducting vigorous, moderate, and walking activity was weighted by the amount of energy expended which allowed us to derive total MET minutes per week. *APOE*-ε4 carrier status ('ε4 non-carrier', 'ε4 carrier') was derived using the rs429358 and rs7412 SNPs, which were directly genotyped on the UK Biobank arrays.[254] Participants with any missing covariate data, or who responded with "prefer not to answer / do not know" were assigned as a separate category for each categorical variable.

Several imaging-related confounders were also included, specifically for the neuroimaging analyses only. These included: head size (i.e., intracranial volume), head position (using x-,y-, and z-axis position coordinates), and head motion.[339] Head size was controlled for

in order to ensure that any differences observed were not merely due to differences in intracranial volume. Moreover, the measures of head position and motion were included in order to mitigate the risk of observing artefacts that may have occurred for various reasons, such as excessive head movement during the scanning procedure. Controlling for such differences was necessary to help obtain more accurate measures of the outcomes being examined in this work.

Statistical Analysis

Descriptive statistics were used to compare baseline characteristics between participants with and without MetS; mean and SD were calculated for normally distributed variables, and median and IQR for skewed variables. Skewness was assessed for the outcome variables by visually inspecting their distributions through histograms. Skewed variables (TMT A and B, and WMH volume) were normalised using natural logarithm transformations as described in previously published work.[345] All outcomes were then standardised (mean = 0, SD = 1) to permit comparison of effect size across outcomes. Therefore, this study reports standardised Beta coefficients (β) and 95% CIs throughout the results.

Separate multivariable linear regression models were used to estimate the association of MetS with neuroimaging outcomes and cognitive domains. Models were adjusted for age at baseline, sex, ethnicity, education, Townsend deprivation index, household income, smoking status, alcohol intake, physical activity level, *APOE*-ε4 carrier status, assessment centre, and the time between the baseline and follow-up imaging assessments. To correct for interactions between age and sex, analyses were also adjusted for age^2 (non-linear effects), sex*age and sex*age^2. As per recommendations outlined in previous literature, quadratic age terms (age^2) were included in the models to account for non-linear age effects across all outcomes.[355] This decision

was further supported by ANOVA (Analysis of Variance) tests comparing models with and without the age^2 term, which demonstrated that its inclusion significantly improved model fit. Similarly, age-sex interaction terms were included to comprehensively account for their potential joint effects on brain health. Age and sex are known to interact in a non-additive manner in the context of brain health outcomes, and thus, the product of these two confounders must be considered.[355] For the neuroimaging analysis only, further adjustments were made for the following imaging-related confounders (i.e., precision variables): head size, head position, and head motion.[355]

In secondary analyses, associations of 1) individual MetS components and 2) the categorical number of MetS components present (from 0 to 5) with each neuroimaging and cognitive outcome were examined. In a sensitivity analysis, the main analysis was repeated using multiple imputation to investigate the potential impact of missing data for the exposure and covariates. The interaction between 1) MetS and age ('<65 years', '65+ years'), and 2) MetS and sex ('female', 'male') was also examined due to prior evidence indicating differences in structural neuroimaging and cognition based on these factors.[341,356-358]

Some MetS components measured at baseline were also available for capture at the imaging assessment (specifically: waist circumference measurements, blood pressure readings, and medication use). Secondly, it was also noted that there was potential for selection bias where a significantly lower proportion of individuals with MetS at baseline attended the follow-up imaging assessment (11,227 / 134,474 = 8%) compared to those without MetS (35,171 / 271,338 = 13%). Therefore, an additional sensitivity analysis was performed in which the main analysis was repeated using an alternative definition of MetS, in which a combination of data was

incorporated from the follow-up imaging assessment in conjunction with baseline blood biomarker readings.

All p-values were two sided, with statistical significance set at $p < 0.05$. All analyses were performed using RStudio version 4.2.2.

RESULTS

The analysis identified 37,395 participants (mean age: 55.01 ± 7.55 years), among which 8,651 (23.1%) had MetS – which is approximately half of that observed in the analysis presented in Chapter 3 (41.7% vs. 23.1%), likely due to the broader baseline age range included here in this study. The average time between baseline and follow-up imaging assessment was similar between participants with and without MetS (MetS: 9.19 ± 2.04 years; No MetS: 9.29 ± 2.0 years). Compared to those without MetS, those with MetS were more likely to be older, male, of non-white ethnicity, have lower education levels, have lower household incomes, reside in more socioeconomically deprived areas, to be previous smokers, less physically active, and *APOE*-ε4 carriers (**Table 6.1**). Among those with MetS, 64.6%, 28.1%, and 7.3% had three, four, and five MetS components, respectively. Among MetS participants, the most prevalent component was elevated blood pressure (93.4%), followed by elevated triglycerides (89.8%), elevated waist circumference (69.7%), reduced HDL cholesterol (51.7%), and elevated HbA1c (38.0%).

Table 6.1: Study cohort characteristics by MetS status

Characteristic	No MetS (N= 28,744)	MetS (N= 8,651)	Overall (N= 37,395)
Age – mean (SD)	54.46 (7.56)	56.85 (7.20)	55.01 (7.55)
Sex			
Female	15,783 (55%)	3,782 (44%)	19,565 (52%)
Male	12,961 (45%)	4,869 (56%)	17,830 (48%)
Ethnicity			
White	27,890 (97%)	8,322 (96%)	36,212 (97%)
Non-White	771 (2.7%)	304 (3.5%)	1,075 (2.9%)
Missing*	83 (0.3%)	25 (0.3%)	108 (0.3%)
Education level			
Primary	1,658 (5.8%)	764 (8.8%)	2,422 (6.5%)
Secondary	5,376 (19%)	1,767 (20%)	7,143 (19%)
Post-secondary non-tertiary	3,555 (12%)	1,167 (14%)	4,722 (13%)
Tertiary	18,072 (63%)	4,919 (57%)	22,991 (62%)
Missing*	83 (0.3%)	34 (0.4%)	117 (0.3%)
Townsend deprivation index			
1 (less deprived)	5,887 (20%)	1,586 (18%)	7,473 (20%)
2	5,836 (20%)	1,636 (19%)	7,472 (20%)
3	5,749 (20%)	1,723 (20%)	7,472 (20%)
4	5,681 (20%)	1,791 (21%)	7,472 (20%)
5 (more deprived)	5,565 (19%)	1,907 (22%)	7,472 (20%)
Missing	26 (<0.1%)	8 (<0.1%)	34 (<0.1%)
Household income (GBP)			
Less than 18,000	2,806 (9.8%)	1,201 (14%)	4,007 (11%)
18,000 to 30,999	5,549 (19%)	1,970 (23%)	7,519 (20%)
31,000 to 51,999	7,903 (27%)	2,397 (28%)	10,300 (28%)
52,000 to 100,000	7,802 (27%)	1,902 (22%)	9,704 (26%)
Greater than 100,000	2,259 (7.9%)	422 (4.9%)	2,681 (7.2%)
Missing*	2,425 (8.5%)	759 (8.8%)	3,184 (8.6%)
Alcohol intake			
Never	833 (2.9%)	372 (4.3%)	1,205 (3.2%)
Former	853 (3.0%)	397 (4.6%)	1,250 (3.3%)
Infrequent†	5,733 (20%)	2,475 (29%)	8,208 (22%)
1-2 times per week	7,622 (27%)	2,194 (25%)	9,816 (26%)
3-4 times per week	8,470 (29%)	1,967 (23%)	10,437 (28%)
Daily or almost daily	5,026 (17%)	1,178 (14%)	6,204 (17%)
Missing*	207 (0.7%)	68 (0.8%)	275 (0.7%)
Smoking status			
Never	17,974 (63%)	4,739 (55%)	22,713 (61%)
Previous	9,049 (31%)	3,231 (37%)	12,280 (33%)
Current	1,667 (5.8%)	656 (7.6%)	2,323 (6.2%)
Missing*	54 (0.2%)	25 (0.3%)	79 (0.2%)
Physical activity level			
Low (MET minutes ≤ 1200)	8,384 (29%)	3,116 (36%)	11,500 (31%)
High (MET minutes > 1200)	16,070 (56%)	4,046 (47%)	20,116 (54%)
Missing	4,290 (15%)	1,489 (17%)	5,779 (15%)
***APOE*-ε4 carrier status**			
Non-carrier	20,708 (72%)	6,108 (71%)	26,816 (72%)
ε4 carrier	7,187 (25%)	2,256 (26%)	9,443 (25%)
Missing	849 (3.0%)	287 (3.3%)	1,136 (3.0%)
Elevated waist circumference	3,243 (11%)	6,030 (70%)	9,273 (25%)
Elevated triglycerides‡	7,831 (27%)	7,771 (90%)	15,602 (42%)
Elevated blood pressure‡	16,065 (56%)	8,081 (93%)	24,146 (65%)
Elevated HbA1c ‡	1,370 (4.8%)	3,288 (38%)	4,658 (12%)
Reduced HDL cholesterol	2,261 (7.9%)	4,472 (52%)	6,733 (18%)

Abbreviations: APOE, apolipoprotein E; GBP, British pound sterling; MET, metabolic equivalent of task; SD, standard deviation. HbA1c = hemoglobin A1c, HDL = high density lipoprotein.

Note: Percentages do not add up to 100 due to rounding.

*Includes 'Prefer not to answer' and/or 'Do not know'.

† Special occasions only or 1-3 times per month.

‡ Includes medication use.

MetS and Neuroimaging Outcomes

Compared to no MetS, the presence of MetS was associated with lower total brain (β: -0.07, 95% CI: -0.09, -0.05) and grey matter volume (β: -0.11, 95% CI: -0.13, -0.09), as well as increased WMH volume (β: 0.09, 95% CI: 0.07, 0.11) (**Table 6.2**). MetS was also associated with lower left (β: -0.04, 95% CI: -0.06, -0.02) and right hippocampal volume (β: -0.05, 95% CI: -0.07, -0.03). No significant association was observed between MetS and white matter volume. Results remained similar after performing multiple imputation for missing exposure and covariate data (**Appendix 6.4**), and when repeating the main analysis using an alternative method for defining MetS (i.e., combination of data captured at baseline and imaging assessments; **Appendix 6.5**).

Table 6.2: Multivariable linear regression analyses examining association between the presence of MetS and A) standardised neuroimaging measures and B) standardised cognitive test scores

	Standardised Beta	95% CI	*P*
A) Neuroimaging Measures*			
Total Brain Volume	-0.07	-0.09, -0.05	**<0.001**
Grey Matter Volume	-0.11	-0.13, -0.09	**<0.001**
White Matter Volume	0.01	-0.02, 0.03	0.5
Left Hippocampal Volume	-0.04	-0.06, -0.02	**<0.001**
Right Hippocampal Volume	-0.05	-0.07, -0.03	**<0.001**
WMH Volume	0.09	0.07, 0.11	**<0.001**
B) Cognitive Test Measures			
Executive Function (TMT A)	0.04	0.01, 0.07	**0.007**
Executive Function (TMT B)	0.06	0.03, 0.09	**<0.001**
Verbal & Numerical Reasoning (FI)	-0.07	-0.10, -0.05	**<0.001**
Working Memory (BDS)	-0.10	-0.13, -0.07	**<0.001**
Processing Speed (SDS)	-0.07	-0.09, -0.04	**<0.001**
Verbal Declarative Memory (PAL)	-0.08	-0.11, -0.05	**<0.001**
Non-Verbal Reasoning (MPC)	-0.03	-0.06, -0.01	**0.033**

Abbreviations: CI, Confidence Interval; WMH, White Matter Hyperintensity; TMT, Trail Making Test; FI, Fluid Intelligence Score; BDS, Backward Digit Span Task; SDS, Symbol Digit Substitution Task; PAL, Paired Associate Learning Task; MPC, Matrix Pattern Completion Test.

All models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and APOE-ε4 carrier status, assessment centre, time between baseline and follow-up imaging assessment.

*Neuroimaging models (only) were further adjusted for imaging-related confounders: head size, head position, head motion.

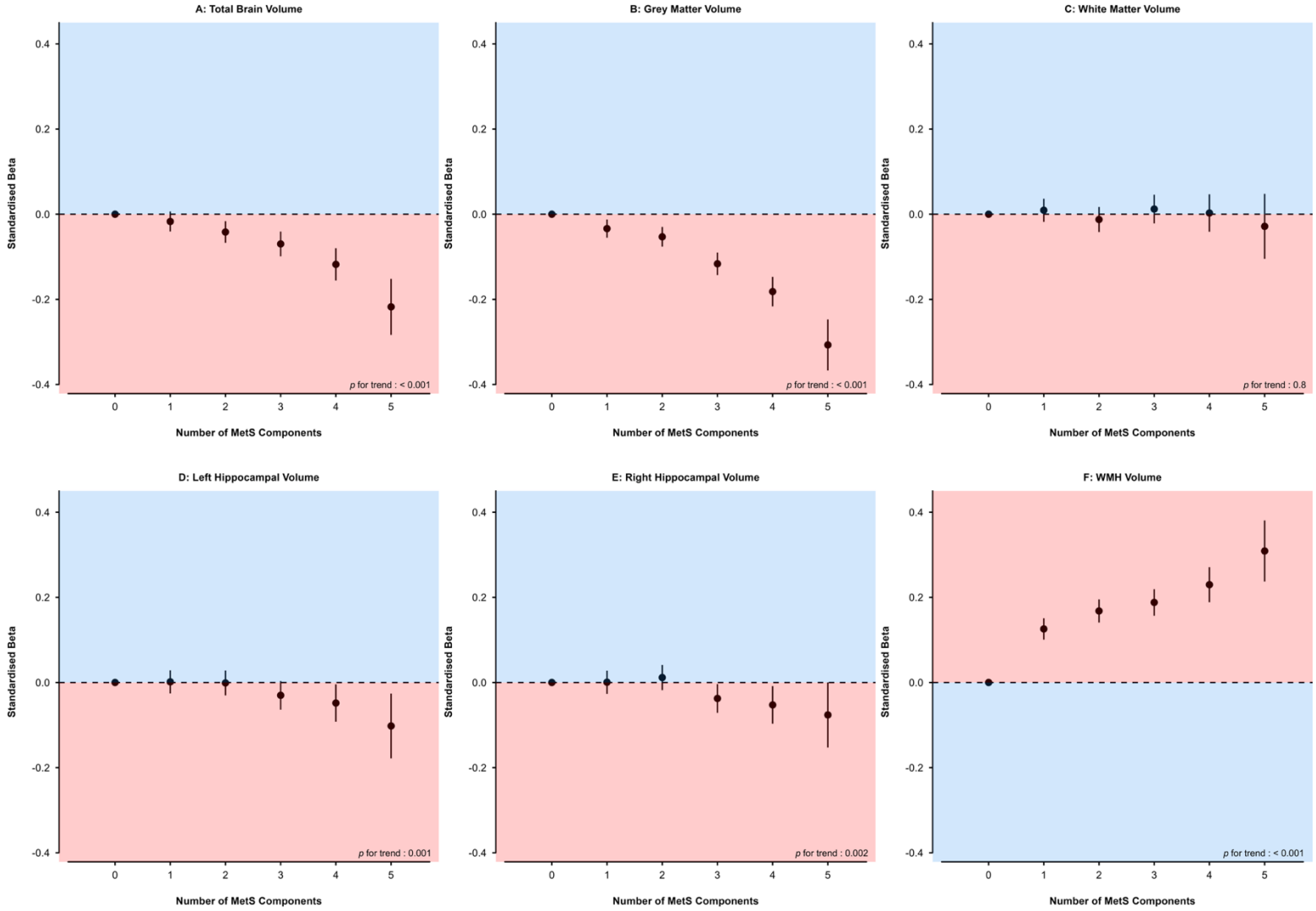
WMH, TMT A, and TMT B were log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1) to permit comparison of effect size across outcomes. Higher scores indicate poorer cognitive performance for TMT (as it measures time taken to complete the test), whereas lower scores reflect poorer performance for all other tests.

A dose-response relationship was observed between the number of MetS components present and several neuroimaging measures (**Figure 6.2**). Specifically, an increasing number of MetS components were associated with lower total brain (β ranging from: -0.02 to -0.22, *p for trend < 0.001*) and grey matter volume (β ranging from: -0.03 to -0.31, *p for trend < 0.001*), and greater WMH volume (β ranging from: 0.13 to 0.31, *p for trend < 0.001*). An increasing number of MetS components also showed a dose-response association with lower left (β ranging from: 0.00 to -0.10, *p for trend = 0.001*) and right hippocampal volume (β ranging from: 0.00 to -0.08, *p for trend = 0.002*). However, there was no association observed between the number of MetS components and white matter volume. Full details for Figure 6.2 are provided in **Appendix 6.6**.

In the analysis of individual components, elevated waist circumference and elevated HbA1c were significantly associated with lower total brain and grey matter volumes, while having elevated blood pressure showed the strongest association with greater WMH volume (further information is provided in **Appendix 6.7**).

Associations between MetS and neuroimaging outcomes were consistent amongst younger (<65 years) and older (65+) participants. However, there was a significant interaction of age with MetS and WMH volume (*p < 0.001*), with the strength of the association being greater among younger participants (<65 years: β: 0.10, 95% CI: 0.07, 0.12 vs. 65+ years: β: 0.05, 95% CI: -0.01, 0.11) (**Appendix 6.8**). Moreover, there was a significant interaction of sex with MetS and total brain, grey matter and white matter volumes (*p < 0.001*), with the strength of these associations being greater in males. Associations among other neuroimaging outcomes remained similar (**Appendix 6.9**).

Figure 6.2: Multivariable linear regression analyses examining the association between the number of MetS components and standardised neuroimaging measures



Abbreviations: MetS, Metabolic Syndrome; WMH, White Matter Hyperintensity

Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and *APOE*-ε4 carrier status, assessment centre, time between baseline and follow-up imaging assessment, head size, head position, head motion.

WMH was log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1) to permit comparison of effect size across outcomes.

Red denotes unfavourable direction (i.e., potential challenge or risk to brain health). Blue denotes favourable direction (i.e., potential neutral or protective effect on brain health).

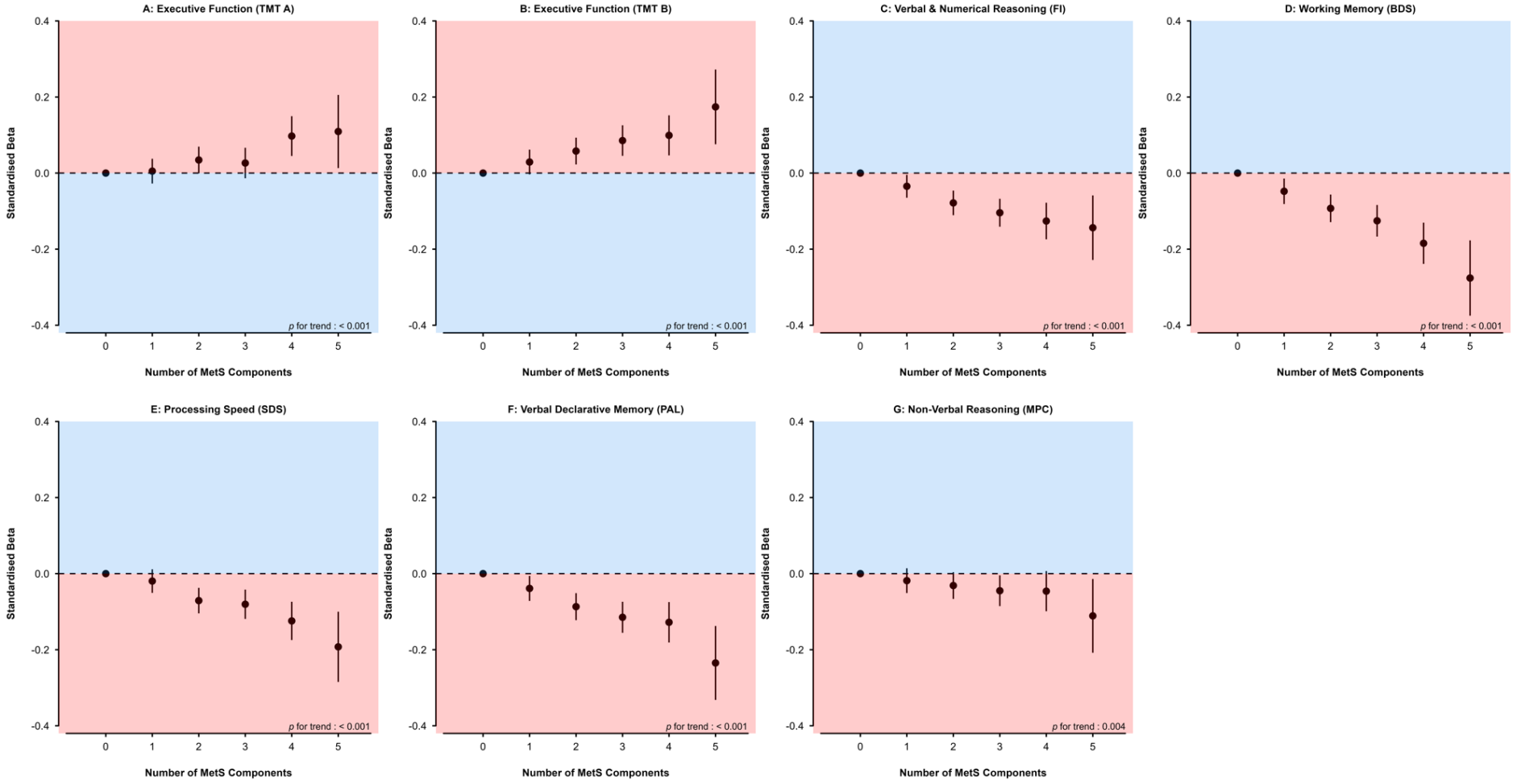
MetS and Cognitive Function Outcomes

MetS participants performed significantly poorer on tests measuring several different domains of cognitive function; this included tests of working memory (β: -0.10, 95% CI: -0.13, -0.07), verbal declarative memory (β: -0.08, 95% CI: -0.11, -0.05), processing speed (β: -0.07, 95% CI: -0.09, -0.04), verbal and numerical reasoning (β: -0.07, 95% CI: -0.10, -0.05), non-verbal reasoning (β: -0.03, 95% CI: -0.06, -0.01), and executive function (TMT B - β: 0.06, 95% CI: 0.03, 0.09; TMT A - β: 0.04, 95% CI: 0.01, 0.07) (**Table 6.2**). Results remained similar after performing multiple imputation for missing exposure and covariate data (**Appendix 6.4**), and when repeating the main analysis using an alternative method for defining MetS (i.e., a combination of data captured at the baseline and imaging assessments; **Appendix 6.5**).

A dose-response relationship was also observed between the number of MetS components and cognitive performance across different domains (**Figure 6.3; Appendix 6.10**). An increasing number of MetS components were associated with poorer cognitive performance on tests of working memory (β ranging from: -0.05 to -0.28, *p for trend* < *0.001*), verbal declarative memory (β ranging from: -0.04 to -0.23, *p for trend* < *0.001*), processing speed (β ranging from: -0.02 to -0.19, *p for trend* < *0.001*), executive function (TMT A or TMT B - β ranging from: 0.01 to 0.17, *p for trend* < *0.001*), and verbal and numerical reasoning (β ranging from: -0.03 to -0.14, *p for trend* < *0.001*). Increasingly poorer performance was also noted in the non-verbal reasoning domain, although less pronounced (β ranging from: -0.02 to -0.11, *p for trend* = *0.004*).

Regarding the individual components, elevated triglycerides and elevated blood pressure were consistently associated with significantly poorer performance across all measured domains of cognition (further details are provided in **Appendix 6.7**).

Figure 6.3: Multivariable linear regression analyses examining the association between the number of MetS components and standardised cognitive test scores



Abbreviations: MetS, Metabolic Syndrome; TMT, Trail Making Test; FI, Fluid Intelligence Score; BDS, Backward Digit Span Task; SDS, Symbol Digit Substitution Task; PAL, Paired Associate Learning Task; MPC, Matrix Pattern Completion Test

Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and *APOE*-ε4 carrier status, assessment centre, time between baseline and follow-up imaging assessment.

TMT A and B were log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1) to permit comparison of effect size across outcomes.

Red denotes poor performance (i.e., potentially indicative of challenges in cognitive function). Blue denotes good performance.

Associations of MetS with poor cognitive performance were generally consistent amongst younger (<65 years) and older (65+ years) participants. However, no significant interaction of age with MetS and cognitive tests were observed for any of the cognitive domains. (**Appendix 6.11**). In contrast, there was a significant interaction of sex with MetS and verbal and numerical reasoning ($p = 0.026$), where the strength of the association was greater among males. Associations among other cognitive outcomes remained similar when comparing by sex (**Appendix 6.12**).

DISCUSSION

In this large population-based study of more than 37,000 mid-to-late-life dementia-free individuals, MetS was associated with lower brain volumes, greater vascular pathology, and poorer cognitive function across several different cognitive domains. Moreover, there was a dose-response association between an increasing number of MetS components and lower brain volumes, vascular pathology and poorer cognitive function. These findings suggest that MetS is associated with poorer global brain health rather than having region- or domain-specific effects, and this might have implications for understanding the previously observed relationships between MetS and dementia risk.

Previous systematic reviews have identified several studies reporting associations of MetS with a number of brain outcomes, including lower total brain volume, silent brain infarcts, decreased grey matter volume in specific brain regions, and increased WMHs.[334,335] However, other research studies have shown inconsistent findings. For instance, Cavalieri et al., found no significant differences in total brain volume between those with and without MetS in a sample

of 819 dementia-free participants with a mean age of approximately 65 years.[356] Additionally, Sala et al., found no association between MetS and grey and white matter volumes among elderly participants (mean age: 66.2 years) from families with a history of longevity.[359] Another study by Tiehuis et al., found that the presence of MetS was associated with smaller brain volumes but not increased WMHs in a sample of 1,232 patients (mean age: 58.6 years) with manifest arterial disease.[338] Similarly, evidence regarding MetS and cognitive performance has been equally varied. While previous studies have been relatively consistent in demonstrating an association between MetS and impaired global cognitive function scores, its impact on individual cognitive domains remains largely inconsistent.[321] Inconsistencies could be due to several methodological differences including: 1) majority of existing studies comprise of relatively small samples; 2) most studies focus primarily on specific disease populations (e.g., MetS in those with mental disorders), limiting their overall generalisability; 3) exposure misclassification resulting from heterogeneity in the specific components and cut-offs used to define MetS; 4) the vast number of cognitive tests used to assess the same cognitive domain, with each having different sensitivity which could impact the ability to detect cognitive issues; and 5) large variation in sample characteristics (i.e., age, sex, education), and covariates accounted for in any analyses.[323] Findings from the study presented in this Chapter contribute to the existing body of research in this area by providing a more comprehensive evaluation of the influence of MetS on multiple neuroimaging and cognitive measures in a large sample of participants.

In this study, MetS was associated with lower brain volumes, increased WMH volume (a known marker of vascular damage), and poor performance on a range of different cognitive domains including memory, reasoning, processing speed, and executive function – parallelling some key hallmarks of dementia. Collectively, these findings suggest that rather than having a

specific localised effect, MetS appears to be associated with a more widespread effect on brain health. These findings also align with and build upon those presented in Chapters 3-4 as well as other dementia research studies from Europe and Asia demonstrating a consistent association between MetS and an increased risk for dementia, irrespective of the dementia subtype under investigation.[204,206,209,210,287]

The study presented here also found that an increasing number of MetS components were associated with greater reductions across several measures of brain volume and poorer performance on various cognitive domains. While several studies have reported similar findings in relation to the number of MetS components and cognitive outcomes[321,322], few comparable studies have explored the relationship of the number of MetS components with structural neuroimaging outcomes, yielding inconsistent findings.[359-361] Additionally, the study here also provides a detailed evaluation of various cognitive domains in relation to the number of MetS components present, showing that the presence of a greater number of MetS components incrementally increases cognitive deficits in areas of memory, processing, and executive function. Taken together, these results indicate that the impact of MetS on brain health is characterised by a dose-response relationship. Further research is necessary to understand whether it is more useful to examine the overall number of MetS components present, rather than focusing solely on its threshold effect (i.e., the presence of 3+ components, which is the established criteria for a MetS diagnosis); this information could provide useful insights for devising prevention strategies aimed at reducing or delaying cognitive decline and dementia.

The current study has several strengths. This study provides the most comprehensive evaluation of the relationship of MetS with several different neuroimaging measures and

validated domain-specific cognitive outcomes.[345] It is also the largest study of its kind, incorporating extensive phenotypic data and specific genotypic information on *APOE*-ε4 carrier status, allowing for a robust assessment of these associations. However, the present study also has several limitations, some of which have already been described within the previous UK Biobank study from Chapter 3. First, MetS was defined using baseline measurements (due to lack of key biomarker data at the follow-up imaging assessments) with neuroimaging and cognitive outcomes assessed several years later; this limits the ability to account for variability in MetS status over time. However, the validity of incorporating baseline biomarker data is supported by previous work demonstrating their high stability over time.[362] Second, this study was also limited by the lack of information on the severity and duration of MetS and each of its individual components. Third, while analyses excluded for prevalent dementia, some cases may have gone undetected; this could introduce selection bias, particularly if the prevalence of undetected cases varies between those with and without MetS. Fourth, the design of this work makes the findings susceptible to residual confounding from unmeasured factors which is an inherent limitation of all observational studies. Moreover, adjustment for multiple comparisons were not made, which increases the potential for Type-I error. Additionally, UK Biobank participants are known to be healthier than the general population, especially among those who attended the follow-up imaging assessment (i.e., healthy-volunteer bias). Thus, it is possible that the findings from this work may underestimate the true magnitude of the association between MetS and brain health.[363] Finally, due to the nature of data availability, this study was unable to assess how MetS influences longitudinal changes in neuroimaging and cognitive measures over time. However, addressing such research questions in the near future should be more achievable as more UK Biobank participants continue to undergo repeat imaging assessments.[364]

In conclusion, the findings from this Chapter reveal that having MetS, a cluster of risk factors associated with cognitive decline and dementia, was linked to significantly lower brain volumes and greater vascular pathology, which were paralleled by impaired performance across a range of different cognitive domains. Taken together, these findings demonstrate that MetS is related to poorer global brain health, aligning with previously observed associations presented in Chapters 3-4 which show that MetS was linked to an elevated risk of dementia of any cause.[204,206,209,210,287] Overall, this research extends the growing body of evidence linking poor metabolic health to compromised brain health. Further research is necessary to understand whether reversal or improvement of MetS (as well as its individual components) can improve brain health and reduce the risk of developing dementia.

CHAPTER 7

Concluding Remarks

CHAPTER SUMMARY

This Chapter summarises the work presented throughout this DPhil thesis, and provides an interpretation of the findings in the context of existing knowledge surrounding the relationship between MetS and the risk for developing dementia. The Chapter also further discusses potential implications of the thesis findings in relation to public health, the strengths and limitations of the work, and provides suggestions for future directions of research.

SUMMARY OF MAIN FINDINGS

The overall aim of the work presented in this DPhil thesis was to contribute towards a deeper understanding of the association between MetS and the risk of developing dementia. In order to achieve this aim, insights were gathered through conducting three large-scale prospective observational analyses and a thorough systematic review and meta-analysis, offering an improved understanding of the scientific evidence on the relationship between MetS and dementia risk.

In **Chapter 2**, findings were presented from a systematic review of prospective cohort studies investigating the relationship between MetS and risk of incident dementia (including key subtypes). The systematic review indicated that the relationship between MetS and risk of dementia remains inconsistent across identified published studies at the time, likely owing to the large variations observed in study characteristics such as differences in sample sizes, follow-up length, and lack of comprehensive confounder adjustments across the studies. Additional key knowledge gaps were also discussed and highlighted. Insights from this Chapter laid the foundation for the work and analyses conducted in the subsequent Chapters.

In **Chapter 3**, the relationship between MetS and the risk of developing incident dementia was investigated using data from the UK Biobank cohort. The analysis found that MetS was associated with an increased risk of developing incident all-cause dementia. Further investigations revealed that this risk also varied according to (1) follow-up length: associations were evident only during longer follow-up periods; (2) the number of MetS components present among participants: only the presence of 4 or 5 components was significantly associated with an elevated risk for dementia; and (3) the *APOE*-ε4 carrier status of participants: being an ε4 non-

carrier was associated a greater risk for developing dementia, however, the absolute background risk was notably greater in ε4 carriers.

In **Chapter 4**, the relationship between MetS and risk for developing dementia was further investigated, specifically using data from the EPIC-Norfolk cohort. While using the EPIC-Norfolk cohort allowed for similar examination of associations as the UK Biobank study from Chapter 3, the wide baseline age range and longer follow-up length in EPIC-Norfolk also enabled further distinct investigations of previously unanswered research questions: specifically, determining whether the presence of MetS at mid-life vs. late-life and the duration living with MetS influences the risk for developing incident dementia. Findings from these analyses revealed that: (1) in the overall cohort, MetS was associated with an increased risk of developing incident all-cause dementia, which support findings from Chapter 3; (2) in age-specific analyses, similar associations were observed in participants with MetS at mid-life, while associations were attenuated when examining those with MetS at late-life; (3) an increasing number of MetS components was also associated with a greater risk for dementia; and (4) those with a prolonged duration of MetS had a 26% increased risk of developing dementia when compared to individuals in the low MetS group, and no association was found for those with increasing MetS.

Subsequently, in **Chapter 5**, findings were presented from an updated systematic review and meta-analysis of prospective studies on MetS and dementia. Specifically, the systematic review from Chapter 2 was updated in order to incorporate relevant results from the prospective analyses presented in Chapters 3-4 (described briefly above), along with the any new and relevant published literature captured from electronic healthcare databases since the last search date; this ensured that this work summarised the latest evidence on the relationship between MetS and

incident dementia. Overall, a total of 14 studies were identified in the updated systematic review, which included more than 4.3 million participants who were initially free of dementia. The subsequent meta-analysis revealed that MetS was associated with a significantly increased risk of developing incident all-cause dementia. No significant association was observed for incident Alzheimer's disease or vascular dementia, although there was a notable positive trend observed for the association of MetS with vascular dementia; these findings also seemed to align with the pathological mechanisms observed in the development of vascular dementia (however, further research is certainly warranted). Moreover, meta-regression analyses showed that the relationship between MetS and dementia may potentially differ based on the age of participants under study, and based on the criteria used to ascertain MetS status. However, these findings were based on a limited number of studies, and therefore, additional evidence is necessary in order to reach stronger conclusions.

After establishing a potential link between MetS and dementia risk in the previous Chapters, the aim of **Chapter 6** was to investigate the relationship between MetS and various neuroimaging and cognitive outcomes in the UK Biobank to help understand MetS' potential impact on early changes in brain health, and provide insights regarding possible mechanisms implicated in the MetS-dementia relationship. The findings from this Chapter showed that, compared to no MetS, having MetS was associated with lower brain volumes, greater vascular pathology (as indicated by increased WMH volume), and poorer cognitive performance on a range of tests measuring different cognitive domains. These findings further helped to understand the previously observed associations of MetS and dementia risk.

INTERPRETATION OF THESIS FINDINGS

Overall, the findings presented in this thesis provide compelling evidence that MetS is a significant independent risk factor for the development of dementia, and offer insights regarding how this relationship might be impacted by different key traits/factors. By integrating results from several sources of evidence – including three large-scale population-based studies (each of which had unique aspects that allowed for investigating the MetS-dementia relationship from different angles), and a subsequent systematic review and meta-analysis of these associations – several key themes and overarching insights emerged. These insights are outlined below.

MetS and Risk for Dementia: A Consistent Link

A consistent link between MetS and future risk of dementia was observed in two separate large-scale cohorts, highlighting the robustness of this association. The risk of dementia observed in those with MetS was remarkably similar across the two cohort studies presented in Chapters 3-4; in the UK Biobank cohort, MetS was linked to a 12% increased risk of dementia, while in EPIC-Norfolk, there was an 11% increased risk. The similarity in risk across these two distinct cohorts strengthens the validity of the findings, as similar trends were found irrespective of differences in the study populations. These findings were also in line with the results from the meta-analyses presented in Chapter 5.

It is also worth noting that, in this thesis, the observed effect sizes for the association of MetS and dementia were considerably smaller than the effect sizes for some of the related individual risk factors reported by the Lancet Commission (such as hypertension, obesity, and diabetes).[17] These differences may be explained by: i) the varying strength of associations between individual components and dementia risk, with some exerting stronger direct effects

than others; ii) the co-occurrence of different risk factors resulting in unique interactions and complex pathways through which they impact dementia risk, which may differ from their individual effects when studied in isolation; and iii) differences in measurement criteria between the risk factors reported in the Lancet Commission versus the MetS definition, where some component cut-offs in the MetS criteria reflect pre-disease states rather than established disease states. Nevertheless, MetS as a composite measure offers valuable insights into the real-world cumulative impact of widespread metabolic dysfunction.

Significance of Having MetS at Mid-Life

A notable finding that emerged from this thesis was that age played a key role in the MetS-dementia relationship. Specifically, mid-life MetS was linked to an elevated risk of developing dementia, but this was not the case in late-life. This observation indicates that perhaps the timing of MetS is a key factor to consider when thinking of ways to reduce the risk of dementia in this vulnerable population, with its effect during mid-life presenting as a particularly sensitive period in which the benefits of risk reduction and prevention strategies may be most effective to curb future development of dementia and related conditions.

Effect of Cumulative and Chronic MetS

Findings from this thesis also indicated that the presence of a greater number of MetS components, and a prolonged duration of MetS played a key role in dementia risk. Specifically, a linear trend was observed, in which an increasing number of MetS components present was linked to poorer brain health and a greater risk of developing dementia. Additionally, a sustained and prolonged exposure to MetS was also linked to greater dementia risk. Taken together, these two insights highlight that perhaps early identification of high risk individuals with MetS

(particularly in those individuals presenting with more MetS components) and maintaining and managing one's metabolic health over long periods of time might be beneficial for staving off some of the adverse effects of MetS that can impact the brain.

MetS and Potential Vascular Contributions

Lastly, several insights can be gathered from the thesis findings regarding MetS and brain health, particularly vascular contributions. Specifically, findings from the meta-analysis revealed that MetS – given its vascular contributions – may be more directly linked to vascular dementia than Alzheimer's disease, and this interpretation is supported by several other studies showing similar differential links at the mechanistic level (discussed in previous Chapters).[316-319] This was also further supported by the thesis findings related to the impact of MetS on brain health, which revealed that MetS was linked to a significant increase in WMH volume, a known indicator of vascular pathology which appears to have strong links to the development of vascular dementia more so than Alzheimer's disease, particularly due to the resulting cerebrovascular changes that lead to dementia of the vascular type.[316-319]

PUBLIC HEALTH PERSPECTIVES

The findings presented in this thesis may have several significant implications that are of public health relevance, particularly in the context of dementia prevention strategies, clinical practice, and health policy. While the results presented in this thesis do not establish causation, they do suggest potential noteworthy links between MetS, brain health and dementia risk. Overall, this research could help shape future initiatives aimed at improving care for those living with MetS while also preventing further development of MetS symptoms in those who may be at risk, and this could subsequently mitigate risk for dementia and other future related complications. The considerations below outline several long-term translational possibilities stemming from the work presented in this thesis, however, further research is still necessary.

Early Detection and Management of MetS

Early detection and subsequent management of those living with MetS may be an effective strategy to help reduce their risk of developing dementia later in life. This can include regular screening programs to measure blood pressure, blood glucose, blood lipid levels, and waist line – all for which tools are readily available to healthcare providers to evaluate such measures, and these can also be further facilitated through at-home or digital health initiatives.[365] Given the age-specific links observed between MetS and dementia, these screening programs might be particularly beneficial when implemented in mid-life, a population in which future dementia risk was shown to be particularly elevated.

There are also several approaches that can be used to help prevent, manage and potentially reverse MetS, and this could subsequently help mitigate further neurological and cognitive issues from developing. This is especially promising as many of the conditions inherent

in MetS have been shown to be modifiable or amenable to change.[3,16,77] The approaches that can be considered include a combination of lifestyle modifications, pharmacological treatment, and educational interventions which are further detailed below.

Lifestyle Changes

Several lifestyle changes including weight loss, physical exercise, and dietary modifications could help reverse or control symptoms of MetS. For instance, promising evidence comes from previous work examining a multi-faceted health management program (consisting of a calorie-restricted diet, behaviour change, and physical activity counselling) focused on weight loss and reductions in waist circumference; this research found that larger relative decreases in waist circumference were associated with greater improvements in MetS components including blood pressure, lipids, and blood glucose levels.[366] Moreover, results from a multicentre clinical trial conducted by the Diabetes Prevention Program Research Group revealed that a lifestyle modification program aimed at helping participants achieve a goal of at least 7% weight loss and at least 150 minutes of physical activity per week was associated with a 58% reduction in the incidence of Type-2 diabetes among participants with impaired glucose tolerance, and this lifestyle intervention was more effective than using Metformin.[367] Similar promising evidence reporting effects of lifestyle interventions on MetS-related components have been reported in other studies as well.[368,369]

Physical activity regimens that incorporate a combination of aerobic and resistance training have shown the most benefits in the context of MetS[370], and additional evidence indicates that those unable to exercise could benefit from simply reducing their sedentary behaviour by just one hour per day.[371,372] Moreover, evidence suggests that physical activity can

improve cognitive functioning in patients with diabetes.[373] Other observational evidence has illustrated that more leisure-time physical activity, particularly during mid-life, was associated with better brain health outcomes, such as larger brain volumes and less cognitive decline.[374-376]

Several specific diets have also shown to be particularly promising in helping to manage MetS and its components, which include: 1) the Mediterranean diet, which emphasises consumption of healthy fats, fruits, vegetables, whole grains, nuts[377,378]; 2) a low-fat diet[379,380]; 3) a low sodium diet, such as the DASH (Dietary Approaches to Stop Hypertension) diet[381,382]; 4) a diet that emphasises consumption of foods with a low glycaemic index, which involves replacing refined foods with whole-foods in which carbohydrates are slowly absorbed, and has been associated with improvements in the management of blood sugar and dyslipidaemia[383,384];5) a high-fiber diet; and 6) an 8-hour time-restricted eating regimen.[385] Additionally, smoking cessation and avoidance of excess alcohol consumption have also been suggested as strategies for managing and reducing MetS.[386]

Other interventional studies have further revealed promising results in managing MetS components to improve brain health, and mitigate the risk of cognitive decline and dementia. The SPRINT MIND (Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension - Memory in Diabetes) trial demonstrated that aggressive blood pressure control was linked to reduced WMH progression.[373,387] The Sydney Memory and Aging Study observed less cognitive decline and dementia in diabetics treated with metformin versus those not treated.[387] The ACCORDION MIND (an extension of the MIND sub-study of the Action to Control Cardiovascular Risk in Diabetes) trial noted short-term increases in brain volume from intensive management of hyperglycaemia, though benefits did not persist in the

long-term.[373] Conversely, trials targeting hypercholesterolaemia did not show a beneficial impact on brain health.[373] Perhaps the most promising findings come from the FINGER (the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) trial – a multidomain intervention involving a diet, exercise, cognitive training, and vascular risk monitoring program in older adults with high rates of elevated blood pressure, body mass index and total cholesterol.[373,387] Results from this trial indicated that, compared to controls, the intervention group exhibited significantly less cognitive decline (although no significant changes were observed in brain volume or WMHs).[373,387] Further large-scale intervention studies with longer follow-up are necessary to understand how reversal of MetS as a whole, or its components, might impact overall brain health and the risk for developing dementia.

While lifestyle and dietary modifications have been shown to be effective in managing MetS, it is important to acknowledge the complexity of maintaining or implementing such changes into the daily lives of individuals. Individuals' circumstances might make it difficult to implement these changes, which could be due to factors such as time constraints limiting the ability to implement changes, limited access to resources, affordability, pre-existing health conditions, and broader environmental and social factors. Therefore, a syndemic approach in this context – which emphasises the need to address both individual and population-level determinants of health and their interactions[388,389] – might also help improve the overall health of these communities who are at risk of experiencing adverse outcomes related to dementia.

Pharmacological Therapies and Surgical Treatments

While lifestyle and dietary modifications can help manage MetS, several pharmacological treatments also play a significant role in managing the condition or its symptoms, especially when

non-pharmacological interventions may have proven insufficient. For instance, medications such as statins, anti-hypertensives such as ACE (Angiotensin-Converting Enzyme) inhibitors, and anti-diabetics such as Metformin, are already considered in the standard care for treating MetS patients. Other newer treatments, such as a novel cannabinoid receptor-1 (CB1R) inverse agonist, INV-202, has also shown promising findings in terms of improving symptoms of MetS.[390] Combining these treatments with appropriate lifestyle and dietary modifications can be an effective strategy to manage MetS and ultimately help mitigate its potential negative impact on brain health and future dementia risk.

Surgical interventions could also be considered in more complex cases, particularly bariatric surgery (i.e., weight-loss surgery).[391,392] This type of surgery comes in three forms: 1) a gastric band procedure, in which a band is placed around the stomach to reduce its size, with the goal to make individuals feel satiated with less food; 2) gastric bypass, in which the size of the upper stomach is reduced to a small pouch and the small intestine is rearranged accordingly, and as a result, less calories are absorbed; and 3) a sleeve gastrectomy, in which a part of the stomach is physically removed, with the goal of helping individuals feel satiated with less food.[391,392]

Increasing Awareness and Education of MetS

Individuals may be affected by MetS for the rest of their lives, and thus, education and consistent re-education is important as new findings and novel therapies or prevention regimens continue to emerge. However, in the United Kingdom and elsewhere, it has been reported that many healthcare providers, particularly those in primary care, have limited knowledge of MetS which impacts the uptake and level of screening and management techniques implemented to

address the condition.[393-395] In turn, this lack of awareness impacts patients and their understanding and knowledge of MetS and the potential consequences associated with the condition.[396] Addressing these gaps in knowledge is especially important, as clinicians in primary care play an essential role in helping to promote healthy lifestyle and behavioural choices for the treatment and management of patients living with MetS. Therefore, educational initiatives might prove useful to tackle MetS, which could involve providing additional training to healthcare professionals to improve their understanding of MetS and dementia risk reduction guidelines so that they can identify at-risk patients earlier, and subsequently provide these patients with well-informed guidance about the steps they can take to improve their metabolic health and reduce their risk of cognitive decline and dementia. Healthcare providers can play an effective role in the health of these patients if they are better equipped with the right knowledge to ensure that patients are provided with the most appropriate treatment plans – which may include a combination of lifestyle modifications, pharmacological treatments, or other therapies – and regularly reviewing these regimens to maintain their metabolic health in the long-term.

Public health campaigns and strategies focusing on improving the knowledge and understanding of MetS in the broader community may also be beneficial. These can include social media initiatives to disseminate the risks associated with poor metabolic health and its link with dementia, digital health tools to track metabolic health and overall fitness goals (such as WHO's 'mDementia' Prevention program, which is a digital health initiative aimed at providing population-level tools and access to risk reduction strategies)[16], or in-person activities such as educational seminars. Other strategies that may be effective could involve providing communities with regular free health screening programs to assess and monitor specific aspects of their metabolic or neurological health through measuring their blood pressure, blood

biomarkers, and cognitive health assessments. To ensure a broad reach, it is essential that these initiatives are designed in a way that is relevant to a broad population of diverse cultures and offered in multiple languages.

Public Health Framing and Utility of MetS

This work can inform dementia risk reduction strategies, for which different approaches can be considered depending on the context. From an epidemiological and clinical perspective, targeting individual risk factors inherent in MetS remains crucial, as these individual conditions ultimately drive dementia risk. However, MetS as a whole construct offers unique clinical utility, as it can help healthcare providers, especially those in primary care, to identify high-risk patients and initiate useful discussions about preventive measures to reduce their risk for dementia. Therefore, from the perspective of public health policy interventions, focusing on targeted screening for MetS as comprehensive syndrome and implementing programs that focus on holistic lifestyle changes aimed at addressing multiple metabolic risk factors in MetS could be particularly effective. Similarly, from a public health messaging standpoint, it may be more compelling to convey the concept of 'poor metabolic health' (i.e., MetS) and its link to dementia, since the clustering of MetS conditions is more reflective of real-world health patterns compared to focusing on individual risk factors alone. However, it is equally crucial to clearly define what poor metabolic health means in the context of co-occurring conditions that characterise MetS, so that the general public can better understand its implications, and subsequently make actionable lifestyle changes to mitigate their risk.

STRENGTHS AND LIMITATIONS

By leveraging data from two different cohorts and subsequently conducting a meta-analysis, this thesis represents one of largest and most comprehensive investigations of the observational associations between MetS, brain health, and the subsequent risk of developing dementia. In addition to the large sample size and long follow-up length, the standardised and uniform methods of exposure assessment, use of repeat measurements, biomarkers, genetics, imaging and cognition data allowed for a robust examination of the impact of MetS on brain health and dementia risk, and with much greater precision and accuracy than studies previously reporting on these relationships.

However, despite these strengths, there are several key limitations that must be considered when interpreting the findings presented in this thesis (some of which have been highlighted in previous Chapters). First, both the UK Biobank and EPIC-Norfolk cohorts are known to be healthier than the general population, and susceptible to healthy-volunteer bias, particularly in the context of participants attending follow-up assessments.[288,289,363] Therefore, it is possible that the findings reported in this thesis may underestimate the true magnitude of the actual associations. Additionally, both cohorts consist of predominantly White British participants, with limited representation of other ethnicities. This further restricts the overall generalisability of the findings. Moreover, while dementia subtypes were included in the systematic review, the associations of MetS with different dementia subtypes (i.e., Alzheimer's or vascular dementia) were not investigated in the cohort studies (Chapter 3-4) since medical records data have low accuracy for identifying subtypes.[251,282,290] This limits the insights that can be gathered about the potential associations between MetS and dementia-specific subtypes, which in turn, further hinders the ability draw conclusions about which mechanisms might be

driving any observations within these possible relationships. Finally, the observational nature of this work means that residual confounding and reverse causation cannot be ruled out as potential contributors of bias. Residual confounding remains a possibility in this work as there may be some additional confounders that were not considered or controlled for appropriately due to the lack of data availability on these measures (including the lack of repeat imaging data to observe any changes over time). Reverse causation also still remains a concern, particularly due to the extended prodromal period inherent in the development of dementia, which could span up to 30 years prior to a formal diagnosis by a clinician[219]; however, this thesis incorporated a large sample size with a high number of dementia cases and long follow-up which hopefully helps to reduce the chances of reverse causation as a potential limitation in this work. Given the challenges of establishing causality in observational studies, future research could overcome this concern by conducting a large-scale randomised controlled trial involving participants with MetS, separated into two groups – with one receiving targeted treatment/interventions aimed at reversing or improve their MetS, while the other remains untreated – and following them over several decades to assess whether they develop dementia. While conducting such trials would be quite resource-intensive and complex, they could provide robust evidence clarifying the potentially causal relationship between MetS and dementia risk.

FUTURE DIRECTIONS

The Need for Research Using Diverse Samples

While the results presented within this thesis highlight the importance of MetS as a potential risk factor for compromised brain health and the development of dementia, it is important to note that the analyses comprised of mainly White participants (both in the UK Biobank and EPIC-Norfolk). The systematic review conducted in this thesis further revealed that most of the evidence available on this topic comes from Europe and high-income countries consisting of predominantly White populations, with a lack of clarity about these relationships in regions with predominantly non-White populations. Ethnic and geographical differences in MetS prevalence have been previously noted[397], and this could impact the trends observed in relation to brain health and dementia risk. Future research – in the form of observational studies and interventional trials – should focus on understanding trends in low-income and middle-income countries, which is where two-thirds of people with dementia live; it is expected that the largest reductions in dementia incidence will be possible in these regions, since dementia rates are particularly elevated in these settings due to a combination of population ageing and a high occurrence of potentially modifiable risk factors in such areas.[17] Further similarly designed studies (i.e., large sample size, long follow-up, adequate confounder adjustment), but with diverse samples, are necessary to provide additional insights regarding the relationship between MetS and dementia risk. Gaining such insights can better inform the development of dementia prevention strategies for those living with MetS, and whether ethnic- or region-specific factors need to be taken into consideration to create the most effective preventative or proactive approaches.

The Need for Longitudinal Repeat Measures Data

Few studies to date have examined how change in MetS status over time is associated with change in outcomes of neuroimaging, cognition and dementia risk. This limitation is mainly due to the lack of repeat assessment data available to conduct these kinds of analyses. Most studies have been limited to measuring MetS at only one time point, and do not capture the potential longitudinal changes in MetS symptoms over time; this is crucial, as repeat assessments can help identify patients who are at the greatest risk of developing future disease, enabling provision of more tailored treatment options earlier on in the disease course.[398]Access to repeat assessments, for both exposure and outcome measures, are fundamental to understanding the longitudinal course of disease and pre-disease states, and this is particularly relevant in the context of dementia given its long prodromal period. Studying the relationship of MetS and dementia using longitudinal repeat measures can be valuable in several ways: 1) it can reveal important insights about the possible mechanisms involved by providing insights about how changes in metabolic health might impact changes in brain health and dementia risk; 2) it can help identify high-risk individuals by tracking how different changes in MetS status and the presence vs. absence of its components over time might differentially impact dementia risk; 3) it can help understand how progression to dementia may occur (i.e., mechanistic insights); 4) it can help evaluate the effectiveness of certain interventions in reducing dementia risk (e.g., lifestyle, pharmacological, or both) by monitoring the impact of these treatments on both exposure and outcome over long periods of time; and 5) may help better establish temporality in the relationship of MetS, changes in markers of brain health and the subsequent risk of developing dementia by clarifying the sequence of events and changes that occur within these associations. Currently, efforts are already underway to capture repeat assessment data on more

than 50,000 participants in the UK Biobank (which will be available in the coming years), providing a promising avenue to address existing gaps in future research work in this area.[364,399]

The Need for Additional Research on Dementia Subtypes

Future research should also focus on studying MetS in the context of specific dementia subtypes, such as Alzheimer's disease, vascular dementia, Lewy Body dementia, or frontotemporal dementia. Much of the work to date has relied on medical records data which, as stated earlier, lack the accuracy to appropriately identify dementia subtypes. Investigating how MetS contributes to the risk of developing specific dementia subtypes can provide detailed insights about the pathophysiology of dementia and specific pathways by which MetS may exert its potential adverse effects on dementia progression. For instance, as highlighted earlier in Chapter 5: understanding the link between MetS and Alzheimer's disease could shed light on how metabolic insults might influence amyloid depositions and neurofibrillary tangles which result in neurodegeneration, while understanding the link of MetS with vascular dementia could help elucidate the potential vascular contributions in these associations. Having a better understanding of these potentially differential influences could help better identify which type of dementia (whether it is a specific effect related to one subtype or a broader impact) that MetS patients might be most susceptible to, and this could inform future prevention strategies and public health or clinical interventions aimed at mitigating this risk. Achieving this requires improved accuracy of medical records to better identify cases of different dementia subtypes, along with improved methods to ascertain dementia through the use of relevant plasma biomarkers associated with specific subtypes – such as neurofilament light chain [NfL], phosphorylated tau181 [p-tau181],[400] or a combined blood test measuring p-tau217 and amyloid-β 42/40 ratios.[401,402] Use of such blood-based biomarkers are particularly promising in this regard

as they provide a low-cost and scalable option for increasing access to pathology-specific diagnoses.[18] Additionally, the use of advanced neuroimaging combined with machine learning techniques may also be a promising avenue for improving diagnostic accuracy, as these methods could help differentiate between varying phenotypes among dementia sub-samples. For instance, this approach could involve an initiative to re-invite these populations to undergo additional assessments to measure known markers of specific dementia subtypes. In order to achieve this, a machine learning algorithm could be trained on a large dataset of brain MRI scans, with each carefully labelled with the corresponding dementia subtype. Based on this training data, the algorithm can then learn to identify distinct patterns of brain changes specific to each subtype. Once the model is adequately trained, it can then be used on new brain MRI scans to predict the most likely dementia subtype relevant to the scan. For instance, the use of deep learning algorithms in this context have shown promising results and may be well-suited to differentiate between dementia subtypes as they can automatically learn to identify distinct patterns and features in very large datasets with high consistency and accuracy.[403]

CONCLUDING REMARKS

In conclusion, this DPhil thesis provides valuable insights regarding the association between MetS, brain health, and dementia risk. The findings from this work have highlighted MetS as a potentially novel risk factor for the development of dementia, which also exerts a notable impact on several aspects of neuroimaging and cognitive markers of brain health even in those without dementia. Several mechanisms might explain these associations, however, further similarly designed research – particularly using more diverse samples, investigating specific dementia subtypes, and leveraging repeat assessments of exposures and outcomes – are needed to fully elucidate the relationship between MetS and dementia. Nonetheless, the work presented in this thesis has established a strong basis for further investigations into the role of MetS on dementia risk, and highlights the importance of assessing this risk factor to help prevent or reduce dementia occurrence in the future.

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APPENDICES

Appendix 1.1: Standardised definitions used for MetS diagnosis in adults

	WHO (1998)[36]	EGIR (1999)[404]	NCEP-ATP III (2001)[37]	Modified NCEP-ATP III (2005)[85] – AHA/NHLBI	AACE (2003)[84]	IDF (2005)[38]	Harmonized Criteria (2009)[26]
Absolutely required	IR Defined as: T2D, IFG (≥110mg/dL or ≥6.1 mmol/L), IGT	IR Insulin levels >75th percentile *among non-diabetic patients*	None	None	IGT/IFG (but not diabetes)	Central obesity (defined as WC with ethnicity-specific values‡, but can be assumed if BMI > 30 kg/m²)	None
Criteria	IR, plus 2 of the following:	IR, plus 2 of the following:	Any 3 or more of the following:	Any 3 or more of the following:	IGT/IFG, plus 2 or more of the following:	Central obesity, plus 2 or more of the following:	Any 3 or more of the following:
Abdominal obesity	WHR > 0.9 (men) or > 0.85 (women); and/or BMI > 30 kg/m2	WC ≥ 94 cm (men), ≥ 80 cm (women)	WC > 102 cm (men), > 88 cm (women)	WC ≥ 102 cm (men), ≥ 88 cm (women)	BMI ≥ 25 kg/m²	Central obesity already required	Elevated WC (population and country-specific)
Elevated blood glucose	IR already required	Fasting glucose ≥ 110 mg/dL (6.1 mmol/L)	Fasting glucose ≥ 110 mg/dL (6.1 mmol/L) †	Fasting glucose ≥ 100 mg/dL (5.6 mmol/L) or Drug treatment for elevated glucose†	IGT/IFG already required	Fasting glucose ≥ 100 mg/dL (5.6 mmol/L) or Previously diagnosed T2D	Fasting glucose ≥ 100 mg/dL (5.6 mmol/L) or Drug treatment of elevated glucose
Elevated triglyceride levels	TG ≥ 150 mg/dL (1.7 mmol/L) and/or HDL-C <35 mg/dL (0.9 mmol/L) in men, <39 mg/dL (1.0 mmol/L) in women	TG > 177 mg/dL (>2.0 mmol/L) or HDL-C <39 mg/dL (1.0 mmol/L) in men or women or Treated for dyslipidaemia	TG ≥ 150 mg/dL (1.7 mmol/L)	TG ≥ 150 mg/dl (1.7 mmol/L) or on drug treatment for elevated TGs	TG ≥ 150 mg/dl (1.7 mmol/L) and/or HDL-C < 40 mg/dl (1.0/mmol/L) in men and < 50 mg/dL (1.3 mmol/L) in women	TG ≥ 150 mg/dL (1.7 mmol/L) or Specific treatment for this lipid abnormality	TG ≥ 150 mg/dL (1.7 mmol/L) or Drug treatment for elevated TG
Reduced HDL cholesterol			HDL-C < 40 mg/dL (1.0 mmol/L) in men and < 50 mg/dL (1.3 mmol/L) in women	HDL-C < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.3 mmol/L) in women or On drug treatment for reduced HDL-C		HDL-C < 40 mg/dl (1.03/mmol/L) in men and < 50 mg/dl (1.29 mmol/L) in women or Specific treatment for this lipid abnormality	HDL-C < 40 mg/dl (1.0 mmol/L) in men and < 50 mg/dl (1.3 mmol/L) in women or Drug treatment for reduced HDL-C
Elevated blood pressure	BP ≥ 140/90 mmHg	BP ≥ 140/90 mmHg or being treated for hypertension	BP ≥ 130/85 mmHg	SBP ≥ 130 or DBP ≥85 mmHg or On antihypertensive drug treatment in a patient with a history of hypertension	BP ≥ 130/85 mmHg	SBP ≥ 130 or DBP ≥ 85 mmHg or Treatment of previously diagnosed hypertension	SBP ≥ 130 and/or DBP ≥85 mmHg or Antihypertensive drug treatment in a patient with a history of hypertension
Other	Microalbuminuria Defined as: urinary albumin secretion rate 20 µg/min or greater, or albumin-to-creatinine ratio 30 mg/g or greater)						

WHO = World Health Organisation, EGIR = European Group for the Study of Insulin Resistance, NCEP-ATPIII = National Cholesterol Education Program Adult Treatment Panel III, AACE = American Association of Clinical Endocrinology, IDF = International Diabetes Federation, AHA/NHBLI = American Heart Association/National Heart, Lung, and Blood Institute

BP = Blood Pressure, TG = Triglycerides, IR = Insulin Resistance, IGT = Impaired Glucose Tolerance, IFG = Impaired Fasting Glucose, BMI = Body Mass Index, HDL-C = High Density Lipoprotein Cholesterol, WC = Waist Circumference, WHR = Waist-to-Hip Ratio, T2D = Type-2 Diabetes

†In 2003, the American Diabetes Association (ADA) changed the criteria for IFG tolerance from 110 mg/dl to 100 mg/dl.

‡ Waist circumference must be: for Europeans, > 94 cm in men and > 80 cm in women; and for South Asians, Chinese, and Japanese, > 90 cm in men and > 80 cm in women. For ethnic South and Central Americans, South Asian data are used, and for sub-Saharan Africans and Eastern Mediterranean and Middle East (Arab) populations, European data are used.

Appendix 2.1: Systematic Review Protocol

Review question: Do prospective studies suggest an association between metabolic syndrome (MetS) and risk of incident all-cause dementia or key dementia subtypes?

Population: Adults (≥18 years)

Exposure: Prevalent MetS

Comparators: No prevalent MetS

Outcomes: Incident all-cause dementia or key dementia subtypes (e.g., Alzheimer's disease, vascular dementia, Lewy body Dementia, and frontotemporal dementia)

Search strategy:

- Selection of relevant MetS (exposure) search terms will be informed by:
    - Key papers discussing standardised definitions of MetS[26,36-38,83-86];
    - MetS review articles[44,87-98];
    - Search strategies of the top 50 most-cited MetS systematic reviews (identified via Web of Science)[99-148]
- Dementia (outcome) search terms will be informed by:
    - Review articles discussing dementia and key dementia subtypes[17,149-151];
    - Search strategies used in previous systematic reviews where all-cause dementia and/or key dementia subtypes are the main outcome[77,152-201]
- Study design search terms will be informed by:
    - Search strategy used in a previous systematic review of prospective studies[201];
    - The Scottish Intercollegiate Guidelines Network (SIGN) search filters for systematic reviews[202]

Our search strategy will include:

- Searches will be developed for MEDLINE, Embase, and PsycINFO and will incorporate relevant subject headings and free-text terms informed by the approach outlined above. All searches will be peer-reviewed by an experienced librarian
- Backward and forward citation searches of included studies via Web of Science
- Automated search alerts set up in OvidSP (for Medline, Embase and PsycINFO databases) to receive regular email updates when new studies are published after the search date

Study selection criteria:

Inclusion criteria:

- Participants must be 18 years or older at study baseline
- Prospective studies examining the association between metabolic syndrome and incident all-cause dementia or key dementia subtypes
- MetS defined as follows: (1) self-reported diagnosis, or diagnosis confirmed through medical history (i.e. medical records); or (2) any combination of ≥ 3 out of the following 6 components (or an appropriate proxy indicator for any component): obesity, elevated fasting blood glucose, elevated triglyceride levels, reduced high-density lipoprotein cholesterol, elevated blood pressure, or microalbuminuria
- Studies must report outcomes as incident dementia or key dementia subtypes (e.g., Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementia)
- Publications must be written in English

Exclusion criteria:

- Studies which do not define the presence or absence of MetS using the following 5 components (or an appropriate proxy indicator): obesity, elevated fasting blood glucose, elevated triglyceride levels, reduced high-density lipoprotein cholesterol, elevated blood pressure
- Studies which define the presence or absence of MetS using a combination of measures outside of the following 6 components: obesity, elevated fasting blood

glucose, elevated triglyceride levels, reduced high-density lipoprotein cholesterol, elevated blood pressure, and microalbuminuria

- Studies with no comparison group or comparison group other than no metabolic syndrome
- Studies with outcomes that are not directly dementia-related (e.g. neuroimaging or biomarkers)
- Studies using only a single cognitive instrument or self-reported dementia to define incident dementia or key dementia subtypes
- Animal studies
- Case reports, narrative reviews, letters, editorials, opinions, book chapters
- Conference abstracts
- Duplicate publications using the same data

Study selection: Two reviewers (DQ & EK) will independently screen titles and abstracts based on the inclusion/exclusion criteria. The same two reviewers will also independently review the full-texts of potentially relevant studies. Any discrepancies will be resolved by discussion, if necessary, with a third reviewer (TJL).

Risk of bias (quality) assessment: Two reviewers (DQ & TJL) will independently assess the risk of bias using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies.[212] The components of the tool will be rated as outlined in previously described methods (described further below).[201] Any discrepancies will be resolved by discussion, if necessary, with a third reviewer (EK).

The Quality Assessment components will be rated individually as strong, moderate or weak as follows:

1. **Selection bias:** will be rated as strong if study participants are likely to be representative of the target population and the participation rate at baseline is greater than 80%, as moderate if participants are at least somewhat likely to be representative of the target population and the participation rate at baseline is 60-79%, and as weak if

participants are not likely to be representative of the target population or the participation rate at baseline is less than 60% or selection and participation rate at baseline are not described.

2. **Design:** will be rated as strong for randomised controlled trials and controlled clinical trials, as moderate for cohort studies, case control studies or interrupted time series and as weak for any other method or if method is not described.

3. **Confounders:** We consider adjusting analyses for sociodemographic confounders (age, sex, education and / or socioeconomic status, and ethnicity in case of a heterogenous sample) as essential. Studies will be rated as strong if analyses are adjusted for sociodemographic and at least three additional confounders and as moderate if adjustment strategy includes sociodemographic and one or two additional confounders. Studies will receive a weak rating if only sociodemographic or not all relevant sociodemographic confounders are adjusted for.

4. **Blinding:** will be rated as strong if the outcome assessor is not aware of participants' MetS status and participants are not aware of the research question / assessment of MetS for research purposes, as moderate if the outcome assessor is not aware of participants' MetS status or participants are not aware of the research question / assessment of MetS for research purposes or blinding is not described and as weak if the outcome assessor is aware of participants' MetS status and participants are aware of the research question / assessment of MetS for research purposes.

5. **Data Collection Methods:** will be rated as strong if data collection tools have been shown or are widely known to be valid and reliable, as moderate if data collection tools have been shown or are widely known to be valid but not reliable or reliability is not described and as weak if data collection tools have been shown or are widely known not to be valid or both validity and reliability are not described.

6. **Withdrawals and Drop-outs (Attrition Bias):** will be rated as strong if the follow-up rate is at least 80%, as moderate if the follow-up rate is 60-79% or follow-up rate

cannot be assessed due to study design (not applicable) and as weak if the follow-up rate is less than 60% or withdrawals and drop-outs are not described.

Data extraction:

One reviewer (DQ) will extract key data from each included study (e.g. study author, publication year, country/region, data source, race and/or ethnicity, study design, setting, analytic sample size, proportion of females, year(s) in which baseline data were collected, baseline age, follow-up length, MetS criteria, dementia criteria, number and percentage of MetS cases, number and percentage of incident dementia cases, reported adjusted effect estimates for dementia and/or key subtypes, and adjustment variables). Data extraction will be checked by a second reviewer (EK or TJL). Any discrepancies will be resolved by discussion, if necessary with a third reviewer (EK or TJL).

Corresponding authors of included studies will be contacted for clarification (if necessary) or to obtain additional data that has not been fully reported.

Evidence synthesis methods:

The identified evidence on the associations between MetS and all-cause dementia and key dementia subtypes will be synthesized narratively and using random effects meta-analysis if appropriate. Heterogeneity between studies will be investigated using the x^2 test for homogeneity and I^2 statistic, and meta-regression if appropriate.

Small study effects will also be explored, including publication bias using funnel plots and Egger's statistic if appropriate; specifically, funnel plots will be used to investigate publication bias if there are at least ten studies included in a meta-analysis.[311]

Secondary and sensitivity analyses may be performed to assess potential differences by exposure definitions, follow-up length, dementia subtypes, study quality, and other important measures.

Appendix 2.2: MEDLINE Search Strategy

#	Query	Results from 9 Feb 2022
1	exp Metabolic Syndrome/	35,457
2	exp Insulin Resistance/	92,146
3	((metabolic* or cardiometabolic* or dysmetabolic* or plurimetabolic* or atherometabolic*) adj3 (syndrome* or disorder* or risk factor* or abnormalit* or dysfunction*)).tw.	108,010
4	MetS*.tw.	14,704
5	(insulin* adj3 resistan*).tw.	92,288
6	((reaven* or atherothrombogenic or proatherogenic or obesity dyslipid?emi* or central fat or central obesity or central adiposity or visceral fat or visceral obesity or visceral adiposity or new world or hyperinsulin* or glucose intolerance or "glucose intolerance hypertension obesity" or GHO or "hypertension-hyperglyc?emia-hyperuric?emia" or "dyslipid?emia insulin resistance obesity and high blood pressure" or DROP) adj syndrome*).tw.	302
7	syndrome x.tw.	1,811
8	android obesity.tw.	156
9	hypertriglycerid?emi* waist.tw.	221
10	"syndrome of affluence".tw.	0
11	((death or deadly) adj quartet).tw.	48
12	"upper-body obesity glucose intolerance hypertriglycerid?emia and hypertension".tw.	4
13	("coronary artery disease hypertension adult onset diabetes obesity and stroke" or "CHAOS").tw.	9,563
14	metabolic trisyndrome.tw.	1
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	211,651
16	exp Dementia/	186,787
17	dement*.tw.	127,642
18	alzheimer*.tw.	163,616
19	16 or 17 or 18	285,725
20	exp Follow-Up Studies/	681,119
21	exp Prospective Studies/	614,448
22	exp Risk Factors/	912,379
23	exp Longitudinal Studies/	155,147
24	exp Proportional Hazards Models/	87,127
25	exp Incidence/	288,630
26	follow up.tw.	1,087,428
27	prospective*.tw.	789,148
28	longitudinal*.tw.	303,312
29	predict*.tw.	1,814,153
30	inciden*.tw.	981,209
31	determinant*1.tw.	258,657
32	hazard*1.tw.	266,665
33	risk.tw.	2,415,270
34	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	6,472,649
35	15 and 19 and 34	1,539

Appendix 2.3: Embase Search Strategy

#	Query	Results from 9 Feb 2022
1	exp metabolic syndrome X/	91,988
2	exp cardiometabolic risk/	11,207
3	exp insulin resistance/	132,942
4	((metabolic* or cardiometabolic* or dysmetabolic* or plurimetabolic* or atherometabolic*) adj3 (syndrome* or disorder* or risk factor* or abnormalit* or dysfunction*)).tw.	161,304
5	MetS*.tw.	24,103
6	(insulin* adj3 resistan*).tw.	133,366
7	((reaven* or atherothrombogenic or proatherogenic or obesity dyslipid?emi* or central fat or central obesity or central adiposity or visceral fat or visceral obesity or visceral adiposity or new world or hyperinsulin* or glucose intolerance or "glucose intolerance hypertension obesity" or GHO or "hypertension-hyperglyc?emia-hyperuric?emia" or "dyslipid?emia insulin resistance obesity and high blood pressure" or DROP) adj syndrome*).tw.	320
8	syndrome x.tw.	2,383
9	android obesity.tw.	254
10	hypertriglycerid?emi* waist.tw.	314
11	"syndrome of affluence".tw.	2
12	((death or deadly) adj quartet).tw.	59
13	"upper-body obesity glucose intolerance hypertriglycerid?emia and hypertension".tw.	4
14	("coronary artery disease hypertension adult onset diabetes obesity and stroke" or "CHAOS").tw.	7,785
15	metabolic trisyndrome.tw.	0
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	329,848
17	exp dementia/	398,130
18	dement*.tw.	185,013
19	alzheimer*.tw.	222,589
20	17 or 18 or 19	460,951
21	exp cohort analysis/	803,740
22	exp major clinical study/	4,368,347
23	exp follow up/	1,795,938
24	exp prospective study/	743,891
25	exp risk factor/	1,190,613
26	exp longitudinal study/	167,614
27	exp proportional hazards model/	94,290
28	exp incidence/	576,749
29	follow up.tw.	1,724,179
30	prospective*.tw.	1,218,999
31	longitudinal*.tw.	408,979
32	predict*.tw.	2,432,785
33	inciden*.tw.	1,395,537
34	determinant*1.tw.	313,346
35	hazard*1.tw.	379,153
36	risk.tw.	3,501,861
37	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	10,879,113
38	16 and 20 and 37	3,511

Appendix 2.4: PsycINFO Search Strategy

#	Query	Results from 9 Feb 2022
1	exp Metabolic Syndrome/	2,407
2	((metabolic* or cardiometabolic* or dysmetabolic* or plurimetabolic* or atherometabolic*) adj3 (syndrome* or disorder* or risk factor* or abnormalit* or dysfunction*)).tw.	7,283
3	MetS*.tw.	1,200
4	(insulin* adj3 resistan*).tw.	2,908
5	((reaven* or atherothrombogenic or proatherogenic or obesity dyslipid?emi* or central fat or central obesity or central adiposity or visceral fat or visceral obesity or visceral adiposity or new world or hyperinsulin* or glucose intolerance or "glucose intolerance hypertension obesity" or GHO or "hypertension-hyperglyc?emia-hyperuric?emia" or "dyslipid?emia insulin resistance obesity and high blood pressure" or DROP) adj syndrome*).tw.	4
6	syndrome x.tw.	84
7	android obesity.tw.	7
8	hypertriglycerid?emi* waist.tw.	6
9	"syndrome of affluence".tw.	0
10	((death or deadly) adj quartet).tw.	0
11	"upper-body obesity glucose intolerance hypertriglycerid?emia and hypertension".tw.	0
12	("coronary artery disease hypertension adult onset diabetes obesity and stroke" or "CHAOS").tw.	4,350
13	metabolic trisyndrome.tw.	0
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	14,273
15	exp Dementia/	84,502
16	dement*.tw.	75,135
17	alzheimer*.tw.	67,378
18	15 or 16 or 17	113,668
19	followup studies/	12,390
20	prospective studies/	1,060
21	risk factors/	90,185
22	exp longitudinal studies/	17,001
23	follow up.tw.	129,683
24	prospective*.tw.	75,414
25	longitudinal*.tw.	135,866
26	predict*.tw.	495,714
27	inciden*.tw.	88,059
28	determinant*1.tw.	58,755
29	hazard*1.tw.	20,424
30	risk.tw.	403,773
31	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	1,116,074
32	14 and 18 and 31	541

Appendix 2.5: Relevant studies captured in previous systematic reviews versus the systematic review presented in this thesis

	Atti et al. (2019)	Zuin et al. (2021)	DPhil Thesis Systematic Review (2022)	Outcomes Among Studies
Muller et al. (2007)	X	X	X	All-cause dementia, AD, VaD
Raffaitin et al. (2009)	X	X	X	All-cause dementia, AD, VaD
Solfrizzi. et al. (2010)	X	X	X	All-cause dementia, AD, VaD, Other dementias^#
Forti et al. (2010)	X	X	X	All-cause dementia, AD, VaD
Creavin et al. (2012)	X		X	All-cause dementia
Exalto et al. (2015)			X	All-cause dementia
Ng et al. (2016)			X	All-cause dementia
Fan et al. (2017)	X		X	All-cause dementia
Peng et al. (2018)			X	Parkinson's disease dementia
Lee et al. (2019)				All-cause dementia, AD, VaD
Lee et al. (2020)			X	All-cause dementia, AD, VaD

AD = Alzheimer's disease, VaD = Vascular dementia, MCI = Mild Cognitive Impairment

^#: Defined as dementia in other diseases classified elsewhere (e.g., dementia in Pick's disease, Creutzfeldt - Jakob disease, Huntington's disease, Parkinson's disease, human immunodeficiency virus [HIV], or other disease)

Appendix 3.1: Variables and medication codes used to define MetS in the UK Biobank cohort

Metabolic syndrome component	Harmonized criteria (2009) *Three or more of the following:*	UKB data field ID	Field code description
Elevated waist circumference	Elevated waist circumference: ≥ 102 cm in males and ≥ 88 cm in females	48	Waist circumference
Elevated triglycerides	≥ 150 mg/dL (1.7 mmol/L)	30870	Triglycerides Blood Biochemistry;
Elevated blood pressure	Systolic: ≥130 mmHg and/or Diastolic ≥85 mmHg*, or antihypertensive medication use *In UKB, BP was measured twice by trained nurses after participants had been at rest for at least 5 minutes. Individual systolic and diastolic BP measurements were averaged within a visit. Automated BP readings were the preferred source of data. However, if this was unavailable, manual readings were used	4080, 4079; 93,94	Systolic BP - automated reading, Diastolic BP - automated reading; Systolic BP - manual reading, Diastolic BP - manual reading
		20003	ATC Codes starting with: C02, C03, C07, C08, C09
Elevated blood glucose	≥100 mg/dL (≥5.6 mmol/L) †, or drug treatment for elevated glucose level †HbA1c used as a proxy indicator, with cut-offs based on the recommendations of the American Diabetes Association: HbA1c ≥5.7%	30750	Glycated haemoglobin (HbA1C)
		20003	ATC Codes starting with: A10
Reduced HDL cholesterol	Males: <40 mg/dL (1.0 mmol/L); Females: <50 mg/dL (1.3 mmol/L), or lipid-modifying medications	30760	HDL cholesterol
		20003	ATC Codes starting with: C10

UKB = UK Biobank, ATC = Anatomical Therapeutic Chemical, HDL = High-density lipoprotein, BP = Blood pressure, HbA1c = Glycated haemoglobin

Appendix 3.2: Detailed description of UK Biobank medication codes (mapped to ATC codes) used to define MetS components

UK Biobank Drug Category	UK Biobank Drug Name	UK Biobank Code	ATC Code
LIPID-MODIFYING MEDICATIONS			
atorvastatin	Atorvastatin	1141146234	C10AA05
lipitor 10mg tablet	Atorvastatin	1141146138	C10AA05
rosuvastatin	Rosuvastatin	1141192410	C10AA07
crestor 10mg tablet	Rosuvastatin	1141192414	C10AA07
simvastatin	Simvastatin	1140861958	C10AA01
simvador 10mg tablet	Simvastatin	1141188146	C10AA01
zocor 10mg tablet	Simvastatin	1140881748	C10AA01
pravastatin	Pravastatin	1140888648	C10AA03
lipostat 10mg tablet	Pravastatin	1140861970	C10AA03
ezetimibe	Ezetimibe	1141192736	C10AX09
ezetrol 10mg tablet	Ezetimibe	1141192740	C10AX09
fenofibrate	Fenofibrate	1140861954	C10AB05
lipantil micro 67mg capsule	Fenofibrate	1141162544	C10AB05
supralip 160mg m/r tablet	Fenofibrate	1141172214	C10AB05
fluvastatin	Fluvastatin	1140888594	C10AA04
lescol 20mg capsule	Fluvastatin	1140864592	C10AA04
gemfibrozil	Gemfibrozil	1140861856	C10AB04
omacor 1g capsule	Omega-3-Acid Ethyl Esters	1141181868	C10AX06
bezafibrate	Bezafibrate	1140861924	C10AB02
questran 4g/sachet powder	Cholestyramine	1140861936	C10AC01
colestyramine	Cholestyramine	1140909780	C10AC01
ciprofibrate	Ciprofibrate	1140862026	C10AB08
bezalip-mono 400mg m/r tablet	Bezafibrate	1140861928	C10AB02
bezalip 200mg tablet	Bezafibrate	1140861926	C10AB02
niacin	Niacin	1140910670	C04AC01 | C10AD02
niaspan 500mg m/r tablet	Niacin	1141188546	C10AD02
nicotinic acid product	Niacin	1140861868	C04AC01 | C10AD02
cholestyramine	Cholestyramine	1140865576	C10AC01
fibrazate xl 400mg m/r tablet	Bezafibrate	1141201306	C10AB02
colestyramine product	Cholestyramine	1141180734	C10AC01
bezafibrate product	Bezafibrate	1141157260	C10AB02
modalim 100mg tablet	Ciprofibrate	1140862028	C10AB08
zimbacol xl 400mg m/r tablet	Bezafibrate	1141171548	C10AB02
colestipol	Colestipol	1140888590	C10AC02
colestid 5g/sachet granules	Colestipol	1140861848	C10AC02

acipimox	Acipimox	1140861892	C10AD06
colestyramine+aspartame 4g/sachet powder	Cholestyramine	1141180722	C10AC01
ANTIHYPERTENSIVE MEDICATIONS			
hydralazine	Hydralazine	1140888686	C02DB02
moxonidine	Moxonidine	1140928284	C02AC05
physiotens 200micrograms tablet	Moxonidine	1140928290	C02AC05
minoxidil	Minoxidil	1140860532	C02DC01 |D11AX01
doxazosin	Doxazosin	1140879778	C02CA04
methyldopa	Methyldopa	1140860470	C02AB
cardura 1mg tablet	Doxazosin	1140860690	C02CA04
doxadura 1mg tablet	Doxazosin	1141194372	C02CA04
clonidine	Clonidine	1140883468	C02AC01 |N02CX02 |S01EA04
indoramin	Indoramin	1140879782	C02CA02
prazosin	Prazosin	1140879794	C02CA01
hypovase 500mcg tablet	Prazosin	1140860580	C02CA01
indapamide	Indapamide	1140866078	C03BA11
natrilix sr 1.5mg m/r tablet	Indapamide	1141146378	C03BA11
hydrochlorothiazide	Hydrochlorothiazide	1140866162	C03AA03
furosemide	Furosemide	1140909708	C03CA01
frusemide	Furosemide	1140866116	C03CA01
spironolactone	Spironolactone	1140866236	C03DA01
spirolone 25mg tablet	Spironolactone	1140866318	C03DA01
chlortalidone	Chlorthalidone	1140909706	C03BA04
eplerenone	Eplerenone	1141201244	C03DA04
hygroton 50mg tablet	Chlorthalidone	1140866146	C03BA04
metolazone	Metolazone	1140866092	C03BA08
bendroflumethiazide	Bendroflumethiazide	1141194794	C03AA01
bendrofluazide	Bendroflumethiazide	1140866122	C03AA01
co-amilofruse	Amiloride |Furosemide	1140923402	C03EB01
bumetanide	Bumetanide	1140866280	C03CA02
co-amilozide	Amiloride |Hydrochlorothiazide	1140923276	C03EA01
amiloride	Amiloride	1140888512	C03DB01
bendroflumethiazide+potassium 2.5mg/7.7mmol m/r tablet	Bendroflumethiazide |Potassium	1141194800	C03AB01
frumil tablet	Amiloride |Furosemide	1140866406	C03CA01

bendrofluazide+potassium 2.5mg/7.7mmol m/r tablet	Bendroflumethiazide |Potassium	1140866450	C03AB01
bzt - bendrofluazide	Bendroflumethiazide	1140910442	C03AA01
dyazide tablet	Triamterene |Hydrochlorothiazide	1140866402	C03EA01
moduretic tablet	Amiloride |Hydrochlorothiazide	1140866420	C03EA01
navispare tablet	Amiloride |Cyclopenthiazide	1140866352	C03EA07
co-triamterzide	Triamterene |Hydrochlorothiazide	1140923272	C03EA01
torasemide	Torasemide	1140888496	C03CA04
moduret 25 tablet	Amiloride |Hydrochlorothiazide	1140866416	C03EA01
burinex a tablet	Bumetanide	1140866356	C03CA02
xipamide	Xipamide	1140866108	C03BA10
cyclopenthiazide	Cyclopenthiazide	1140866156	C03AA07
bisoprolol	Bisoprolol	1140879760	C07AB07
cardicor 1.25mg tablet	Bisoprolol	1141171152	C07AB07
atenolol	Atenolol	1140866738	C07AB03
tenormin 25 tablet	Atenolol	1140866756	C07AB03
metoprolol	Metoprolol	1140879818	C07AB02
carvedilol	Carvedilol	1140909368	C07AG02
propranolol	Propranolol	1140879842	C07AA05
timolol	Timolol	1140879866	C07AA06 |S01ED01
half-inderal la 80mg m/r capsule	Propranolol	1140866800	C07AA05
inderal 10mg tablet	Propranolol	1140866804	C07AA05
bedranol 10mg tablet	Propranolol	1140851556	C07AA05
half beta-prograne 80mg m/r capsule	Propranolol	1140866802	C07AA05
labetalol	Labetalol	1140879824	C07AG01
sotalol	Sotalol	1140879854	C07AA07
beta-cardone 40mg tablet	Sotalol	1140860304	C07AA07
co-tenidone	Chlorthalidone |Atenolol	1140923336	C07CB03
nebivolol	Nebivolol	1141164276	C07AB12
bisoprolol fumarate+hydrochlorothiazide 10mg/6.25mg tablet	Bisoprolol |Hydrochlorothiazide	1140864950	C07BB07
celiprolol	Celiprolol	1140879762	C07AB08
atenolol+bendroflumethiazide	Atenolol |Bendroflumethiazide	1141194810	C07BB03
nebilet 5mg tablet	Nebivolol	1141164280	C07AB12
propranolol hydrochloride+bendrofluazide 80mg/2.5mg capsule	Bendroflumethiazide |Propranolol	1140860418	C07BA05
sotalol hydrochloride+hydrochlorothiazide 80mg/12.5mg tablet	Sotalol |Hydrochlorothiazide	1140860332	C07BA07

tenoret 50 tablet	Chlorthalidone |Atenolol	1140860324	C07CB03
carteolol	Carteolol	1140879822	C07AA15 |S01ED05
betaxolol	Betaxolol	1140879758	C07AB05 |S01ED02
atenolol+bendrofluazide	Atenolol |Bendroflumethiazide	1141146126	C07BB03
tenif capsule	Atenolol |Nifedipine	1140860358	C07FB03
metoprolol tartrate+chlorthalidone 100mg/12.5mg tablet	Metoprolol |Chlorthalidone	1140860308	C07CB02
tenoretic tablet	Chlorthalidone |Atenolol	1140860328	C07CB03
beta-adalat capsule	Atenolol |Nifedipine	1140860356	C07FB03
celectol 200mg tablet	Celiprolol	1140860498	C07AB08
acebutolol	Acebutolol	1140866724	C07AB04
oxprenolol	Oxprenolol	1140879830	C07AA02
prindolol	Pindolol	1140910614	C07AA17
kalten capsule	Atenolol |Amiloride |Hydrochlorothiazide	1140860398	C07DB01
nadolol	Nadolol	1140860192	C07AA12
pindolol	Pindolol	1140860292	C07AA03
atenolol+chlortalidone	Chlorthalidone |Atenolol	1141180778	C07BB03
amlodipine	Amlodipine	1140879802	C08CA01
istin 5mg tablet	Amlodipine	1140861202	C08CA01
amlostin 5mg tablet	Amlodipine	1141200400	C08CA01
nifedipine	Nifedipine	1140861088	C08CA05
adalat 5mg capsule	Nifedipine	1140861090	C08CA05
coracten sr 10mg m/r capsule	Nifedipine	1140861120	C08CA05
adalate 10mg capsule	Nifedipine	1140881702	C08CA05
adipine mr 10 m/r tablet	Nifedipine	1140923572	C08CA05
fortipine la40 m/r tablet	Nifedipine	1141145870	C08CA05
nifedipress mr 10 m/r tablet	Nifedipine	1141157140	C08CA05
tensipine mr 10 m/r tablet	Nifedipine	1140927940	C08CA05
verapamil	Verapamil	1140888510	C08DA01
securon 40mg tablet	Verapamil	1140866466	C08DA01
half securon sr 120mg m/r tablet	Verapamil	1140866460	C08DA01
univer 120mg m/r capsule	Verapamil	1140881692	C08DA01
vertab sr 240 m/r tablet	Verapamil	1141169710	C08DA01
diltiazem	Diltiazem	1140879806	C05AE03 |C08DB01
tildiem 60mg m/r tablet	Diltiazem	1140861128	C08DB01
adizem-60 m/r tablet	Diltiazem	1140861138	C08DB01
adizem-xl plus m/r capsule	Diltiazem	1140926780	C08DB01
dilzem sr 60mg long acting m/r capsule	Diltiazem	1140861166	C08DB01

slozem 120mg m/r capsule	Diltiazem	1140911698	C08DB01
angitil sr 90 m/r capsule	Diltiazem	1140917428	C08DB01
viazem xl 120mg m/r capsule	Diltiazem	1141151474	C08DB01
zemtard 120 xl m/r capsule	Diltiazem	1141167832	C08DB01
calcicard 60mg tablet	Diltiazem	1140851730	C08DB01
felodipine	Felodipine	1140888646	C08CA02
cardioplen xl 5mg m/r tablet	Felodipine	1141199858	C08CA02
vascalpha 5mg m/r tablet	Felodipine	1141190160	C08CA02
felendil xl 5mg m/r tablet	Felodipine	1141188836	C08CA02
plendil 2.5mg m/r tablet	Felodipine	1140928212	C08CA02
felotens xl 5mg m/r tablet	Felodipine	1141188152	C08CA02
neofel xl 5mg m/r tablet	Felodipine	1141200782	C08CA02
felogen xl 5mg m/r tablet	Felodipine	1141188576	C08CA02
cabren 2.5mg m/r tablet	Felodipine	1141187094	C08CA02
lercanidipine	Lercanidipine	1141153026	C08CA13
zanidip 10mg tablet	Lercanidipine	1141153032	C08CA13
lacidipine	Lacidipine	1140861276	C08CA09
diltiazem hcl+hydrochlorothiazide 150mg/12.5mg m/r capsule	Diltiazem |Hydrochlorothiazide	1140926778	C08GA
nicardipine	Nicardipine	1140879810	C08CA04
motens 2mg tablet	Lacidipine	1140861282	C08CA09
cardene 20mg capsule	Nicardipine	1140861176	C08CA04
valsartan	Valsartan	1141145660	C09CA03
diovan 40mg capsule	Valsartan	1141145668	C09CA03
losartan	Losartan	1140916356	C09CA01
cozaar 25mg tablet	Losartan	1141179974	C09CA01
perindopril	Perindopril	1140888560	C09AA04
coversyl 2mg tablet	Perindopril	1140860802	C09AA04
lisinopril	Lisinopril	1140860696	C09AA03
zestril 2.5mg tablet	Lisinopril	1140860714	C09AA03
irbesartan	Irbesartan	1141152998	C09CA04
aprovel 75mg tablet	Irbesartan	1141153006	C09CA04
enalapril	Enalapril	1140888552	C09AA02
innovace 2.5mg tablet	Enalapril	1140860776	C09AA02
fosinopril	Fosinopril	1140888556	C09AA09
ramipril	Ramipril	1140860806	C09AA05
telmisartan	Telmisartan	1141166006	C09CA07
micardis 20mg tablet	Telmisartan	1141172492	C09CA07
tritace 1.25mg tablet	Ramipril	1141188408	C09AA05
lopace 2.5mg capsule	Ramipril	1141199940	C09AA05

candesartan cilexetil	Candesartan	1141156836	C09CA06
amias 2mg tablet	Candesartan	1141156846	C09CA06
cilazapril	Cilazapril	1140860882	C09AA08
olmesartan	Olmesartan	1141193282	C09CA08
losartan potassium+hydrochlorothiazide 50mg/12.5mg tablet	Losartan |Hydrochlorothiazide	1141151016	C09DA01
olmetec 10mg tablet	Olmesartan	1141193346	C09CA08
trandolapril	Trandolapril	1140860904	C09AA10
eprosartan	Eprosartan	1141171336	C09CA02
captopril	Captopril	1140860750	C09AA01
quinapril	Quinapril	1140860728	C09AA06
lisinopril+hydrochlorothiazide 10mg/12.5mg tablet	Lisinopril |Hydrochlorothiazide	1140864952	C09BA03
coaprovel 150mg/12.5mg tablet	Hydrochlorothiazide |Irbesartan	1141172686	C09DA04
enalapril maleate+hydrochlorothiazide 20mg/12.5mg tablet	Enalapril |Hydrochlorothiazide	1140860790	C09BA02
irbesartan+hydrochlorothiazide 150mg/12.5mg tablet	Hydrochlorothiazide |Irbesartan	1141172682	C09DA04
cozaar-comp 50mg/12.5mg tablet	Losartan |Hydrochlorothiazide	1141151018	C09DA01
perindopril+indapamide	Perindopril |Indapamide	1141180592	C09BA04
zestoretic 10 tablet	Lisinopril |Hydrochlorothiazide	1140864618	C09BA03
coversyl plus 4mg/1.25mg tablet	Perindopril |Indapamide	1141180598	C09BA04
co-diovan 80mg/12.5mg tablet	Valsartan |Hydrochlorothiazide	1141201040	C09DA03
valsartan+hydrochlorothiazide 80mg/12.5mg tablet	Valsartan |Hydrochlorothiazide	1141201038	C09DA03
teveten 300mg tablet	Eprosartan	1141171344	C09CA02
micardisplus 40mg/12.5mg tablet	Telmisartan |Hydrochlorothiazide	1141187790	C09DA07
telmisartan+hydrochlorothiazide 40mg/12.5mg tablet	Telmisartan |Hydrochlorothiazide	1141187788	C09DA07
felodipine+ramipril	Ramipril |Felodipine	1141165470	C09BB05
imidapril hydrochloride	Imidapril	1141164148	C09AA16
innozide tablet	Enalapril |Hydrochlorothiazide	1140860784	C09BA02
gopten 500micrograms capsule	Trandolapril	1140860912	C09AA10
capozide tablet	Hydrochlorothiazide |Captopril	1140881714	C09BA01
capoten 12.5mg tablet	Captopril	1140860758	C09AA01
carace 10 plus tablet	Lisinopril |Hydrochlorothiazide	1140864910	C09BA03
triapin mite 2.5mg/2.5mg tablet	Ramipril |Felodipine	1141165476	C09BB05
accupro 5mg tablet	Quinapril	1140881706	C09AA06
MEDICATIONS FOR HYPERGLYCAEMIA			

metformin	Metformin	1140884600	A10BA02
glucophage 500mg tablet	Metformin	1140874686	A10BA02
insulin product	Insulin	1140883066	A10A
gliclazide	Gliclazide	1140874744	A10BB09
glyclizide	Gliclazide	1140910566	A10BB09
diamicron 80mg tablet	Gliclazide	1140874746	A10BB09
glimepiride	Glimepiride	1141152590	A10BB12
amaryl 1mg tablet	Glimepiride	1141156984	A10BB12
pioglitazone	Pioglitazone	1141171646	A10BG03
actos 15mg tablet	Pioglitazone	1141171652	A10BG03
glibenclamide	Glyburide	1140874718	A10BB01
repaglinide	Repaglinide	1141168660	A10BX02
rosiglitazone	Rosiglitazone	1141177600	A10BG02
rosiglitazone 1mg / metformin 500mg tablet	Metformin |Rosiglitazone	1141189090	A10BD03
avandamet 1mg / 500mg tablet	Metformin |Rosiglitazone	1141189094	A10BD03
glipizide	Glipizide	1140874646	A10BB07
avandia 4mg tablet	Rosiglitazone	1141177606	A10BG02
tolbutamide	Tolbutamide	1140874674	A10BB03 |V04CA01
acarbose	Acarbose	1140868902	A10BF01
nateglinide	Nateglinide	1141173882	A10BX03

Appendix 3.3: International Classification of Disease codes used to ascertain dementia

Code Type	Code	Description	AD	VD	FTD	All-Cause Dementia
ICD 9 Code	290.2	Senile dementia, depressed or paranoid type				✓
ICD 9 Code	290.3	Senile dementia with acute confusional state				✓
ICD 9 Code	290.4	Arteriosclerotic dementia		✓		✓
ICD 9 Code	291.2	Other alcoholic dementia				✓
ICD 9 Code	294.1	Dementia in other conditions classified elsewhere				✓
ICD 9 Code	331.0	Alzheimer's disease	✓			✓
ICD 9 Code	331.1	Pick's disease			✓	✓
ICD 9 Code	331.2	Senile degeneration of brain				✓
ICD 9 Code	331.5	Creutzfeldt-Jakob disease			✓	✓
ICD 10 Code	A81.0	Sporadic Creutzfeldt-Jakob disease			✓	✓
ICD 10 Code	F00	Dementia in Alzheimer's disease	✓			✓
ICD 10 Code	F00.0	Dementia in Alzheimer's disease with early onset	✓			✓
ICD 10 Code	F00.1	Dementia in Alzheimer's disease with late onset	✓			✓
ICD 10 Code	F00.2	Dementia in Alzheimer's disease, atypical or mixed type	✓			✓
ICD 10 Code	F00.9	Dementia in Alzheimer's disease, unspecified	✓			✓
ICD 10 Code	F01	Vascular dementia		✓		✓
ICD 10 Code	F01.0	Vascular dementia of acute onset		✓		✓
ICD 10 Code	F01.1	Multi-infarct dementia		✓		✓
ICD 10 Code	F01.2	Subcortical vascular dementia		✓		✓
ICD 10 Code	F01.3	Mixed cortical and sub-cortical vascular dementia		✓		✓
ICD 10 Code	F01.8	Other vascular dementia		✓		✓
ICD 10 Code	F01.9	Vascular dementia, unspecified		✓		✓
ICD 10 Code	F02	Dementia in other diseases classified elsewhere				✓
ICD 10 Code	F02.0	Dementia in Pick's disease			✓	✓
ICD 10 Code	F02.1	Dementia in Creutzfeldt-Jakob disease			✓	✓
ICD 10 Code	F02.2	Dementia in Huntington's disease			✓	✓
ICD 10 Code	F02.3	Dementia in Parkinson's disease			✓	✓
ICD 10 Code	F02.4	Dementia in HIV disease			✓	✓
ICD 10 Code	F02.8	Dementia in other specified diseases classified elsewhere				✓
ICD 10 Code	F03	Unspecified dementia				✓
ICD 10 Code	F05.1	Delirium superimposed on dementia				✓
ICD 10 Code	F10.6	Mental and behavioural disorders due to use of alcohol - amnesic syndrome				✓
ICD 10 Code	G30	Alzheimer's disease	✓			✓
ICD 10 Code	G30.0	Alzheimer's disease with early onset	✓			✓
ICD 10 Code	G30.1	Alzheimer's disease with late onset	✓			✓
ICD 10 Code	G30.8	Other Alzheimer's disease	✓			✓
ICD 10 Code	G30.9	Alzheimer's disease unspecified	✓			✓
ICD 10 Code	G31.0	Circumscribed brain atrophy			✓	✓
ICD 10 Code	G31.1	Senile degeneration of brain				✓
ICD 10 Code	G31.8	Other specified degenerative diseases of nervous system				✓
ICD 10 Code	I67.3	Binswanger's disease		✓		✓

Abbreviations: AD = Alzheimer's disease, VaD = Vascular dementia, FTD = Frontotemporal dementia, ICD, International Classification of Disease

Appendix 3.4: Baseline characteristics according to missing data on MetS components

Characteristic		Non-Missing (N=176,249)	Missing (N=41,048)	Overall (N=217,297)
Age (years)	Mean (SD)	64.1 (2.85)	64.2 (2.85)	64.1 (2.85)
Sex	Female	92052 (52.2%)	22560 (55.0%)	114612 (52.7%)
	Male	84197 (47.8%)	18488 (45.0%)	102685 (47.3%)
Ethnicity	White	170674 (96.8%)	39043 (95.1%)	209717 (96.5%)
	Non-White	4764 (2.7%)	1635 (4.0%)	6399 (2.9%)
	Missing	811 (0.5%)	370 (0.9%)	1181 (0.5%)
Education level	Primary	47225 (26.8%)	11150 (27.2%)	58375 (26.9%)
	Secondary	77685 (44.1%)	17836 (43.5%)	95521 (44.0%)
	Post-secondary non-tertiary	18922 (10.7%)	4294 (10.5%)	23216 (10.7%)
	Tertiary	30021 (17.0%)	7172 (17.5%)	37193 (17.1%)
	Missing	2396 (1.4%)	596 (1.5%)	2992 (1.4%)
Townsend deprivation index, quintiles	1 (least deprived)	35508 (20.2%)	7915 (19.3%)	43423 (20.0%)
	2	35282 (20.0%)	8141 (19.9%)	43423 (20.0%)
	3	35292 (20.0%)	8131 (19.8%)	43423 (20.0%)
	4	35363 (20.1%)	8059 (19.7%)	43422 (20.0%)
	5 (most deprived)	34656 (19.7%)	8766 (21.4%)	43422 (20.0%)
	Missing	48 (0.1%)	36 (0.1%)	184 (0.1%)
Household income (in GBP)	Less than 18,000	48685 (27.6%)	11355 (27.7%)	60040 (27.6%)
	18,000 to 30,999	46630 (26.5%)	10779 (26.3%)	57409 (26.4%)
	31,000 to 51,999	29936 (17.0%)	6723 (16.4%)	36659 (16.9%)
	52,000 to 100,000	14437 (8.2%)	3228 (7.9%)	17665 (8.1%)
	Greater than 100,000	3409 (1.9%)	803 (2.0%)	4212 (1.9%)
	Missing	33152 (18.8%)	8160 (19.9%)	41312 (19.0%)
Smoking status	Never	87285 (49.5%)	20538 (50.0%)	107823 (49.6%)
	Previous	73392 (41.6%)	16709 (40.7%)	90101 (41.5%)
	Current	14508 (8.2%)	3384 (8.2%)	17892 (8.2%)
	Missing	1064 (0.6%)	417 (1.0%)	1481 (0.7%)
Alcohol intake	Never	8430 (4.8%)	2084 (5.1%)	10514 (4.8%)
	Former drinker	6642 (3.8%)	1640 (4.0%)	8282 (3.8%)
	Special occasions only	21283 (12.1%)	5137 (12.5%)	26420 (12.2%)
	1-3 times per month	17401 (9.9%)	4046 (9.9%)	21447 (9.9%)
	1-2 times per week	42078 (23.9%)	9677 (23.6%)	51755 (23.8%)
	3-4 times per week	38895 (22.1%)	8857 (21.6%)	47752 (22.0%)
	Daily or almost daily	41205 (23.4%)	9360 (22.8%)	50565 (23.3%)
	Prefer not to answer	168 (0.1%)	44 (0.1%)	212 (0.1%)
	Missing	147 (0.1%)	203 (0.5%)	350 (0.2%)
Physical activity level	Low (MET minutes ≤ 1200)	47865 (27.2%)	10673 (26.0%)	58538 (26.9%)
	High (MET minutes > 1200)	91059 (51.7%)	20333 (49.5%)	111392 (51.3%)
	Missing	37325 (21.2%)	10042 (24.5%)	47367 (21.8%)
***APOE*-ε4 carrier status**	Non-carrier	125734 (73.7%)	25899 (73.6%)	151633 (73.7%)
	Carrier	44905 (26.3%)	9310 (26.4%)	54215 (26.3%)
	Missing	5610 (3.2%)	5839 (14.2%)	11449 (5.3%)
Waist circumference	Missing	0 (0%)	860 (2.1%)	860 (0.4%)
Triglycerides	Missing	0 (0%)	14205 (34.6%)	14205 (6.5%)
Blood pressure	Missing	0 (0%)	542 (1.3%)	542 (0.2%)
HbA1c	Missing	0 (0%)	15121 (36.8%)	15121 (7.0%)
HDL-cholesterol	Missing	0 (0%)	30850 (75.2%)	30850 (14.2%)
Lipid-modifying medication	Yes	48062 (27.3%)	11076 (27.0%)	59138 (27.2%)
Blood pressure medication	Yes	60432 (34.3%)	14048 (34.2%)	74480 (34.3%)
Blood glucose medication	Yes	8786 (5.0%)	2217 (5.4%)	11003 (5.1%)

Abbreviations: PRS = Polygenic risk score, APOE = Apolipoprotein, SD = standard deviation, MET = metabolic equivalent of task, GBP = British pound sterling, HbA1c = hemoglobin A1c, HDL = high density lipoprotein.

Percentages do not add up to 100 due to rounding.

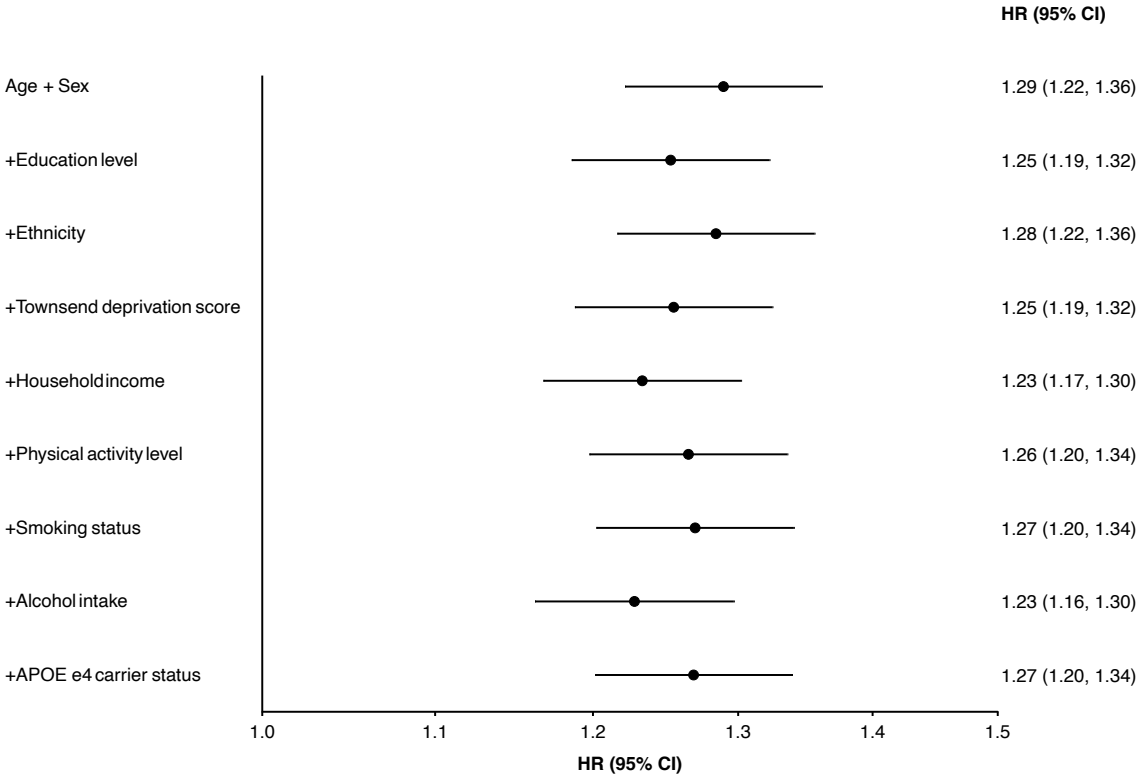
Appendix 3.5: Baseline characteristics according to incident dementia status at the end of follow-up

Characteristic		No Dementia (N=170,994)	Dementia (N=5,255)	Overall (N=176,249)
Age (years)	Mean (SD)	64.1 (2.85)	65.7 (2.71)	64.1 (2.85)
Sex	Female	89570 (52.4%)	2482 (47.2%)	92052 (52.2%)
	Male	81424 (47.6%)	2773 (52.8%)	84197 (47.8%)
Ethnicity	White	165627 (96.9%)	5047 (96.0%)	170674 (96.8%)
	Non-White	4590 (2.7%)	174 (3.3%)	4764 (2.7%)
	Missing	777 (0.5%)	34 (0.6%)	811 (0.5%)
Education level	Primary	45328 (26.5%)	1897 (36.1%)	47225 (26.8%)
	Secondary	75752 (44.3%)	1933 (36.8%)	77685 (44.1%)
	Post-secondary non-tertiary	18405 (10.8%)	517 (9.8%)	18922 (10.7%)
	Tertiary	29224 (17.1%)	797 (15.2%)	30021 (17.0%)
	Missing	2285 (1.3%)	111 (2.1%)	2396 (1.4%)
Townsend deprivation index, quintiles	1 (least deprived)	34294 (20.1%)	927 (17.6%)	35221 (20.0%)
	2	34284 (20.0%)	936 (17.8%)	35220 (20.0%)
	3	34258 (20.0%)	962 (18.3%)	35220 (20.0%)
	4	34171 (20.0%)	1049 (20.0%)	35220 (20.0%)
	5 (most deprived)	33846 (19.8%)	1374 (26.1%)	35220 (20.0%)
	Missing	141 (0.1%)	7 (0.1%)	148 (0.1%)
Household income (in GBP)	Less than 18,000	46821 (27.4%)	1864 (35.5%)	48685 (27.6%)
	18,000 to 30,999	45362 (26.5%)	1268 (24.1%)	46630 (26.5%)
	31,000 to 51,999	29395 (17.2%)	541 (10.3%)	29936 (17.0%)
	52,000 to 100,000	14226 (8.3%)	211 (4.0%)	14437 (8.2%)
	Greater than 100,000	3354 (2.0%)	55 (1.0%)	3409 (1.9%)
	Missing	31836 (18.6%)	1316 (25.0%)	33152 (18.8%)
Smoking status	Never	84921 (49.7%)	2364 (45.0%)	87285 (49.5%)
	Previous	71056 (41.6%)	2336 (44.5%)	73392 (41.6%)
	Current	14011 (8.2%)	497 (9.5%)	14508 (8.2%)
	Missing	1006 (0.6%)	58 (1.1%)	1064 (0.6%)
Alcohol intake	Never	8044 (4.7%)	386 (7.3%)	8430 (4.8%)
	Former drinker	6291 (3.7%)	351 (6.7%)	6642 (3.8%)
	Special occasions only	20538 (12.0%)	745 (14.2%)	21283 (12.1%)
	1-3 times per month	16863 (9.9%)	538 (10.2%)	17401 (9.9%)
	1-2 times per week	40932 (23.9%)	1146 (21.8%)	42078 (23.9%)
	3-4 times per week	37913 (22.2%)	982 (18.7%)	38895 (22.1%)
	Daily or almost daily	40118 (23.5%)	1087 (20.7%)	41205 (23.4%)
	Prefer not to answer	159 (0.1%)	9 (0.2%)	168 (0.1%)
	Missing	136 (0.1%)	11 (0.2%)	147 (0.1%)
Physical activity level	Low (MET minutes ≤ 1200)	46436 (27.2%)	1429 (27.2%)	47865 (27.2%)
	High (MET minutes > 1200)	88584 (51.8%)	2475 (47.1%)	91059 (51.7%)
	Missing	35974 (21.0%)	1351 (25.7%)	37325 (21.2%)
***APOE*-ε4 carrier status**	Non-carrier	123352 (72.1%)	2382 (45.3%)	125734 (71.3%)
	Carrier	42220 (24.7%)	2685 (51.1%)	44905 (25.5%)
	Missing	5422 (3.2%)	188 (3.6%)	5610 (3.2%)
Elevated waist circumference	Present	63888 (37.3%)	2118 (40.3%)	66066 (37.5%)
Elevated triglycerides	Present	74819 (43.8%)	2277 (43.3%)	77096 (43.7%)
Elevated blood pressure*	Present	143196 (83.7%)	4623 (88.0%)	147819 (83.9%)
Elevated HbA1c*	Present	42774 (25.0%)	1757 (33.4%)	44531 (25.3%)
Reduced HDL-cholesterol*	Present	66106 (38.7%)	2573 (49.0%)	68679 (39.0%)

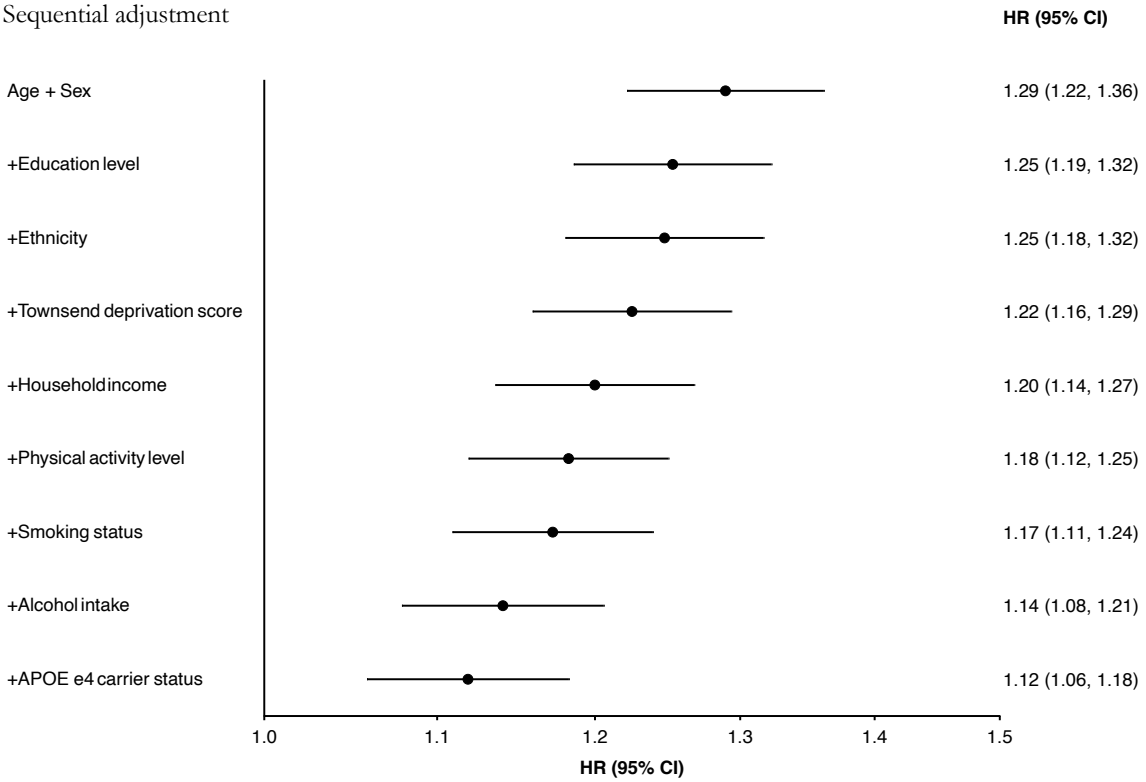
Abbreviations: PRS = Polygenic risk score, APOE = Apolipoprotein, SD = standard deviation, MET = metabolic equivalent of task, GBP = British pound sterling, HbA1c = hemoglobin A1c, HDL = high density lipoprotein. Percentages do not add up to 100 due to rounding.
*Includes medication use

Appendix 3.6: Individual and sequential adjustment of covariates in Cox proportional hazards model investigating the association between MetS and incident dementia

A) Individual adjustment



B) Sequential adjustment



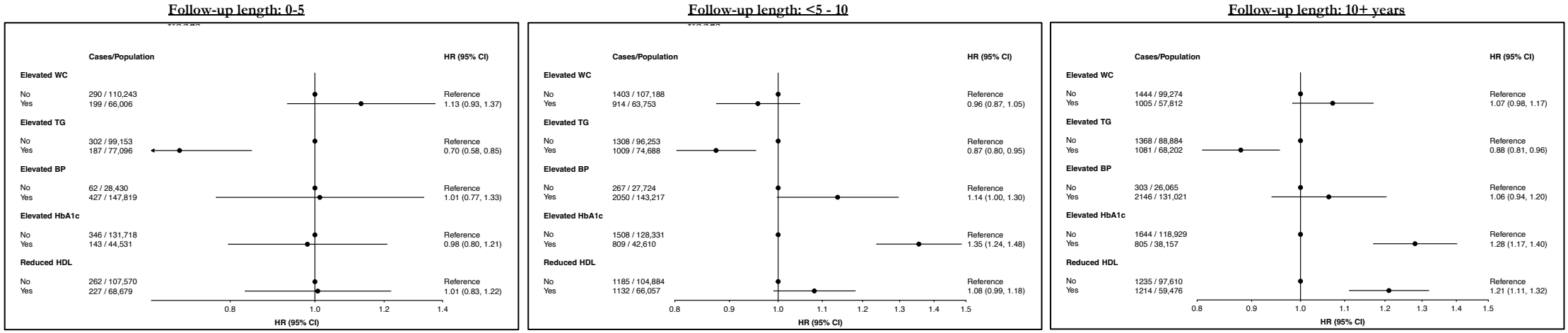
Appendix 3.7: Sensitivity analyses of association between MetS and incident dementia

Sensitivity Analysis Performed	MetS	Cases/Population	HR (95%CI)
Age as a time scale	No	2676 / 102,739	Ref.
	Yes	2579 / 73,510	1.12 (1.07, 1.18)
Excluding Participants in Wales	No	2644 / 98,806	Ref.
	Yes	2556 / 70,229	1.13 (1.07, 1.19)
Additional adjustment for CVD	No	2676 / 102,739	Ref.
	Yes	2579 / 73,510	1.05 (1.01, 1.13)
Treating death as a competing risk	No	2676 / 102,739	Ref.
	Yes	2579 / 73,510	1.09 (1.04, 1.16)
Using NCEP-ATP III criteria to define MetS	No	3012 / 109,739	Ref.
	Yes	2243 / 66,510	1.10 (1.03, 1.16)
Multiple Imputation	No	3348 / 126,471	Ref.
	Yes	3240 / 90,826	1.11 (1.06, 1.17)

CVD = Cardiovascular disease; NCEP-ATP III = National Cholesterol Education Program – Adult Treatment Panel III; MetS = Metabolic syndrome

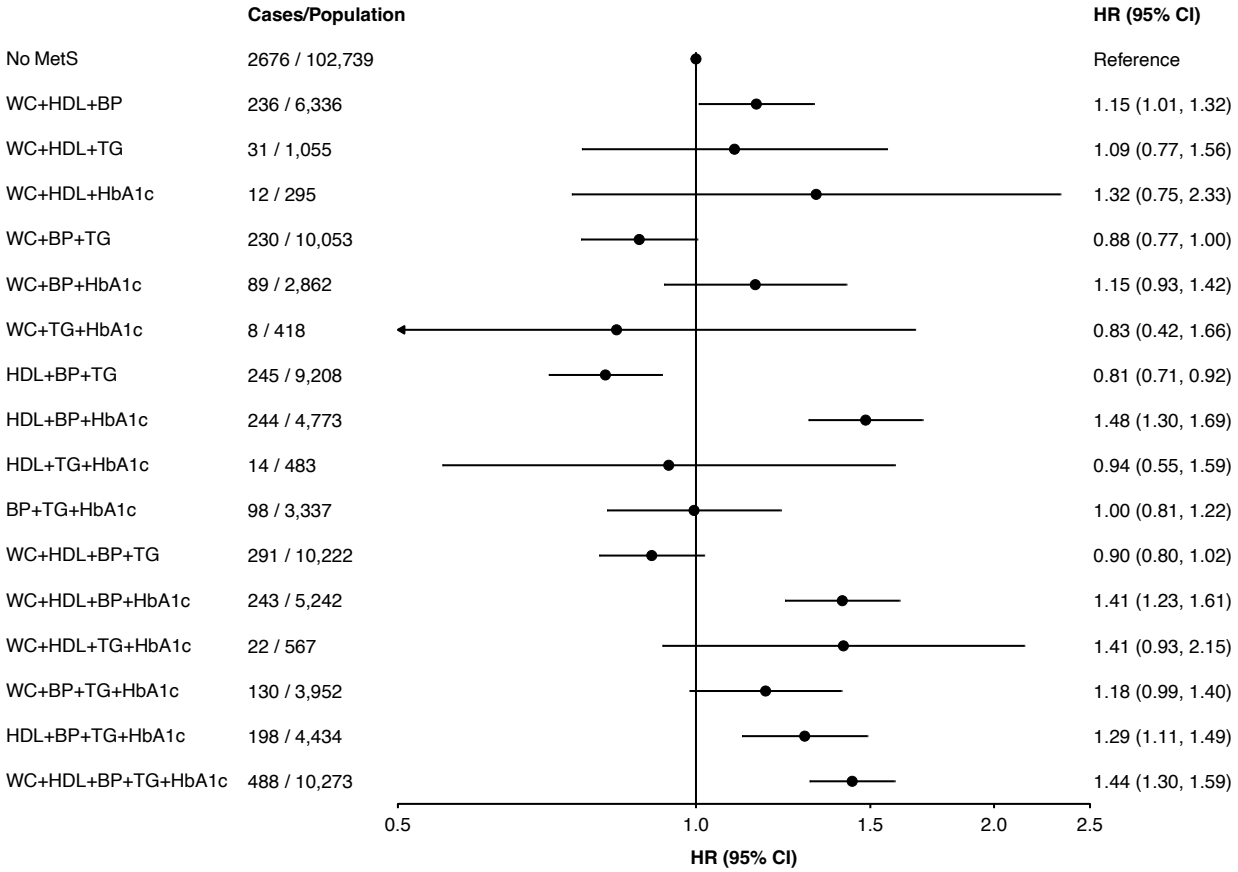
Models adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity, APOE-ε4 carrier status.

Appendix 3.8: Cox proportional hazards models investigating the association between individual MetS components and incident dementia according to varying follow-up length



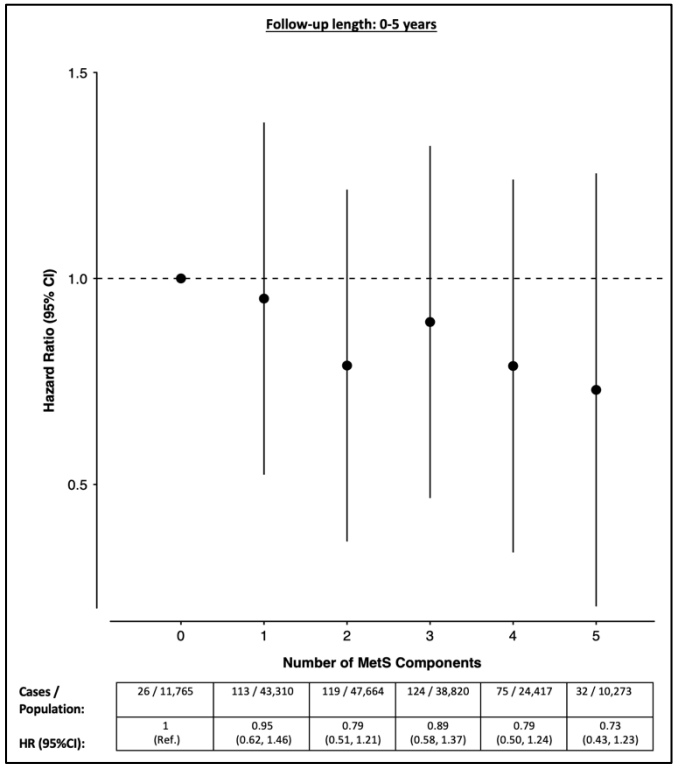
HR = Hazard Ratio, CI = Confidence Interval, WC: Elevated Waist Circumference, HDL: Reduced High-Density Lipoprotein, TG: Elevated Triglycerides, BP: Elevated Blood Pressure, HbA1c: Elevated HbA1c
Models adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity, APOE-ε4 carrier status.

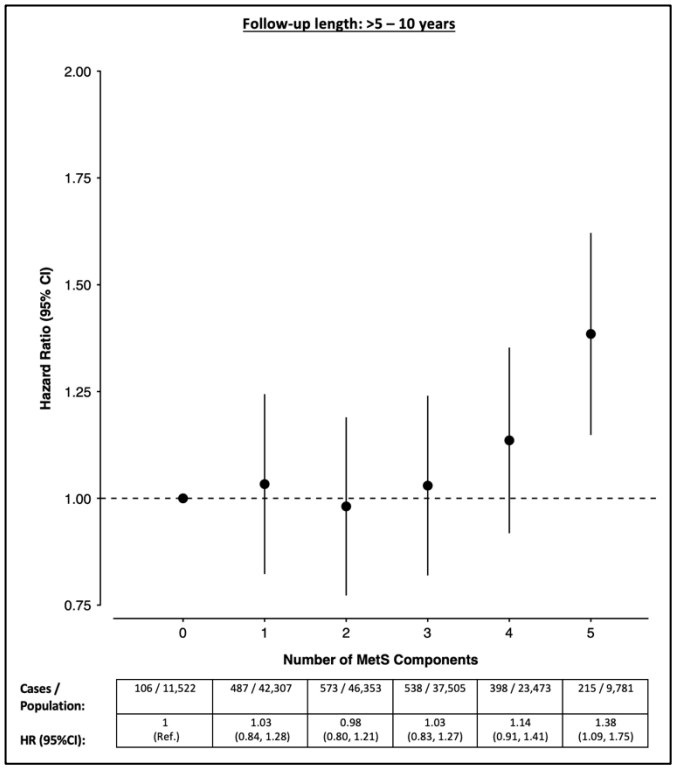
Appendix 3.9: Cox proportional hazards model investigating the association between all possible MetS combinations and incident dementia

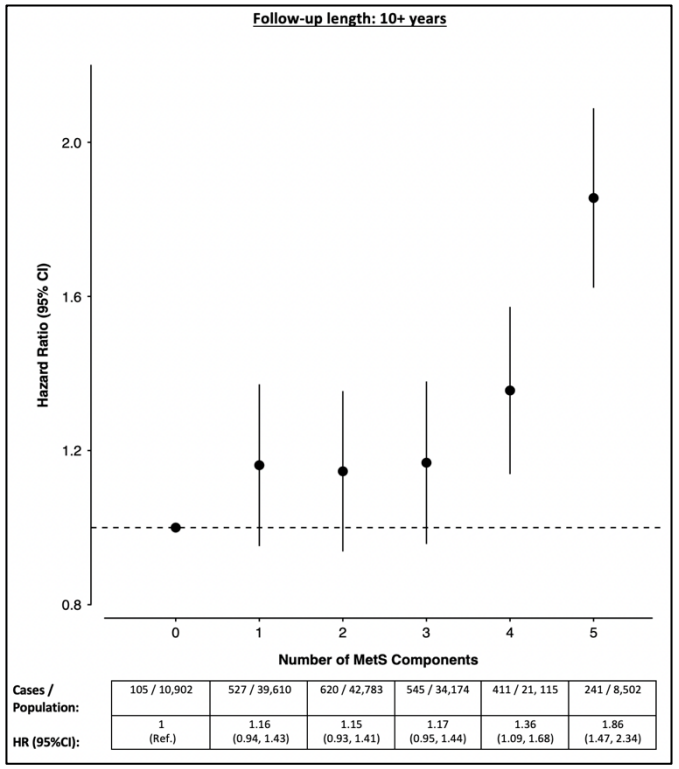


HR = Hazard Ratio, CI = Confidence Interval, WC: Elevated Waist Circumference, HDL: Reduced High-Density Lipoprotein, TG: Elevated Triglycerides, BP: Elevated Blood Pressure, HbA1c: Elevated HbA1c
Model adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity, APOE-ε4 carrier status.

Appendix 3.10: Cox proportional hazards models investigating the association between the number of MetS components and incident dementia according to varying follow-up length







HR = Hazard Ratio, CI = Confidence Interval
Models adjusted for age, sex, ethnicity, Townsend deprivation index, education, household income, smoking status, alcohol intake, physical activity, APOE-ε4 carrier status.

Appendix 4.1: Variables used to define MetS in the EPIC-Norfolk Cohort

MetS component	Harmonized criteria (2009) ≥ 3 *of the following:*	EPIC-Norfolk variable name	Variable description
Elevated waist circumference	Elevated waist circumference: ≥ 102 cm in males and ≥ 88 cm in females	ALT_WAIST_HC1	Waist circumference
Elevated triglycerides	≥ 150 mg/dL (1.7 mmol/L)	TRIGLYC	Triglycerides
Elevated blood pressure	Systolic: ≥130 mmHg and/or Diastolic ≥85 mmHg*, or antihypertensive medication use	ALT_SYSTOLIC1_HC1 ALT_DIASTOLIC1_HC1	Systolic BP Diastolic BP
		ANTIHYP_1HC	Anti-hypertensive drugs
Elevated blood glucose	≥100 mg/dL (≥5.6 mmol/L) †, or drug treatment for elevated glucose level †HbA1c used as a proxy indicator, with cut-offs based on the recommendations of the American Diabetes Association: HbA1c ≥5.7%	HBA1C	Glycated haemoglobin (HbA1c)
		DMDRG_0I DMDRG_1HC INSULIN_1HC	Insulin drugs Diabetes drugs Insulin
Reduced HDL cholesterol	Males: <40 mg/dL (1.0 mmol/L); Females: <50 mg/dL (1.3 mmol/L), or lipid-modifying medications	HDL	HDL cholesterol
		LIPID_1HC	Lipid-modifying medications

MetS = Metabolic syndrome; EPIC = European Prospective Investigation into Cancer; HDL = High-density lipoprotein, BP = Blood pressure, HbA1c = Glycated haemoglobin

Appendix 4.2: International Classification of Disease codes used to ascertain dementia in EPIC-Norfolk

Code Type	Code	Description	AD	VD	FTD	All-Cause Dementia
ICD 10 Code	F00	Dementia in Alzheimer's disease	✓			✓
ICD 10 Code	F00.0	Dementia in Alzheimer's disease with early onset	✓			✓
ICD 10 Code	F00.1	Dementia in Alzheimer's disease with late onset	✓			✓
ICD 10 Code	F00.2	Dementia in Alzheimer's disease, atypical or mixed type	✓			✓
ICD 10 Code	F00.9	Dementia in Alzheimer's disease, unspecified	✓			✓
ICD 10 Code	F01	Vascular dementia		✓		✓
ICD 10 Code	F01.0	Vascular dementia of acute onset		✓		✓
ICD 10 Code	F01.1	Multi-infarct dementia		✓		✓
ICD 10 Code	F01.2	Subcortical vascular dementia		✓		✓
ICD 10 Code	F01.3	Mixed cortical and sub-cortical vascular dementia		✓		✓
ICD 10 Code	F01.8	Other vascular dementia		✓		✓
ICD 10 Code	F01.9	Vascular dementia, unspecified		✓		✓
ICD 10 Code	F02	Dementia in other diseases classified elsewhere				✓
ICD 10 Code	F02.0	Dementia in Pick's disease			✓	✓
ICD 10 Code	F02.1	Dementia in Creutzfeldt-Jakob disease			✓	✓
ICD 10 Code	F02.2	Dementia in Huntington's disease			✓	✓
ICD 10 Code	F02.3	Dementia in Parkinson's disease			✓	✓
ICD 10 Code	F02.4	Dementia in HIV disease			✓	✓
ICD 10 Code	F02.8	Dementia in other specified diseases classified elsewhere				✓
ICD 10 Code	F03	Unspecified dementia				✓
ICD 10 Code	F05.1	Delirium superimposed on dementia				✓
ICD 10 Code	F10.6	Mental and behavioural disorders due to use of alcohol - amnesic syndrome				✓
ICD 10 Code	G30	Alzheimer's disease	✓			✓
ICD 10 Code	G30.0	Alzheimer's disease with early onset	✓			✓
ICD 10 Code	G30.1	Alzheimer's disease with late onset	✓			✓
ICD 10 Code	G30.8	Other Alzheimer's disease	✓			✓
ICD 10 Code	G30.9	Alzheimer's disease unspecified	✓			✓
ICD 10 Code	G31.0	Circumscribed brain atrophy			✓	✓
ICD 10 Code	G31.1	Senile degeneration of brain				✓
ICD 10 Code	G31.8	Other specified degenerative diseases of nervous system				✓

Abbreviations: AD = Alzheimer's disease, VaD = Vascular dementia, FTD = Frontotemporal dementia, ICD, International Classification of Disease

Appendix 4.3: Characteristics by dementia status at end of follow-up in EPIC-Norfolk

Characteristic	No Dementia (N = 17,497)[a]	Dementia (N = 2,653)[a]	Overall (N = 20,150)[a]
Follow-up time (in years)	19.0 (6.5)	17.4 (4.7)	18.8 (6.3)
Age	61.9 (7.5)	66.9 (6.1)	62.6 (7.5)
Sex			
Male	8,256 (47%)	1,037 (39%)	9,293 (46%)
Female	9,241 (53%)	1,616 (61%)	10,857 (54%)
Education level			
No qualifications	6,956 (40%)	1,287 (49%)	8,243 (41%)
Lower secondary	1,700 (9.7%)	225 (8.5%)	1,925 (9.6%)
Upper secondary	6,846 (39%)	904 (34%)	7,750 (38%)
Higher education or equivalent	1,995 (11%)	237 (8.9%)	2,232 (11%)
Socioeconomic status			
1 (least deprived)	3,625 (21%)	525 (20%)	4,150 (21%)
2	3,499 (20%)	515 (19%)	4,014 (20%)
3	3,453 (20%)	504 (19%)	3,957 (20%)
4	3,474 (20%)	541 (20%)	4,015 (20%)
5 (most deprived)	3,446 (20%)	568 (21%)	4,014 (20%)
Smoking status			
Current	1,963 (11%)	213 (8.0%)	2,176 (11%)
Former	7,738 (44%)	1,209 (46%)	8,947 (44%)
Never	7,796 (45%)	1,231 (46%)	9,027 (45%)
Physical activity level			
Inactive	5,837 (33%)	1,036 (39%)	6,873 (34%)
Moderately inactive	4,925 (28%)	767 (29%)	5,692 (28%)
Moderately active	3,798 (22%)	481 (18%)	4,279 (21%)
Active	2,937 (17%)	369 (14%)	3,306 (16%)
Alcohol intake frequency			
Current	14,914 (85%)	2,153 (81%)	17,067 (85%)
Former	1,702 (9.7%)	295 (11%)	1,997 (9.9%)
Never	881 (5.0%)	205 (7.7%)	1,086 (5.4%)
***APOE*-ε4 carrier**	4,506 (26%)	1,212 (46%)	5,718 (28%)
Elevated WC	4,904 (28%)	786 (30%)	5,690 (28%)
Elevated TG	8,477 (48%)	1,343 (51%)	9,820 (49%)
Elevated BP	12,069 (69%)	2,024 (76%)	14,093 (70%)
Elevated HbA1c	4,847 (28%)	903 (34%)	5,750 (29%)
Reduced HDL	4,069 (23%)	661 (25%)	4,730 (23%)
MetS at baseline	5,965 (34%)	1,054 (40%)	7,019 (35%)
# of MetS Components Present			
0	1,975 (11%)	191 (7.2%)	2,166 (11%)
1	4,704 (27%)	641 (24%)	5,345 (27%)
2	4,853 (28%)	767 (29%)	5,620 (28%)
3	3,475 (20%)	603 (23%)	4,078 (20%)
4	1,892 (11%)	342 (13%)	2,234 (11%)
5	598 (3.4%)	109 (4.1%)	707 (3.5%)

Abbreviations: MetS = Metabolic syndrome; WC = Waist circumference; TG = Triglycerides; BP = Blood pressure; HbA1c = Glycated haemoglobin A1C; HDL = High-density Lipoprotein

[a]Mean (SD); n (%).

Appendix 4.4: Characteristics of participants with non-missing and missing data

Characteristic	Non-Missing[a] (N= 13,139)[b]	Missing (N= 7,011)[b]	Overall (N= 20,150)[b]
Follow-up time (in years)	19.0 (6.1)	18.7 (8.2)	18.8 (6.3)
Age	62.3 (7.5)	63.1 (7.5)	62.56 (7.5)
Sex			
Male	6,080 (46%)	3,213 (46%)	9,293 (46%)
Female	7,059 (54%)	3,798 (54%)	10,857 (54%)
Education level			
No qualifications	5,129 (39%)	3,105 (44%)	8,234 (41%)
Lower secondary	1,286 (9.8%)	638 (9.1%)	1,924 (9.6%)
Upper secondary	5,182 (39%)	2,562 (37%)	7,744 (38%)
Higher education or equivalent	1,542 (12%)	689 (9.9%)	2,231 (11%)
Missing	0	17	17
Socioeconomic status			
1 (least deprived)	2,727 (21%)	1,288 (18%)	4,015 (20%)
2	2,755 (21%)	1,259 (18%)	4,014 (20%)
3	2,568 (20%)	1,446 (21%)	4,014 (20%)
4	2,553 (19%)	1,461 (21%)	4,014 (20%)
5 (most deprived)	2,536 (19%)	1,478 (21%)	4,014 (20%)
Missing	0	79 (1.1%)	79 (0.4%)
Smoking status			
Current	1,403 (11%)	753 (11%)	2,156 (11%)
Former	5,819 (44%)	3,050 (45%)	8,869 (44%)
Never	5,917 (45%)	3,004 (44%)	8,921 (45%)
Missing	0	204	204
Physical activity level			
Inactive	4,343 (33%)	2,530 (36%)	6,873 (34%)
Moderately inactive	3,689 (28%)	2,003 (29%)	5,692 (28%)
Moderately active	2,850 (22%)	1,429 (20%)	4,279 (21%)
Active	2,257 (17%)	1,049 (15%)	3,306 (16%)
Alcohol intake frequency			
Current	11,239 (86%)	5,757 (84%)	16,996 (85%)
Former	1,218 (9.3%)	753 (11%)	1,971 (9.8%)
Never	682 (5.2%)	380 (5.5%)	1,062 (5.3%)
Missing	0	121	121
***APOE*-ε4 carrier**	3,751 (29%)	947 (28%)	4,698 (28%)
Missing	0	3,594	3,594
Dementia at follow-up	1,684 (13%)	969 (14%)	2,653 (13%)
# of Missing MetS Components			
0	7,060 (54%)	835 (12%)	7,895 (39%)
1	5,898 (45%)	4,474 (64%)	10,372 (51%)
2	181 (1.4%)	422 (6.0%)	603 (3.0%)
3	0	1,261 (18%)	1,261 (6.3%)
4	0	10 (0.1%)	10 (<0.1%)
5	0	9 (0.1%)	9 (<0.1%)

Abbreviations: APOE = Apolipoprotein E; MetS = Metabolic syndrome

[a]Sample consists of participants with complete data on all 5 MetS components and covariates (i.e., complete cases), and those who had missing values on MetS components but where their MetS status could still be ascertained. For instance, if a participant had missing values on 2 out of 5 components, but still met the criteria for MetS based on the 3 components they had available (i.e., standard threshold required for MetS diagnosis), then these participants were included in this analysis.

[b]Mean (SD); n (%);

Appendix 4.5: Association between MetS and incident all-cause dementia among a complete-case sample (N = 13,139)

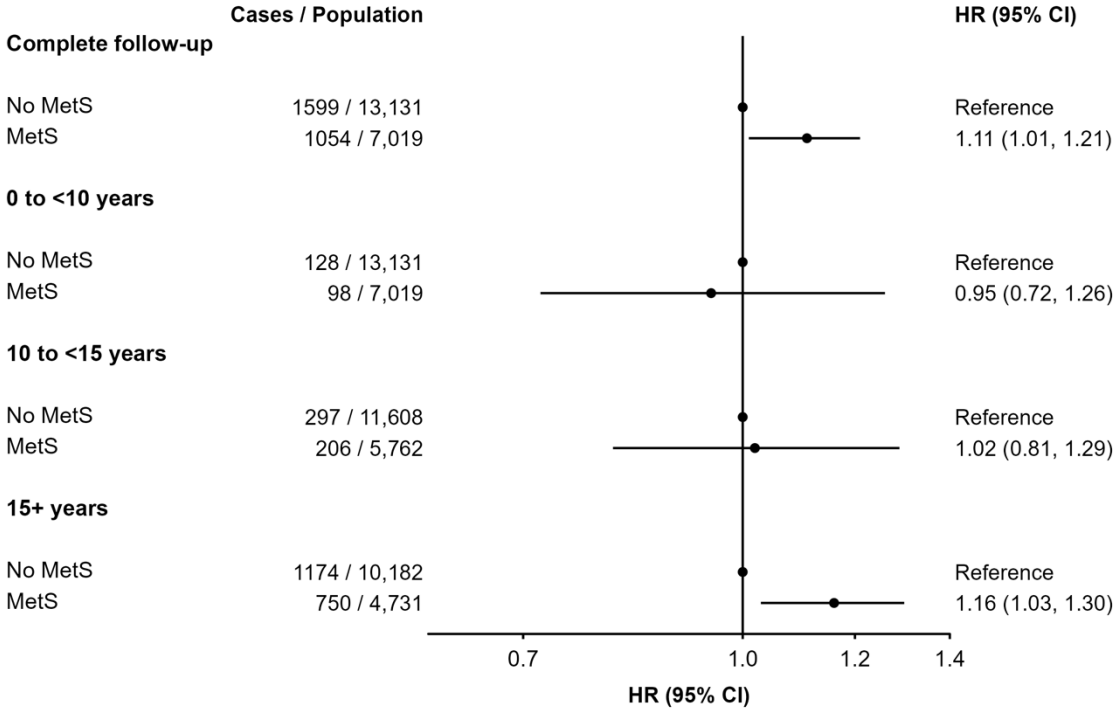
Complete-Case Sample[a]	Cases/Population	HR (95%CI)
MetS		
No	1,009 / 8,567	Ref.
Yes	675 / 4,572	1.11 (1.01, 1.22)

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, , Ref. = Reference group, MetS = Metabolic syndrome

Model adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake frequency, physical activity, APOE-ε4 carrier status.

[a]Sample consisted of participants with complete data on all five MetS components and covariates (i.e., complete cases), and those who had missing values on MetS components but where their MetS status could still be ascertained. For instance, if a participant had missing values on two out of five components, but still met the criteria for MetS based on the three components they had available (i.e., standard threshold required for MetS diagnosis), then these participants were included in this analysis.

Appendix 4.6: Association between MetS and incident all-cause dementia according to different follow-up periods



Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, MetS = Metabolic syndrome
Models adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake frequency, physical activity, APOE-ε4 carrier status.

Appendix 4.7: Association between MetS and incident all-cause dementia accounting for death as a competing risk

	Cases/Population	HR (95% CI)
Competing Risk Analysis		
Full sample		
No MetS	1,599 / 13,131	Ref.
MetS	1,054 / 7,019	1.10 (1.02, 1.19)
Age: 50-59 years		
No MetS	268 / 5,976	Ref.
MetS	117 / 2,109	1.10 (0.85, 1.41)
Age: 60-59 years		
No MetS	786 / 4,864	Ref.
MetS	550 / 3,076	1.20 (1.04, 1.39)
Age: 70-79 years		
No MetS	545 / 2,291	Ref.
MetS	387 / 1,834	0.95 (0.80, 1.13)

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, , Ref. = Reference group, MetS = Metabolic syndrome

Model adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake frequency, physical activity, APOE-ε4 carrier status.

Appendix 4.8: Detailed results for Figure 4.3

Number of MetS Components	Cases / Population	HR (95% CI)	p for trend
All Ages			
0	191 / 2,166	Ref.	
1	641 / 5,345	1.02 (0.84, 1.22)	
2	767 / 5,620	1.04 (0.87, 1.25)	
3	603 / 4,078	1.12 (0.91, 1.37)	**0.033**
4	342 / 2,234	1.15 (0.91, 1.46)	
5	109 / 707	1.16 (0.80, 1.68)	
50-59 years			
0	66 / 1,422	Ref.	
1	112 / 2,470	0.91 (0.66, 1.26)	
2	90 / 2,084	0.89 (0.62, 1.26)	
3	64 / 1,309	0.93 (0.65, 1.34)	0.3
4	32 / 630	0.97 (0.56, 1.66)	
5	21 / 170	1.88 (0.98, 3.60)	
60-69 years			
0	83 / 586	Ref.	
1	323 / 1,971	1.15 (0.87, 1.50)	
2	380 / 2,307	1.13 (0.88, 1.46)	
3	316 / 1,770	1.30 (0.94, 1.79)	**0.004**
4	185 / 990	1.47 (1.04, 2.09)	
5	49 / 316	1.30 (0.74, 2.26)	
70-79 years			
0	42 / 158	Ref.	
1	206 / 904	0.94 (0.65, 1.36)	
2	297 / 1,229	1.05 (0.72, 1.52)	
3	223 / 999	1.01 (0.68, 1.49)	0.6
4	125 / 614	0.91 (0.61, 1.36)	
5	39 / 221	0.88 (0.51, 1.51)	

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, MetS = Metabolic syndrome, Ref. = Reference Group
Models adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake frequency, physical activity, APOE-ε4 carrier status

Appendix 4.9: Estimation of trajectories of MetS duration - Model fit statistics

Trajectories	Log-likelihood	Number of parameters	BIC	% of participants within each group
1	19348.33	4	38734.47	100
2	-17518.30	8	35112.22	38.523048; 61.47695
3	-14603.76	12	29320.97	36.171214; 41.63531; 22.19348
4	-14516.73	16	29184.73	49.498275; 28.30825; 10.39511; 11.79837
5	No convergence			

Abbreviations: BIC = Bayesian Information Criterion

Appendix 4.10: Association between trajectories of MetS duration and incident all-cause dementia after accounting for unequal time intervals between health checks

	Cases / Population	HR (95% CI)	p-value
Trajectories of MetS duration[a] (data: attended ≥2 health checks)			
Consistently Low MetS	838 / 6,600	Ref.	
Increasing MetS	259 / 2,545	1.02 (0.89, 1.18)	0.8
Prolonged MetS	513 / 3,611	1.26 (1.12, 1.40)	**<0.001**

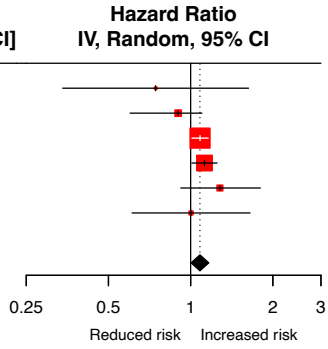
Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, MetS = Metabolic syndrome, Ref. = Reference Group
Models adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake frequency, physical activity, APOE-ε4 carrier status.
[a]Unequal time intervals between health checks were accounted for in the creation of these duration trajectories

Appendix 5.1: Subgroup meta-analysis according to age group (restricted to studies of participants aged 65+ years)

A) All–cause dementia

Study Author, Year	Weight (%)	Hazard Ratio [95% CI]
Forti, 2010 (65–74 years)	0.89%	0.74 [0.34, 1.63]
Muller, 2007	5.69%	0.90 [0.60, 1.10]
Qureshi, 2023 (UK Biobank)	53.72%	1.08 [1.01, 1.16]
Qureshi, 2024 (EPIC–Norfolk)	32.82%	1.12 [1.01, 1.25]
Raffaitin, 2009	4.69%	1.28 [0.92, 1.80]
Solfrizzi, 2010	2.19%	1.00 [0.61, 1.65]
Total (95% CI)		**1.08 [1.00, 1.16]**

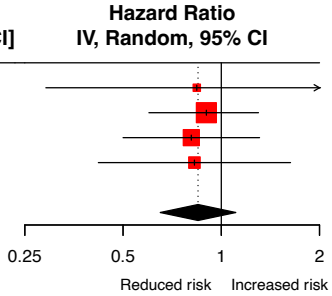
Heterogeneity: $Tau^2 = 0.001$; $Chi^2 = 5.90$, df = 5 (P = 0.32); $I^2 = 15\%$
Test for overall effect: Z = 2.06 (P = 0.04)



B) Alzheimer's disease

Study Author, Year	Weight (%)	Hazard Ratio [95% CI]
Forti, 2010 (65–74 years)	6.27%	0.84 [0.29, 2.44]
Muller, 2007	47.59%	0.90 [0.60, 1.30]
Raffaitin, 2009	30.67%	0.81 [0.50, 1.31]
Solfrizzi, 2010	15.47%	0.83 [0.42, 1.63]
Total (95% CI)		**0.85 [0.65, 1.11]**

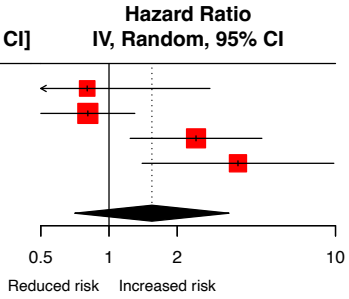
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.08$, df = 3 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = –1.21 (P = 0.23)



C) Vascular Dementia

Study Author, Year	Weight (%)	Hazard Ratio [95% CI]
Forti, 2010 (65–74 years)	18.54%	0.80 [0.23, 2.79]
Muller, 2007	30.92%	0.81 [0.50, 1.30]
Raffaitin, 2009	27.85%	2.42 [1.24, 4.73]
Solfrizzi, 2010	22.69%	3.71 [1.40, 9.83]
Total (95% CI)		**1.55 [0.71, 3.39]**

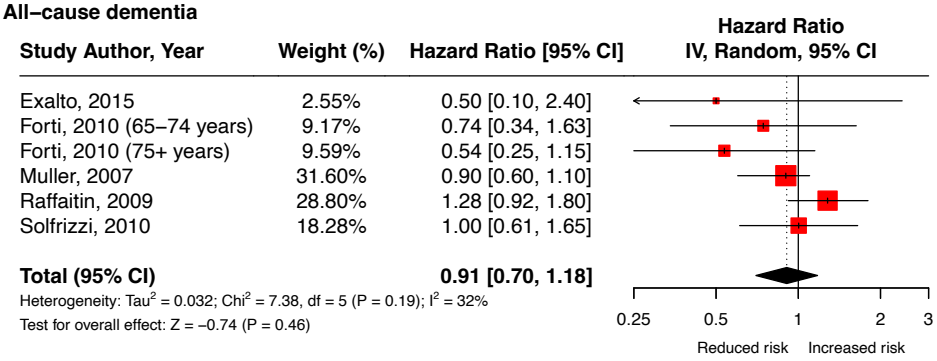
Heterogeneity: $Tau^2 = 0.458$; $Chi^2 = 12.18$, df = 3 (P < 0.01); $I^2 = 75\%$
Test for overall effect: Z = 1.09 (P = 0.28)



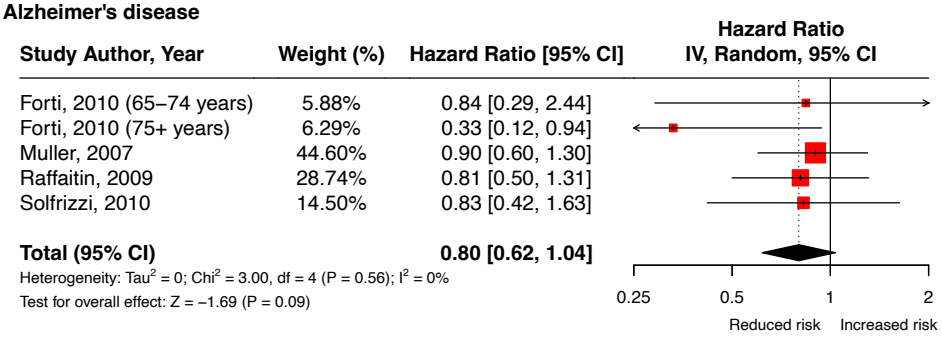
Abbreviations: CI = Confidence Interval; df = Degrees of Freedom

Appendix 5.2: Subgroup meta-analysis according to metabolic syndrome criteria used in studies – Studies using the NCEP-ATP III criteria

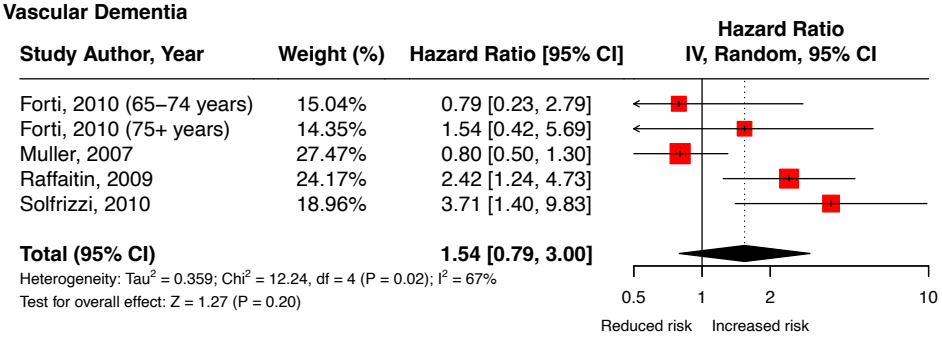
A) All–cause dementia



B) Alzheimer's disease



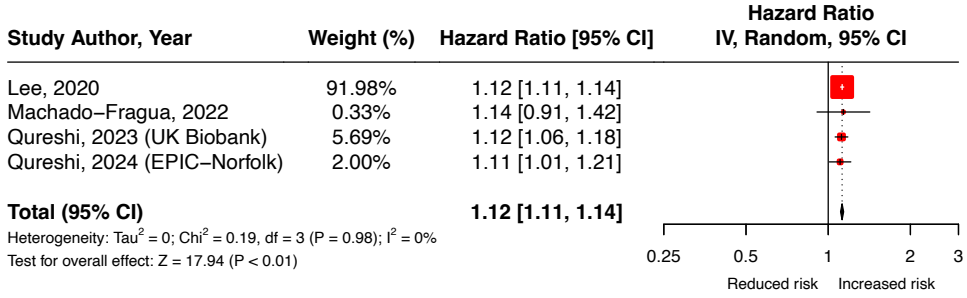
C) Vascular Dementia



Abbreviations: CI = Confidence Interval; df = Degrees of Freedom

Appendix 5.3: Subgroup meta-analysis according to metabolic syndrome criteria used in studies – Studies using the 2009 Harmonized Criteria

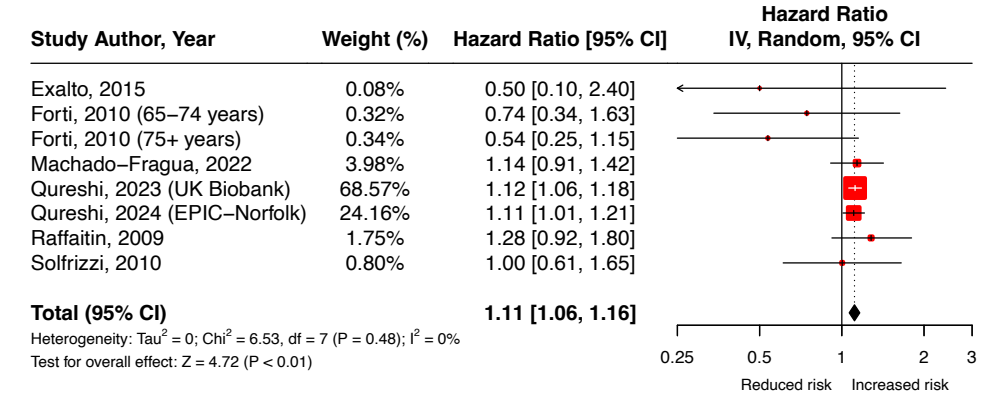
A) All–cause dementia



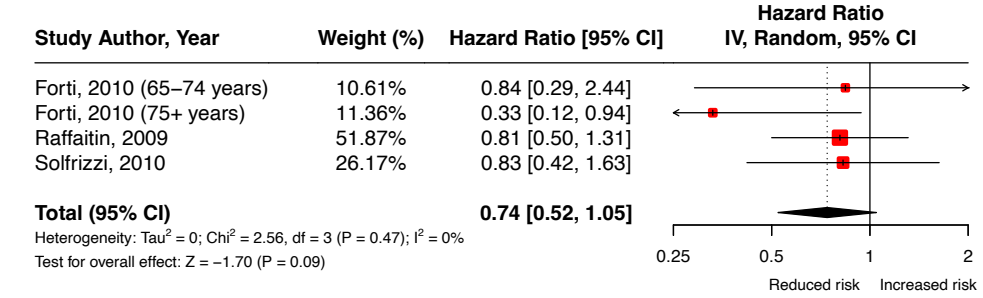
Abbreviations: CI = Confidence Interval; df = Degrees of Freedom

Appendix 5.4: Subgroup meta-analysis according to ethnicity – Predominantly White populations

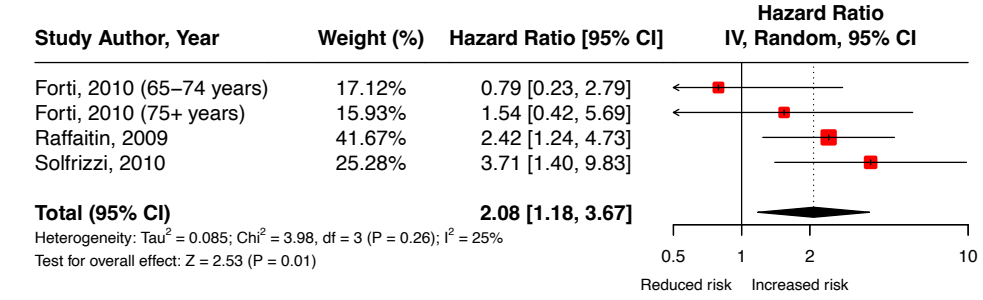
A) All–cause dementia



B) Alzheimer's disease

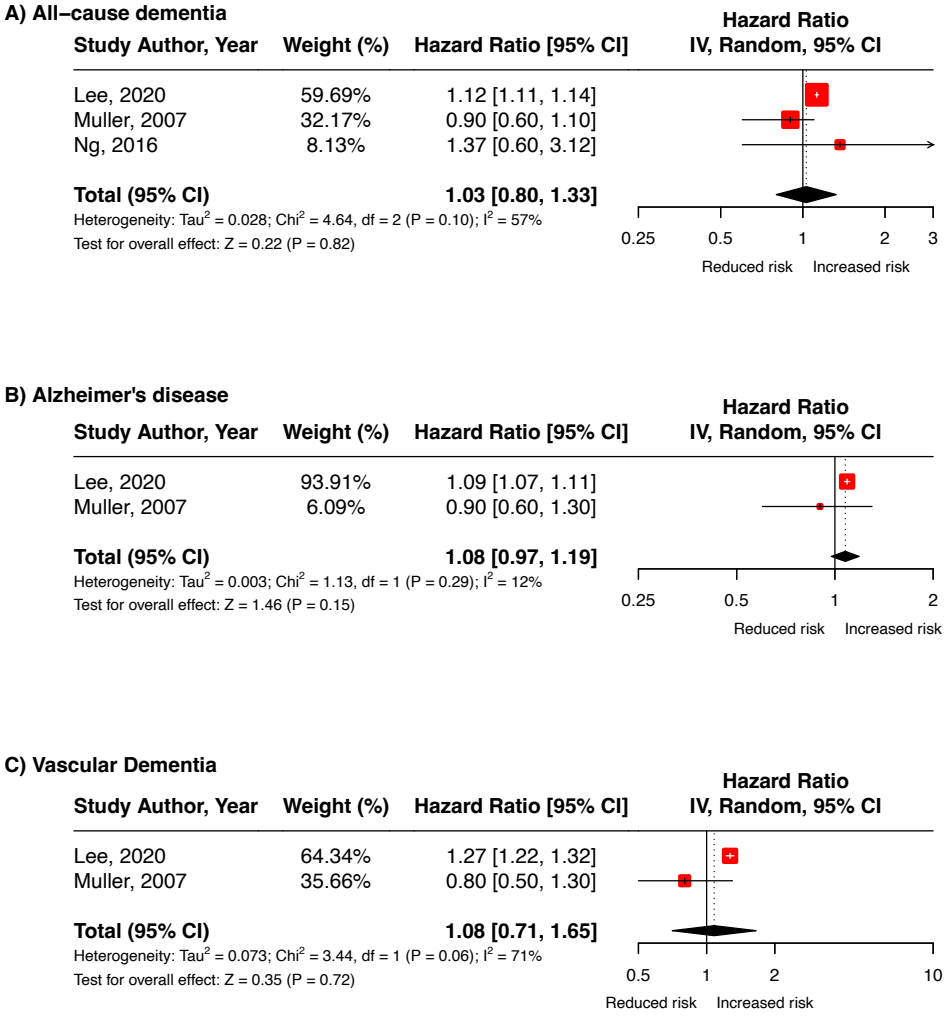


C) Vascular Dementia



Abbreviations: CI = Confidence Interval; df = Degrees of Freedom

Appendix 5.5: Subgroup meta-analysis according to ethnicity – Predominantly Non-White populations



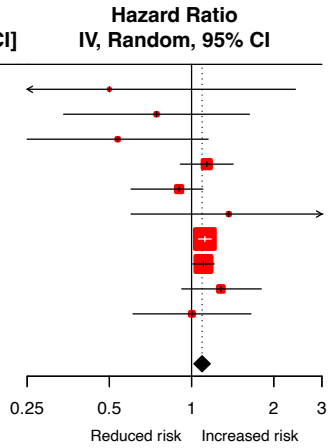
Abbreviations: CI = Confidence Interval; df = Degrees of Freedom

Appendix 5.6: Subgroup meta-analysis according to study quality – Excluding weak studies

A) All–cause dementia

Study Author, Year	Weight (%)	Hazard Ratio [95% CI]
Exalto, 2015	0.19%	0.50 [0.10, 2.40]
Forti, 2010 (65–74 years)	0.77%	0.74 [0.34, 1.63]
Forti, 2010 (75+ years)	0.81%	0.54 [0.25, 1.15]
Machado–Fragua, 2022	8.40%	1.14 [0.91, 1.42]
Muller, 2007	4.81%	0.90 [0.60, 1.10]
Ng, 2016	0.69%	1.37 [0.60, 3.12]
Qureshi, 2023 (UK Biobank)	47.42%	1.12 [1.06, 1.18]
Qureshi, 2024 (EPIC–Norfolk)	31.07%	1.11 [1.01, 1.21]
Raffaitin, 2009	3.97%	1.28 [0.92, 1.80]
Solfrizzi, 2010	1.87%	1.00 [0.61, 1.65]
Total (95% CI)		**1.09 [1.02, 1.17]**

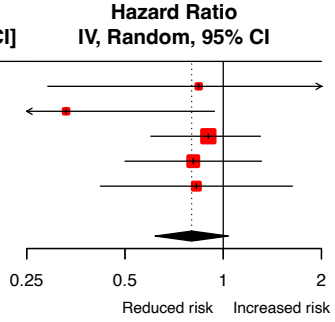
Heterogeneity: $Tau^2 = 0.002$; $Chi^2 = 10.84$, df = 9 (P = 0.29); $I^2 = 17\%$
Test for overall effect: Z = 2.52 (P = 0.01)



B) Alzheimer's disease

Study Author, Year	Weight (%)	Hazard Ratio [95% CI]
Forti, 2010 (65–74 years)	5.88%	0.84 [0.29, 2.44]
Forti, 2010 (75+ years)	6.29%	0.33 [0.12, 0.94]
Muller, 2007	44.60%	0.90 [0.60, 1.30]
Raffaitin, 2009	28.74%	0.81 [0.50, 1.31]
Solfrizzi, 2010	14.50%	0.83 [0.42, 1.63]
Total (95% CI)		**0.80 [0.62, 1.04]**

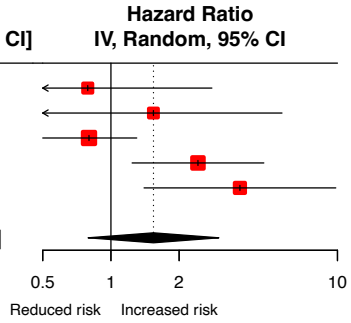
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.00$, df = 4 (P = 0.56); $I^2 = 0\%$
Test for overall effect: Z = −1.69 (P = 0.09)



C) Vascular Dementia

Study Author, Year	Weight (%)	Hazard Ratio [95% CI]
Forti, 2010 (65–74 years)	15.04%	0.79 [0.23, 2.79]
Forti, 2010 (75+ years)	14.35%	1.54 [0.42, 5.69]
Muller, 2007	27.47%	0.80 [0.50, 1.30]
Raffaitin, 2009	24.17%	2.42 [1.24, 4.73]
Solfrizzi, 2010	18.96%	3.71 [1.40, 9.83]
Total (95% CI)		**1.54 [0.79, 3.00]**

Heterogeneity: $Tau^2 = 0.359$; $Chi^2 = 12.24$, df = 4 (P = 0.02); $I^2 = 67\%$
Test for overall effect: Z = 1.27 (P = 0.20)



Abbreviations: CI = Confidence Interval; df = Degrees of Freedom

Appendix 5.7: Egger's test results for publication bias in meta-analyses of all-cause dementia

Outcome	t-value	Degrees of freedom	p-value	Bias estimate	Standard error	Tau^2
All-cause dementia	-1.97	9	0.0798	-0.56	0.2838	0.691

Appendix 6.1: Variables and medication codes used to define MetS in the UK Biobank cohort

Metabolic syndrome component	Harmonized Criteria (2009) *Three or more of the following:*	UKB data field ID	Field code description
Elevated waist circumference	Elevated waist circumference: ≥ 102 cm in males and ≥ 88 cm in females	48	Waist circumference
Elevated triglycerides	≥ 150 mg/dL (1.7 mmol/L) or lipid-modifying medication use	30870	Triglycerides Blood Biochemistry;
		20003	ATC Codes starting with: C10
Elevated blood pressure	Systolic: ≥130 mmHg and/or Diastolic ≥85 mmHg*, or antihypertensive medication use *In UKB, BP was measured twice by trained nurses after participants had been at rest for at least 5 minutes. Individual systolic and diastolic BP measurements were averaged within a visit. Automated BP readings were the preferred source of data. However, if this was unavailable, manual readings were used	4080, 4079; 93,94	Systolic BP - automated reading, Diastolic BP - automated reading; Systolic BP - manual reading, Diastolic BP - manual reading
		20003	ATC Codes starting with: C02, C03, C07, C08, C09
Elevated blood glucose	≥100 mg/dL (≥5.6 mmol/L) †, or drug treatment for elevated glucose level †HbA1c used as a proxy indicator, with cut-offs based on the recommendations of the American Diabetes Association: HbA1c ≥5.7%	30750	Glycated haemoglobin (HbA1c)
		20003	ATC Codes starting with: A10
Reduced HDL-cholesterol	Males: <40 mg/dL (1.0 mmol/L); Females: <50 mg/dL (1.3 mmol/L)	30760	HDL-cholesterol

UKB = UK Biobank, ATC = Anatomical Therapeutic Chemical, HDL = High-density lipoprotein, BP = Blood pressure, HbA1c = Glycated haemoglobin

Appendix 6.2: Detailed description of UK Biobank medication codes (mapped to ATC codes) used to define MetS components

UK Biobank Drug Category	UK Biobank Drug Name	UK Biobank Code	ATC Code
LIPID-MODIFYING MEDICATIONS			
atorvastatin	Atorvastatin	1141146234	C10AA05
lipitor 10mg tablet	Atorvastatin	1141146138	C10AA05
rosuvastatin	Rosuvastatin	1141192410	C10AA07
crestor 10mg tablet	Rosuvastatin	1141192414	C10AA07
simvastatin	Simvastatin	1140861958	C10AA01
simvador 10mg tablet	Simvastatin	1141188146	C10AA01
zocor 10mg tablet	Simvastatin	1140881748	C10AA01
pravastatin	Pravastatin	1140888648	C10AA03
lipostat 10mg tablet	Pravastatin	1140861970	C10AA03
ezetimibe	Ezetimibe	1141192736	C10AX09
ezetrol 10mg tablet	Ezetimibe	1141192740	C10AX09
fenofibrate	Fenofibrate	1140861954	C10AB05
lipantil micro 67mg capsule	Fenofibrate	1141162544	C10AB05
supralip 160mg m/r tablet	Fenofibrate	1141172214	C10AB05
fluvastatin	Fluvastatin	1140888594	C10AA04
lescol 20mg capsule	Fluvastatin	1140864592	C10AA04
gemfibrozil	Gemfibrozil	1140861856	C10AB04
omacor 1g capsule	Omega-3-Acid Ethyl Esters	1141181868	C10AX06
bezafibrate	Bezafibrate	1140861924	C10AB02
questran 4g/sachet powder	Cholestyramine	1140861936	C10AC01
colestyramine	Cholestyramine	1140909780	C10AC01
ciprofibrate	Ciprofibrate	1140862026	C10AB08
bezalip-mono 400mg m/r tablet	Bezafibrate	1140861928	C10AB02
bezalip 200mg tablet	Bezafibrate	1140861926	C10AB02
niacin	Niacin	1140910670	C04AC01 | C10AD02
niaspan 500mg m/r tablet	Niacin	1141188546	C10AD02
nicotinic acid product	Niacin	1140861868	C04AC01 | C10AD02
cholestyramine	Cholestyramine	1140865576	C10AC01
fibrazate xl 400mg m/r tablet	Bezafibrate	1141201306	C10AB02
colestyramine product	Cholestyramine	1141180734	C10AC01
bezafibrate product	Bezafibrate	1141157260	C10AB02
modalim 100mg tablet	Ciprofibrate	1140862028	C10AB08
zimbacol xl 400mg m/r tablet	Bezafibrate	1141171548	C10AB02
colestipol	Colestipol	1140888590	C10AC02
colestid 5g/sachet granules	Colestipol	1140861848	C10AC02

acipimox	Acipimox	1140861892	C10AD06
colestyramine+aspartame 4g/sachet powder	Cholestyramine	1141180722	C10AC01
ANTIHYPERTENSIVE MEDICATIONS			
hydralazine	Hydralazine	1140888686	C02DB02
moxonidine	Moxonidine	1140928284	C02AC05
physiotens 200micrograms tablet	Moxonidine	1140928290	C02AC05
minoxidil	Minoxidil	1140860532	C02DC01 |D11AX01
doxazosin	Doxazosin	1140879778	C02CA04
methyldopa	Methyldopa	1140860470	C02AB
cardura 1mg tablet	Doxazosin	1140860690	C02CA04
doxadura 1mg tablet	Doxazosin	1141194372	C02CA04
clonidine	Clonidine	1140883468	C02AC01 |N02CX02 |S01EA04
indoramin	Indoramin	1140879782	C02CA02
prazosin	Prazosin	1140879794	C02CA01
hypovase 500mcg tablet	Prazosin	1140860580	C02CA01
indapamide	Indapamide	1140866078	C03BA11
natrilix sr 1.5mg m/r tablet	Indapamide	1141146378	C03BA11
hydrochlorothiazide	Hydrochlorothiazide	1140866162	C03AA03
furosemide	Furosemide	1140909708	C03CA01
frusemide	Furosemide	1140866116	C03CA01
spironolactone	Spironolactone	1140866236	C03DA01
spirolone 25mg tablet	Spironolactone	1140866318	C03DA01
chlortalidone	Chlorthalidone	1140909706	C03BA04
eplerenone	Eplerenone	1141201244	C03DA04
hygroton 50mg tablet	Chlorthalidone	1140866146	C03BA04
metolazone	Metolazone	1140866092	C03BA08
bendroflumethiazide	Bendroflumethiazide	1141194794	C03AA01
bendrofluazide	Bendroflumethiazide	1140866122	C03AA01
co-amilofruse	Amiloride |Furosemide	1140923402	C03EB01
bumetanide	Bumetanide	1140866280	C03CA02
co-amilozide	Amiloride |Hydrochlorothiazide	1140923276	C03EA01
amiloride	Amiloride	1140888512	C03DB01
bendroflumethiazide+potassium 2.5mg/7.7mmol m/r tablet	Bendroflumethiazide |Potassium	1141194800	C03AB01
frumil tablet	Amiloride |Furosemide	1140866406	C03CA01
bendrofluazide+potassium 2.5mg/7.7mmol m/r tablet	Bendroflumethiazide |Potassium	1140866450	C03AB01

bzt - bendrofluazide	Bendroflumethiazide	1140910442	C03AA01
dyazide tablet	Triamterene |Hydrochlorothiazide	1140866402	C03EA01
moduretic tablet	Amiloride |Hydrochlorothiazide	1140866420	C03EA01
navispare tablet	Amiloride |Cyclopenthiazide	1140866352	C03EA07
co-triamterzide	Triamterene |Hydrochlorothiazide	1140923272	C03EA01
torasemide	Torasemide	1140888496	C03CA04
moduret 25 tablet	Amiloride |Hydrochlorothiazide	1140866416	C03EA01
burinex a tablet	Bumetanide	1140866356	C03CA02
xipamide	Xipamide	1140866108	C03BA10
cyclopenthiazide	Cyclopenthiazide	1140866156	C03AA07
bisoprolol	Bisoprolol	1140879760	C07AB07
cardicor 1.25mg tablet	Bisoprolol	1141171152	C07AB07
atenolol	Atenolol	1140866738	C07AB03
tenormin 25 tablet	Atenolol	1140866756	C07AB03
metoprolol	Metoprolol	1140879818	C07AB02
carvedilol	Carvedilol	1140909368	C07AG02
propranolol	Propranolol	1140879842	C07AA05
timolol	Timolol	1140879866	C07AA06 |S01ED01
half-inderal la 80mg m/r capsule	Propranolol	1140866800	C07AA05
inderal 10mg tablet	Propranolol	1140866804	C07AA05
bedranol 10mg tablet	Propranolol	1140851556	C07AA05
half beta-prograne 80mg m/r capsule	Propranolol	1140866802	C07AA05
labetalol	Labetalol	1140879824	C07AG01
sotalol	Sotalol	1140879854	C07AA07
beta-cardone 40mg tablet	Sotalol	1140860304	C07AA07
co-tenidone	Chlorthalidone |Atenolol	1140923336	C07CB03
nebivolol	Nebivolol	1141164276	C07AB12
bisoprolol fumarate+hydrochlorothiazide 10mg/6.25mg tablet	Bisoprolol |Hydrochlorothiazide	1140864950	C07BB07
celiprolol	Celiprolol	1140879762	C07AB08
atenolol+bendroflumethiazide	Atenolol |Bendroflumethiazide	1141194810	C07BB03
nebilet 5mg tablet	Nebivolol	1141164280	C07AB12
propranolol hydrochloride+bendrofluazide 80mg/2.5mg capsule	Bendroflumethiazide |Propranolol	1140860418	C07BA05
sotalol hydrochloride+hydrochlorothiazide 80mg/12.5mg tablet	Sotalol |Hydrochlorothiazide	1140860332	C07BA07
tenoret 50 tablet	Chlorthalidone |Atenolol	1140860324	C07CB03

carteolol	Carteolol	1140879822	C07AA15 |S01ED05
betaxolol	Betaxolol	1140879758	C07AB05 |S01ED02
atenolol+bendrofluazide	Atenolol |Bendroflumethiazide	1141146126	C07BB03
tenif capsule	Atenolol |Nifedipine	1140860358	C07FB03
metoprolol tartrate+chlorthalidone 100mg/12.5mg tablet	Metoprolol |Chlorthalidone	1140860308	C07CB02
tenoretic tablet	Chlorthalidone |Atenolol	1140860328	C07CB03
beta-adalat capsule	Atenolol |Nifedipine	1140860356	C07FB03
celectol 200mg tablet	Celiprolol	1140860498	C07AB08
acebutolol	Acebutolol	1140866724	C07AB04
oxprenolol	Oxprenolol	1140879830	C07AA02
prindolol	Pindolol	1140910614	C07AA17
kalten capsule	Atenolol |Amiloride |Hydrochlorothiazide	1140860398	C07DB01
nadolol	Nadolol	1140860192	C07AA12
pindolol	Pindolol	1140860292	C07AA03
atenolol+chlortalidone	Chlorthalidone |Atenolol	1141180778	C07BB03
amlodipine	Amlodipine	1140879802	C08CA01
istin 5mg tablet	Amlodipine	1140861202	C08CA01
amlostin 5mg tablet	Amlodipine	1141200400	C08CA01
nifedipine	Nifedipine	1140861088	C08CA05
adalat 5mg capsule	Nifedipine	1140861090	C08CA05
coracten sr 10mg m/r capsule	Nifedipine	1140861120	C08CA05
adalate 10mg capsule	Nifedipine	1140881702	C08CA05
adipine mr 10 m/r tablet	Nifedipine	1140923572	C08CA05
fortipine la40 m/r tablet	Nifedipine	1141145870	C08CA05
nifedipress mr 10 m/r tablet	Nifedipine	1141157140	C08CA05
tensipine mr 10 m/r tablet	Nifedipine	1140927940	C08CA05
verapamil	Verapamil	1140888510	C08DA01
securon 40mg tablet	Verapamil	1140866466	C08DA01
half securon sr 120mg m/r tablet	Verapamil	1140866460	C08DA01
univer 120mg m/r capsule	Verapamil	1140881692	C08DA01
vertab sr 240 m/r tablet	Verapamil	1141169710	C08DA01
diltiazem	Diltiazem	1140879806	C05AE03 |C08DB01
tildiem 60mg m/r tablet	Diltiazem	1140861128	C08DB01
adizem-60 m/r tablet	Diltiazem	1140861138	C08DB01
adizem-xl plus m/r capsule	Diltiazem	1140926780	C08DB01
dilzem sr 60mg long acting m/r capsule	Diltiazem	1140861166	C08DB01

slozem 120mg m/r capsule	Diltiazem	1140911698	C08DB01
angitil sr 90 m/r capsule	Diltiazem	1140917428	C08DB01
viazem xl 120mg m/r capsule	Diltiazem	1141151474	C08DB01
zemtard 120 xl m/r capsule	Diltiazem	1141167832	C08DB01
calcicard 60mg tablet	Diltiazem	1140851730	C08DB01
felodipine	Felodipine	1140888646	C08CA02
cardioplen xl 5mg m/r tablet	Felodipine	1141199858	C08CA02
vascalpha 5mg m/r tablet	Felodipine	1141190160	C08CA02
felendil xl 5mg m/r tablet	Felodipine	1141188836	C08CA02
plendil 2.5mg m/r tablet	Felodipine	1140928212	C08CA02
felotens xl 5mg m/r tablet	Felodipine	1141188152	C08CA02
neofel xl 5mg m/r tablet	Felodipine	1141200782	C08CA02
felogen xl 5mg m/r tablet	Felodipine	1141188576	C08CA02
cabren 2.5mg m/r tablet	Felodipine	1141187094	C08CA02
lercanidipine	Lercanidipine	1141153026	C08CA13
zanidip 10mg tablet	Lercanidipine	1141153032	C08CA13
lacidipine	Lacidipine	1140861276	C08CA09
diltiazem hcl+hydrochlorothiazide 150mg/12.5mg m/r capsule	Diltiazem |Hydrochlorothiazide	1140926778	C08GA
nicardipine	Nicardipine	1140879810	C08CA04
motens 2mg tablet	Lacidipine	1140861282	C08CA09
cardene 20mg capsule	Nicardipine	1140861176	C08CA04
valsartan	Valsartan	1141145660	C09CA03
diovan 40mg capsule	Valsartan	1141145668	C09CA03
losartan	Losartan	1140916356	C09CA01
cozaar 25mg tablet	Losartan	1141179974	C09CA01
perindopril	Perindopril	1140888560	C09AA04
coversyl 2mg tablet	Perindopril	1140860802	C09AA04
lisinopril	Lisinopril	1140860696	C09AA03
zestril 2.5mg tablet	Lisinopril	1140860714	C09AA03
irbesartan	Irbesartan	1141152998	C09CA04
aprovel 75mg tablet	Irbesartan	1141153006	C09CA04
enalapril	Enalapril	1140888552	C09AA02
innovace 2.5mg tablet	Enalapril	1140860776	C09AA02
fosinopril	Fosinopril	1140888556	C09AA09
ramipril	Ramipril	1140860806	C09AA05
telmisartan	Telmisartan	1141166006	C09CA07
micardis 20mg tablet	Telmisartan	1141172492	C09CA07
tritace 1.25mg tablet	Ramipril	1141188408	C09AA05
lopace 2.5mg capsule	Ramipril	1141199940	C09AA05

candesartan cilexetil	Candesartan	1141156836	C09CA06
amias 2mg tablet	Candesartan	1141156846	C09CA06
cilazapril	Cilazapril	1140860882	C09AA08
olmesartan	Olmesartan	1141193282	C09CA08
losartan potassium+hydrochlorothiazide 50mg/12.5mg tablet	Losartan |Hydrochlorothiazide	1141151016	C09DA01
olmetec 10mg tablet	Olmesartan	1141193346	C09CA08
trandolapril	Trandolapril	1140860904	C09AA10
eprosartan	Eprosartan	1141171336	C09CA02
captopril	Captopril	1140860750	C09AA01
quinapril	Quinapril	1140860728	C09AA06
lisinopril+hydrochlorothiazide 10mg/12.5mg tablet	Lisinopril |Hydrochlorothiazide	1140864952	C09BA03
coaprovel 150mg/12.5mg tablet	Hydrochlorothiazide |Irbesartan	1141172686	C09DA04
enalapril maleate+hydrochlorothiazide 20mg/12.5mg tablet	Enalapril |Hydrochlorothiazide	1140860790	C09BA02
irbesartan+hydrochlorothiazide 150mg/12.5mg tablet	Hydrochlorothiazide |Irbesartan	1141172682	C09DA04
cozaar-comp 50mg/12.5mg tablet	Losartan |Hydrochlorothiazide	1141151018	C09DA01
perindopril+indapamide	Perindopril |Indapamide	1141180592	C09BA04
zestoretic 10 tablet	Lisinopril |Hydrochlorothiazide	1140864618	C09BA03
coversyl plus 4mg/1.25mg tablet	Perindopril |Indapamide	1141180598	C09BA04
co-diovan 80mg/12.5mg tablet	Valsartan |Hydrochlorothiazide	1141201040	C09DA03
valsartan+hydrochlorothiazide 80mg/12.5mg tablet	Valsartan |Hydrochlorothiazide	1141201038	C09DA03
teveten 300mg tablet	Eprosartan	1141171344	C09CA02
micardisplus 40mg/12.5mg tablet	Telmisartan |Hydrochlorothiazide	1141187790	C09DA07
telmisartan+hydrochlorothiazide 40mg/12.5mg tablet	Telmisartan |Hydrochlorothiazide	1141187788	C09DA07
felodipine+ramipril	Ramipril |Felodipine	1141165470	C09BB05
imidapril hydrochloride	Imidapril	1141164148	C09AA16
innozide tablet	Enalapril |Hydrochlorothiazide	1140860784	C09BA02
gopten 500micrograms capsule	Trandolapril	1140860912	C09AA10
capozide tablet	Hydrochlorothiazide |Captopril	1140881714	C09BA01
capoten 12.5mg tablet	Captopril	1140860758	C09AA01
carace 10 plus tablet	Lisinopril |Hydrochlorothiazide	1140864910	C09BA03
triapin mite 2.5mg/2.5mg tablet	Ramipril |Felodipine	1141165476	C09BB05
accupro 5mg tablet	Quinapril	1140881706	C09AA06
MEDICATIONS FOR HYPERGLYCAEMIA			

metformin	Metformin	1140884600	A10BA02
glucophage 500mg tablet	Metformin	1140874686	A10BA02
insulin product	Insulin	1140883066	A10A
gliclazide	Gliclazide	1140874744	A10BB09
glyclizide	Gliclazide	1140910566	A10BB09
diamicron 80mg tablet	Gliclazide	1140874746	A10BB09
glimepiride	Glimepiride	1141152590	A10BB12
amaryl 1mg tablet	Glimepiride	1141156984	A10BB12
pioglitazone	Pioglitazone	1141171646	A10BG03
actos 15mg tablet	Pioglitazone	1141171652	A10BG03
glibenclamide	Glyburide	1140874718	A10BB01
repaglinide	Repaglinide	1141168660	A10BX02
rosiglitazone	Rosiglitazone	1141177600	A10BG02
rosiglitazone 1mg / metformin 500mg tablet	Metformin |Rosiglitazone	1141189090	A10BD03
avandamet 1mg / 500mg tablet	Metformin |Rosiglitazone	1141189094	A10BD03
glipizide	Glipizide	1140874646	A10BB07
avandia 4mg tablet	Rosiglitazone	1141177606	A10BG02
tolbutamide	Tolbutamide	1140874674	A10BB03 |V04CA01
acarbose	Acarbose	1140868902	A10BF01
nateglinide	Nateglinide	1141173882	A10BX03

Appendix 6.3: UK Biobank variables used to define neuroimaging and cognitive test measures

Outcome	UK Biobank Data Field ID	Data Field Description
Neuroimaging Measures		
Total Brain Volume	25009	Volume of brain, grey+white
Grey Matter Volume	25005	Volume of grey matter
White Matter Volume	25007	Volume of white matter
Left Hippocampal Volume	25019	Volume of hippocampus (left)
Right Hippocampal Volume	25020	Volume of hippocampus (right)
White Matter Hyperintensity Volume	25781	Total volume of white matter hyperintensities (from T1-/T2- FLAIR images)
Cognitive Test Measures		
Executive Function (Trail Making Test A)	6348	Duration (in deciseconds) to complete numeric path (trail #1)
Executive Function (Trail Making Test B)	6350	Duration (in deciseconds) to complete alphanumeric path (trail #2)
Verbal & Numerical Reasoning (Fluid Intelligence)	20016	Fluid intelligence score (based on # of questions answered correctly in two minutes)
Working Memory (Backward Digit Span Task)	4282	Maximum number of digits correctly remembered in the reverse order
Complex Processing Speed (Symbol Digit Substitution)	23324	Number of symbol digit matches made correctly in 60 seconds
Verbal Declarative Memory (Paired Associate Learning)	20197	Number of word pairs correctly associated
Non-Verbal Reasoning (Matrix Pattern Completion)	6373	Number of puzzles correctly solved in 3 minutes

Appendix 6.4: Association between the presence of MetS and A) standardised neuroimaging measures and B) standardised cognitive test scores using a multiple imputation sample

	Standardised Beta	95% CI	*P*
A) Neuroimaging Measure*			
Total Brain Volume	-0.07	-0.09, -0.05	**<0.001**
Grey Matter Volume	-0.11	-0.13, -0.10	**<0.001**
White Matter Volume	0.00	-0.02, 0.02	0.7
Left Hippocampal Volume	-0.04	-0.06, -0.02	**<0.001**
Right Hippocampal Volume	-0.05	-0.07, -0.03	**<0.001**
WMH Volume	0.11	0.09, 0.13	**<0.001**
B) Cognitive Test Measure			
Executive Function (TMT A)	0.05	0.02, 0.08	**<0.001**
Executive Function (TMT B)	0.07	0.05, 0.10	**<0.001**
Verbal & Numerical Reasoning (FI)	-0.08	-0.10, -0.06	**<0.001**
Working Memory (BDS)	-0.10	-0.12, -0.07	**<0.001**
Processing Speed (SDS)	-0.08	-0.10, -0.05	**<0.001**
Verbal Declarative Memory (PAL)	-0.09	-0.12, -0.07	**<0.001**
Non-Verbal Reasoning (MPC)	-0.04	-0.06, -0.01	**0.005**

Abbreviations: CI, Confidence Interval; WMH, White Matter Hyperintensity; TMT, Trail Making Test; FI, Fluid Intelligence Score; BDS, Backward Digit Span Task; SDS, Symbol Digit Substitution Task; PAL, Paired Associate Learning Task; MPC, Matrix Pattern Completion Test.

Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and APOE-ε4 carrier status, assessment centre, time between baseline and follow-up imaging assessment.

*Neuroimaging models (only) were further adjusted for imaging-related confounders: head size, head position, head motion.

WMH, TMT A, and TMT B were log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1) to permit comparison of effect size across outcomes.

Appendix 6.5: Main results with MetS defined using a combination of data captured from the baseline and follow-up imaging assessment

	Standardised Beta	95% CI	*P*
A) Neuroimaging Measures*			
Total Brain Volume	-0.09	-0.11, -0.07	**<0.001**
Grey Matter Volume	-0.13	-0.15, -0.11	**<0.001**
White Matter Volume	-0.02	-0.04, 0.01	0.2
Left Hippocampal Volume	-0.04	-0.06, -0.02	**<0.001**
Right Hippocampal Volume	-0.05	-0.08, -0.03	**<0.001**
WMH Volume	0.11	0.08, 0.13	**<0.001**
B) Cognitive Test Measures			
Executive Function (TMT A)	0.05	0.02, 0.07	**0.002**
Executive Function (TMT B)	0.04	0.01, 0.07	**0.012**
Verbal & Numerical Reasoning (FI)	-0.05	-0.07, -0.02	**<0.001**
Working Memory (BDS)	-0.10	-0.13, -0.07	**<0.001**
Processing Speed (SDS)	-0.08	-0.11, -0.06	**<0.001**
Verbal Declarative Memory (PAL)	-0.09	-0.12, -0.06	**<0.001**
Non-Verbal Reasoning (MPC)	-0.03	-0.06, 0.00	**0.031**

Abbreviations: CI, Confidence Interval; WMH, White Matter Hyperintensity; TMT, Trail Making Test; FI, Fluid Intelligence Score; BDS, Backward Digit Span Task; SDS, Symbol Digit Substitution Task; PAL, Paired Associate Learning Task; MPC, Matrix Pattern Completion Test.

Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and APOE-ε4 carrier status, assessment centre, time between baseline and follow-up imaging assessment.

*Neuroimaging models (only) were further adjusted for imaging-related confounders: head size, head position, head motion.

WMH, TMT A, and TMT B were log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1) to permit comparison of effect size across outcomes. Higher scores indicate poorer cognitive performance for TMT (as it measures time taken to complete the test), whereas lower scores reflect poorer performance for all other tests.

Appendix 6.6: Detailed results for Figure 6.2

Neuroimaging Measure	Standardised Beta	95% CI	*P for trend*
Total Brain Volume			
1	-0.02	-0.04, 0.01	
2	-0.04	-0.07, -0.02	
3	-0.07	-0.10, -0.04	**<0.001**
4	-0.12	-0.16, -0.08	
5	-0.22	-0.28, -0.15	
Grey Matter Volume			
1	-0.03	-0.06, -0.01	
2	-0.05	-0.08, -0.03	
3	-0.12	-0.14, -0.09	**<0.001**
4	-0.18	-0.22, -0.15	
5	-0.31	-0.37, -0.25	
White Matter Volume			
1	0.01	-0.02, 0.04	
2	-0.01	-0.04, 0.02	
3	0.01	-0.02, 0.05	0.8
4	0.00	-0.04, 0.05	
5	-0.03	-0.10, 0.05	
Left Hippocampal Volume			
1	0.00	-0.03, 0.03	
2	0.00	-0.03, 0.03	
3	-0.03	-0.06, 0.00	**0.001**
4	-0.05	-0.09, 0.00	
5	-0.10	-0.18, -0.03	
Right Hippocampal Volume			
1	0.00	-0.03, 0.03	
2	0.01	-0.02, 0.04	
3	-0.04	-0.07, 0.00	**0.002**
4	-0.05	-0.10, -0.01	
5	-0.08	-0.15, 0.00	
WMH Volume			
1	0.13	0.10, 0.15	
2	0.17	0.14, 0.20	
3	0.19	0.16, 0.22	**<0.001**
4	0.23	0.19, 0.27	
5	0.31	0.24, 0.38	

Abbreviations: CI, Confidence Interval; WMH, White Matter Hyperintensity.

Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and APOE-ε4 carrier status, assessment centre, time between baseline and follow-up imaging assessment, head size, head position, and head motion.

WMH was log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1) to permit comparison of effect size across outcomes.

Appendix 6.7: Associations of individual MetS components with standardised neuroimaging and cognitive tests measures

	Elevated WC		Elevated TG		Elevated BP		Elevated HbA1c		Reduced HDL cholesterol	
	Standardised Beta (95% CI)	***p***	**Standardised Beta (95% CI)**	***p***	**Standardised Beta (95% CI)**	***p***	**Standardised Beta (95% CI)**	***p***	**Standardised Beta (95% CI)**	***p***
Neuroimaging Measure*										
Total Brain Volume	-0.10 (-0.12, -0.08)	**<0.001**	-0.01 (-0.03, 0.00)	0.12	-0.03 (-0.05, -0.01)	**0.002**	-0.09 (-0.12, -0.07)	**<0.001**	-0.03 (-0.05, -0.01)	**0.016**
Grey Matter Volume	-0.15 (-0.17, -0.13)	**<0.001**	-0.02 (-0.03, 0.00)	**0.030**	-0.06 (-0.08, -0.05)	**<0.001**	-0.12 (-0.14, -0.10)	**<0.001**	-0.03 (-0.05, -0.01)	**0.001**
White Matter Volume	0.00 (-0.02, 0.02)	0.9	0.00 (-0.02, 0.02)	0.7	0.02 (0.00, 0.04)	**0.043**	-0.03 (-0.06, 0.00)	**0.034**	-0.01 (-0.03, 0.02)	0.5
Left Hippocampal Volume	-0.10 (-0.12, -0.08)	**<0.001**	0.01 (-0.01, 0.03)	0.3	0.00 (-0.02, 0.02)	0.9	-0.03 (-0.06, 0.00)	0.058	0.00 (-0.03, 0.02)	>0.9
Right Hippocampal Volume	-0.08 (-0.10, -0.06)	**<0.001**	0.02 (0.00, 0.04)	**0.036**	0.00 (-0.02, 0.02)	0.7	-0.06 (-0.09, -0.03)	**<0.001**	0.00 (-0.03, 0.02)	0.9
WMH Volume	0.08 (0.06, 0.10)	**<0.001**	0.05 (0.03, 0.07)	**<0.001**	0.17 (0.15, 0.18)	**<0.001**	0.06 (0.03, 0.09)	**<0.001**	0.05 (0.03, 0.07)	**<0.001**
Cognitive Test Measure										
Executive Function (TMT A)	0.01 (-0.01, 0.04)	0.3	0.03 (0.01, 0.06)	**0.008**	0.03 (0.00, 0.05)	**0.033**	0.07 (0.03, 0.10)	**<0.001**	0.03 (0.00, 0.06)	**0.033**
Executive Function (TMT B)	0.04 (0.01, 0.07)	**0.005**	0.04 (0.02, 0.07)	**<0.001**	0.05 (0.03, 0.08)	**<0.001**	0.06 (0.03, 0.10)	**<0.001**	0.04 (0.01, 0.07)	**0.005**
Verbal & Numerical Reasoning (FI)	-0.05 (-0.07, -0.02)	**<0.001**	-0.05 (-0.07, -0.03)	**<0.001**	-0.06 (-0.08, -0.04)	**<0.001**	-0.05 (-0.08, -0.01)	**0.004**	-0.06 (-0.08, -0.03)	**<0.001**
Working Memory (BDS)	-0.08 (-0.11, -0.05)	**<0.001**	-0.08 (-0.10, -0.05)	**<0.001**	-0.09 (-0.11, -0.06)	**<0.001**	-0.04 (-0.08, -0.01)	**0.025**	-0.05 (-0.09, -0.02)	**<0.001**
Processing Speed (SDS)	0.08 (-0.10, -0.05)	**<0.001**	-0.04 (-0.06, -0.02)	**<0.001**	-0.05 (-0.07, -0.02)	**<0.001**	-0.08 (-0.11, -0.05)	**<0.001**	-0.03 (-0.05, 0.00)	0.088
Verbal Declarative Memory (PAL)	-0.10 (-0.12, -0.07)	**<0.001**	-0.07 (-0.10, -0.05)	**<0.001**	-0.06 (-0.09, -0.04)	**<0.001**	-0.03 (-0.06, 0.01)	0.13	-0.02 (-0.05, 0.01)	0.3
Non-Verbal Reasoning (MPC)	-0.03 (-0.05, 0.00)	0.051	-0.03 (-0.05, 0.00)	**0.030**	-0.05 (-0.07, -0.02)	**<0.001**	-0.01 (-0.04, 0.03)	0.7	0.01 (-0.02, 0.04)	0.5

Abbreviations: WC, Waist Circumference; TG, Triglycerides; BP, Blood Pressure; HbA1c, Glycated Haemoglobin; HDL, High-Density Lipoprotein; WMH, White Matter Hyperintensity; TMT, Trail Making Test; FI, Fluid Intelligence Score; BDS, Backward Digit Span Task; SDS, Symbol Digit Substitution Task; PAL, Paired Associate Learning Task; MPC, Matrix Pattern Completion Test.

Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and APOE-ε4 carrier status, assessment centre, time between baseline and follow-up imaging assessment.

*Neuroimaging models (only) were further adjusted for imaging-related confounders: head size, head position, head motion.

WMH, and TMT A and B were log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1) to permit comparison of effect size across outcomes.

Appendix 6.8: Association between the presence of MetS and standardised neuroimaging measures according to age groups

Neuroimaging Measure	Standardised Beta	95% CI	*P* (interaction)
Total Brain Volume			
<65 years	-0.07	-0.09, -0.04	0.7
65+ years	-0.09	-0.14, -0.04	
Grey Matter Volume			
<65 years	-0.11	-0.13, -0.09	0.12
65+ years	-0.13	-0.18, -0.08	
White Matter Volume			
<65 years	0.01	-0.01, 0.04	0.06
65+ years	-0.01	-0.08, 0.06	
Left Hippocampal Volume			
<65 years	-0.03	-0.06, -0.01	0.4
65+ years	-0.09	-0.15, -0.03	
Right Hippocampal Volume			
<65 years	-0.04	-0.07, -0.02	0.2
65+ years	-0.08	-0.14, -0.01	
WMH Volume			
<65 years	0.10	0.07, 0.12	**<0.001**
65+ years	0.05	-0.01, 0.11	

Abbreviations: CI, Confidence Interval; WMH, White Matter Hyperintensity.

Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and APOE-ε4 carrier status, assessment centre, time between baseline and follow-up imaging assessment, head size, head position, and head motion.

WMH was log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1) to permit comparison of effect size across outcomes.

Appendix 6.9: Association between the presence of MetS and standardised neuroimaging measures according to sex

Neuroimaging Measure	Standardised Beta	95% CI	*P* (interaction)
Total Brain Volume			
Females	-0.01	-0.04, 0.02	**<0.001**
Males	-0.12	-0.15, -0.09	
Grey Matter Volume			
Females	-0.08	-0.11, -0.05	**<0.001**
Males	-0.14	-0.16, -0.11	
White Matter Volume			
Females	0.07	0.04, 0.11	**<0.001**
Males	-0.05	-0.08, -0.02	
Left Hippocampal Volume			
Females	-0.02	-0.06, 0.01	0.3
Males	-0.05	-0.09, -0.02	
Right Hippocampal Volume			
Females	-0.04	-0.07, -0.01	0.6
Males	-0.06	-0.09, -0.02	
WMH Volume			
Females	0.10	0.07, 0.13	0.3
Males	0.08	0.05, 0.11	

Abbreviations: CI, Confidence Interval; WMH, White Matter Hyperintensity.

Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and APOE-ε4 carrier status, assessment centre, time between baseline and follow-up imaging assessment, head size, head position, and head motion.

WMH was log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1) to permit comparison of effect size across outcomes.

Appendix 6.10: Detailed results for Figure 6.3

Cognitive Test Measure	Standardised Beta	95% CI	*P for trend*
Executive Function (TMT A)			
1	0.01	-0.03, 0.04	
2	0.03	0.00, 0.07	
3	0.03	-0.01, 0.07	**<0.001**
4	0.10	0.05, 0.15	
5	0.11	0.01, 0.21	
Executive Function (TMT B)			
1	0.03	0.00, 0.06	
2	0.06	0.02, 0.09	
3	0.09	0.05, 0.13	**<0.001**
4	0.10	0.05, 0.15	
5	0.17	0.08, 0.27	
Verbal & Numerical Reasoning (FI)			
1	-0.03	-0.06, 0.00	
2	-0.08	-0.11, -0.05	
3	-0.10	-0.14, -0.07	**<0.001**
4	-0.13	-0.17, -0.08	
5	-0.14	-0.23, -0.06	
Working Memory (BDS)			
1	-0.05	-0.08, -0.01	
2	-0.09	-0.13, -0.06	
3	-0.13	-0.17, -0.08	**<0.001**
4	-0.18	-0.24, -0.13	
5	-0.28	-0.37, -0.18	
Processing Speed (SDS)			
1	-0.02	-0.05, 0.01	
2	-0.07	-0.10, -0.04	
3	-0.08	-0.12, -0.04	**<0.001**
4	-0.12	-0.17, -0.07	
5	-0.19	-0.28, -0.10	
Verbal Declarative Memory (PAL)			
1	-0.04	-0.07, -0.01	
2	-0.09	-0.12, -0.05	
3	-0.11	-0.16, -0.07	**<0.001**
4	-0.13	-0.18, -0.07	
5	-0.23	-0.33, -0.14	
Non-Verbal Reasoning (MPC)			
1	-0.02	-0.05, 0.01	
2	-0.03	-0.07, 0.00	
3	-0.04	-0.09, 0.00	**0.004**
4	-0.05	-0.10, 0.01	
5	-0.11	-0.21, -0.01	

Abbreviations: CI, Confidence Interval; TMT, Trail Making Test; FI, Fluid Intelligence Score; BDS, Backward Digit Span Task; SDS, Symbol Digit Substitution Task; PAL, Paired Associate Learning Task; MPC, Matrix Pattern Completion Test.

Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and APOE-ε4 carrier status, assessment centre, and time between baseline and follow-up imaging assessment.

TMT A and B were log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1) to permit comparison of effect size across outcomes.

Appendix 6.11: Association between the presence of MetS and standardised cognitive test scores according to age groups

Cognitive Test Measure	Standardised Beta	95% CI	*P* (interaction)
Executive Function (TMT A)			
<65 years	0.04	0.01, 0.07	0.6
65+ years	0.05	-0.04, 0.15	
Executive Function (TMT B)			
<65 years	0.06	0.03, 0.09	0.059
65+ years	0.09	0.00, 0.18	
Verbal & Numerical Reasoning (FI)			
<65 years	-0.07	-0.09, -0.04	0.2
65+ years	-0.09	-0.16, -0.02	
Working Memory (BDS)			
<65 years	-0.09	-0.12, -0.06	0.3
65+ years	-0.13	-0.22, -0.04	
Processing Speed (SDS)			
<65 years	-0.07	-0.10, -0.04	0.081
65+ years	-0.05	-0.13, 0.02	
Verbal Declarative Memory (PAL)			
<65 years	-0.08	-0.11, -0.05	0.3
65+ years	-0.08	-0.17, 0.00	
Non-Verbal Reasoning (MPC)			
<65 years	-0.03	-0.06, 0.00	0.7
65+ years	0.00	-0.08, 0.08	

Abbreviations: CI, Confidence Interval; TMT, Trail Making Test; FI, Fluid Intelligence Score; BDS, Backward Digit Span Task; SDS, Symbol Digit Substitution Task; PAL, Paired Associate Learning Task; MPC, Matrix Pattern Completion Test.

Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and APOE-ε4 carrier status, assessment centre, and time between baseline and follow-up imaging assessment.

TMT A and B were log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1) to permit comparison of effect size across outcomes.

Appendix 6.12: Association between the presence of MetS and standardised cognitive test scores according to sex

Cognitive Test Measure	Standardised Beta	95% CI	*P* (interaction)
Executive Function (TMT A)			
Females	0.01	-0.03, 0.05	0.087
Males	0.06	0.02, 0.10	
Executive Function (TMT B)			
Females	0.05	0.00, 0.09	0.2
Males	0.08	0.04, 0.12	
Verbal & Numerical Reasoning (FI)			
Females	-0.04	-0.08, 0.00	**0.026**
Males	-0.10	-0.13, -0.06	
Working Memory (BDS)			
Females	-0.09	-0.13, -0.05	0.5
Males	-0.10	-0.14, -0.06	
Processing Speed (SDS)			
Females	-0.08	-0.12, -0.04	>0.9
Males	-0.06	-0.09, -0.02	
Verbal Declarative Memory (PAL)			
Females	-0.07	-0.11, -0.03	0.6
Males	-0.09	-0.13, -0.05	
Non-Verbal Reasoning (MPC)			
Females	-0.01	-0.05, 0.03	0.15
Males	-0.05	-0.09, -0.01	

Abbreviations: CI, Confidence Interval; TMT, Trail Making Test; FI, Fluid Intelligence Score; BDS, Backward Digit Span Task; SDS, Symbol Digit Substitution Task; PAL, Paired Associate Learning Task; MPC, Matrix Pattern Completion Test.

Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and APOE-ε4 carrier status, assessment centre, and time between baseline and follow-up imaging assessment.

TMT A and B were log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1) to permit comparison of effect size across outcomes.