Determining the causal effects of lipid levels on risk of dementia: a triangulation of new and existing evidence

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A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of

Doctor of Philosophy

in the Faculty of Health Sciences

December 2021

Word count: 48,351

Abstract

Background: Identification of causal relationships between modifiable risk factors and incidence of dementia is central to the development of evidence-based prevention strategies. As such, this thesis sought to triangulate the causal effects of lipid levels (total cholesterol, LDL-c, HDL-c, and triglycerides) on risk of incident dementia (all-cause dementia, Alzheimer's disease, and vascular dementia) using existing and new evidence.

Methods: Four distinct analyses were conducted. Firstly, a systematic review was used to summarise the evidence base. Existing evidence was then supplemented via two primary studies: i) a cohort study of lipid regulating agents and dementia incidence in the Clinical Practice Research Datalink (CPRD); and ii) an individual participant data (IPD) meta-analysis of lipid levels and dementia incidence. Finally, a novel quantitative triangulation framework was proposed, and was then used to integrate the results of the previous three studies.

Results: The systematic review did not identify a consistent effect of blood lipids on any dementia outcome across the study designs considered, though there was some suggestion of a protective effect of LDL-c lowering on all-cause dementia and Alzheimer's disease in observational studies of statin use. Analysis of the CPRD data provided weak evidence for a protective effect of statins on all-cause dementia and Alzheimer's disease but suggested a harmful association with vascular dementia, likely due to confounding by indication. The IPD meta-analysis provided some evidence for the association of triglycerides and vascular dementia only. Finally, the quantitative triangulation analysis did not provide strong evidence for the causal effect of blood lipids on dementia outcomes.

Conclusions: This thesis provides new evidence concerning the role of blood lipids as a modifiable risk factor for dementia and highlights the uncertainty that still remains in relation to this causal question. In addition, it has developed new evidence synthesis methods and tools.

For Brendan McHugh

~

For Ciara Gardiner

Acknowledgements

Professional

First and foremost, I must thank my primary supervisor, Julian Higgins, for his tireless support and encouragement. I'd also like to thank my other supervisors - Yoav Ben-Shlomo, Liz Coulthard and George Davey Smith - for all their input over the past three years. Thanks also to Rupert Payne and Emma Anderson for their engaging discussion and useful feedback during my annual progress reviews.

I am extremely grateful to all those who contributed their time and energy to my research projects: Athena Sheppard, Emily Hennessy, Matthew Lee, Lena Schmidt, Alexandra McAleenan, Vincent Cheng, Francesca Spiga, Sarah Dawson and Rebecca Turner. A special mention goes to Mark Newbury of the Dementia Platform UK, who supported my applications for data access - I am extremely grateful for his help and commitment in chasing cohort owners.

I also want to thank the many people who raised issues or otherwise provided feedback on the open-source tools built as part of this thesis - it's been a joy to watch others build on my work. A special mention must go to Randall Boyes and Alex J Fowler for their input/work on the `robvis` tool.

Personal

Ciara, I'd need (at least) another 48,351 words to accurately describe all the ways in which you supported me through this endeavour. It can't have been fun being locked down in a small flat with a grumpy and stressed PhD student, nor trying to support the same student remotely from Dublin. In the Discussion, I talk about lessons learned during this thesis, but the biggest takeaway of this whole experience for me is that I am incredibly lucky to have found you and to get to take on life while holding your hand. Thank you and I love you.

Mum and Dad, thank you for your never-ending love and support. Everything I am comes from you, and you've done so much to get me to the point where a PhD thesis seemed possible.

There are several people without whom I would not have survived the process of writing a dissertation during COVID times. Ben, Doug, Christin - thank you!

Finally, a big thanks to Vivienne Gardiner, who sacrificed a substantial amount of time to proof-read this thesis.

Funding

I have been supported throughout my studies by an NIHR Doctoral Research Fellowship (DRF-2018-11-ST2-048). The views expressed in this thesis are my own and do not necessarily represent those of the NIHR or the Department of Health and Social Care.

Canynge Hall, Bristol
17 December 2021

Author's declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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List of Abbreviations

AC . . . . Agreement coefficient

ACE . . . . . . Acetylcholinesterase

AD . . . . Alzheimer's disease

ADGC . . . . Alzheimer's Disease Genetics Consortium

API . . . . . . Application programming interface

ApoE . . . . . Apolipoprotein E

BAS . . . . . . Bile acid sequestrants

BMI . . . . . . Body mass index

CAD . . . . . . Coronary arterial disease

CaPS . . . . . Caerphilly Prospective Study

CBS . . . . . . Coronary bypass surgery

CCI . . . . . . Charlson co-morbidity index

CIND . . . . . Cognitive impairment not dementia

CKD . . . . . . Chronic kidney disease

CPRD . . . . . Clinical Practice Research Datalink

CRAN . . . . . Comprehensive R Archive Network

CSV . . . . . . Comma separated value

CVD . . . . . . Cardiovascular disease

DOI . . . . . . Digital object identifier

DPUK . . . . . Dementia Platform UK

DSM . . . . . . Diagnostic and Statistical Manual of Mental Disorders

EHR . . . . . . Electronic health record

EPIC . . . . . European Prospective Investigation of Cancer

FAGs . . . . . Fatty acid groups

GLGC . . . . . Global Lipids Genetic Consortium

GWAS . . . . . Genome wide association studies

HDL . . . . . . High density lipoprotein

HES . . . . . . Hospital episode statistics

HMG-CoA . . 3-hydroxy-3-methylglutaryl-coenzyme-A

HMGCR . . . HMG-CoA reductase

HR . . . . Hazard ratio

ICD . . . . . . International Classification of Diseases

IGAP . . . . . International Genomics of Alzheimer's Project

IHD . . . . . . Ischemic heart disease

IMD . . . . . . Index of multiple deprivation

IPD . . . . . . Individual participant data

IV . . . . Instrumental variable

JUPITER . . Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin

LDL-c . . . . . Low density lipoprotein cholesterol

LRA . . . . . . Lipid regulating agent

MCI . . . . . . Mild cognitive impairment

MICE . . . . . Multiple imputation by chained equations

MMSE . . . . Mini Mental State Exam

MoCA . . . . . Montreal Cognitive Assessment

MR . . . . . . Mendelian randomization

NAG . . . . . . Nicotinic acid groups

NINDS-ADRA National Institute of Neurological Disorders and Stroke - Alzheimer's Disease and Related Disorders Association

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

NOS . . . . . . Newcastle-Ottowa Scale

NRSE . . . . . Non-randomised studies of exposures

NRSI . . . . . Non-randomised studies of interventions

OR . . . . Odds ratio

PAD . . . . . . Peripheral arterial disease
PCSK9i . . . . PCSK9 inhibitors
PDF . . . . . . Portable document format
PR . . . . Proportional hazards
PROSPER . . Prospective Study of Pravastatin in the Elderly
PYAR . . . . . Participant-years-at-risk
RCT . . . . . . Randomised controlled trial
REML . . . . . Restricted maximum likelihood
RoB-ME . . . Risk of bias due to missing evidence
RR . . . . Risk/rate ratio
SD . . . . Standard deviation
SNP . . . . . . Single nucleotide polymorphism
TC . . . . Total cholesterol
TG . . . . Triglycerides
VaD . . . . . . Vascular dementia

Alles in allem genommen haben wir hier offenbar einen eigenartigen Krankheitsprozeß vor uns.

~

Considering everything, it seems we are dealing here with a special illness.

— Alois Alzheimer, 1907[1,2]

1

Background, Theoretical framework, Aims & Objectives

Contents

Lay summary

Around 850,000 people in the UK live with dementia, and by 2040, nearly twice as many will have the condition. Despite many promising candidates, no cure for dementia currently exists, meaning the focus is on finding ways to prevent the condition. The best way to do this is to find risk factors (characteristics that influence a person's chance of developing a disease) for dementia that we can easily change. Avoiding a risk factor does not guarantee that a person will not develop dementia but makes it less likely. A key risk factor for dementia may be the levels of lipids (fatty substances such as cholesterol) in a person's blood, though not all existing research agrees. The aim of this thesis is to use all available evidence to assess whether blood lipid levels are in fact a risk factor for dementia.

This introductory chapter provides background information on both dementia and blood lipids, and on the potential link between them. It introduces the theory used to frame the research presented here, and then maps the formal aims and objectives of the research project to the relevant chapters of this thesis. Finally, it summarises the outputs (journal articles, presentations and software) that were created as part of this thesis.

1.1 Introduction

This chapter provides an overview of the broad context of this thesis, introducing the core concepts used throughout and providing some background on each. It briefly discusses the underlying pathologies and diagnosis of dementia, its public health importance, and the current state of treatment and prevention research. It then provides background on blood lipids and lipid-modifying treatments, and summarises the types of evidence used to examine the effect of these exposures on dementia outcomes.

It then introduces evidence synthesis as the key framework used to guide the research presented in the remaining chapters. Finally, it outlines the aims, objectives, and structure of this thesis, and briefly summarises the contributions to the scientific literature that arose from this research.

1.2 Dementia

1.2.1 Definition and underlying pathologies

Defined by the Diagnostic and Statistical Manual of Mental Disorders as a "major neurocognitive disorder", dementia is a progressive disease which impairs cognitive functions including speech, memory and executive reasoning.[3] At advanced stage, the condition causes severe behavioral and personality changes,[4] culminating in reduced motor control that affects patients' ability to swallow or breathe.[5] The condition has several distinct underlying causes, including Alzheimer's disease and vascular dementia.[6]

Alzheimer's disease is the most common cause of dementia, accounting for approximately 60-80% of cases. Characterised by substantial cognitive impairment and difficulty with high level executive function, it is an insidious disease, with initial onset thought to occur up to 15 years prior to symptomatic presentation.[7] Much remains unknown about Alzheimer's pathogenesis, despite research implicating the "amyloid hypothesis",[7] as a potential mechanism of disease. Under this hypothesis, the build-up of amlyoid plaques (composed mainly of amlyoid-β peptide) and neurofibrillary tangles (composed mainly of tau protein) triggers a range of physiological changes, including inflammation and cell death, that result in cognitive impairment.[7]

Vascular dementia (VaD) is the second largest underlying pathology of dementia, accounting for ~10-25% of cases. Vascular dementia is caused by a range of cerebrovascular disorders, and as a result, presentation of symptoms can vary widely.[8] Similarly, due to the varied underlying pathophysiology, vascular dementia can onset either quite rapidly following a cerebrovascular event such as a stroke or over a long time-frame due to a series of small infarcts.[9] Vascular dementia regularly co-occurs in patients with Alzheimer's disease.[8] This presentation is described as "mixed" dementia,[10] and occurs in approximately 25% of cases.[6]

The remaining 10-30% of cases are caused by other dementia subtypes (e.g., Lewy body or frontotemporal dementias) or other neurological diseases (e.g., Parkinson's disease).[6]

1.2.2 Diagnostic criteria

Dementia is difficult to diagnose, primarily due to its slow onset, in addition to the confusion of initial symptoms with normal ageing.[7] Dementia is diagnosed on the basis of behavioral and cognitive changes as assessed by an experienced clinician, using one of several diagnostic criteria.

One of the most commonly used sets of criteria for diagnosing dementia cases are the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (Table 1.1).[3] Outlined in Table 1.1, these form the broad definition of a dementia diagnosis, and are supported by a detailed patient history, evidence from carers and family members, and objective assessments of cognitive ability using neurocognitive tests.

Many cognitive assessment tools exist for the purpose of informing a diagnosis of dementia,[11] with two of the best known of these being the Mini Mental State Exam (MMSE) and Montreal Cognitive Assessment (MoCA) scale. The distinction between these memory scales and diagnostic criteria presented above should be noted. For example, the MMSE is used to provide evidence for part A of the criteria presented in 1.1. Taken alone, it does not indicate the absence or presence of dementia, instead merely indicating cognitive impairment which could have another cause (for example, temporary delirium as a result of an infection or surgery).

Table 1.1: Overview of the DSM-5 criteria for dementia (major neurocognitive disorder) - These published criteria[3] are commonly used to define dementia cases. Criterion A captures the cognitive decline aspect of dementia, while Criteria B-D ensure that the impairment observed is sufficient to interfere with daily living and cannot explained by other causes. Note that all criteria (A-D) must be met.

Criterion	Major neurocognitive event (previously dementia)
A	Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains:* - Learning and memory - Language - Executive function - Complex attention - Perceptual-motor - Social cognition
B	The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
C	The cognitive deficits do not occur exclusively in the context of a delirium.
D	The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

* From DSM: Evidence of decline is based on concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function and a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

Differentiating between the underlying causes of a dementia diagnosis is challenging but necessary, because whether the patient has Alzheimer's disease or vascular dementia will affect expected progression and potential treatment options available (see Section 1.2.4). Cause-specific criteria exist for the diagnosis of dementia sub-types. For example, the NINCDS-ADRDA criteria are commonly used to assess patients for Alzheimer's disease,[12] while vascular dementia is diagnosed using the NINCDS-AIREN criteria.[13]

1.2.3 Public health importance

Dementia is quickly becoming a critically important public health issue. Despite the age-specific incidence and prevalence of dementia remaining relatively constant over time,[14] an ageing population is set to create a dementia epidemic, particularly in westernised countries.[15] While approximately 525,000 patients have received a dementia diagnosis, the true number of people currently living with dementia in the UK is thought to be closer to 850,000, with this figure expected to double by 2040.[16] Globally, the prevalence of dementia is expected to reach 75 million by 2030.[14] Dementia is a leading cause of death in the UK,[17] and one of the few without a proven treatment.

Dementia also has a substantial economic impact. In 2015, the estimated total cost of dementia in England was £24.2 billion. Health care costs alone were £3.8 billion, with the remainder being divided between unpaid care and social care costs.[18] Globally, the cost of dementia care is expected to rise to $1tr by 2030.[19] As such, the urgent need to reduce the burden of dementia, both at the personal and system level, is clear.

1.2.4 Treatments

Developing treatments for dementia is regularly deemed to be one of the most challenging markets in the pharmaceutical world, with trials of seemingly promising therapeutics being regularly abandoned due to futility.[20]. At present, there are no known curative treatments for dementia, regardless of the underlying cause, though several available therapeutics can help alleviate the symptoms of Alzheimer's disease.

The most common of these are acetylcholinesterase (ACE) inhibitors, which inhibit the degradation of the neurotransmitter acetylcholine by competitively binding the ACE enzyme. Acetylcholine plays a key role in controlling the cholingeric synapses, which are highly concentrated in regions of the brain (such as the neocortex) that control higher level brain functions such as memory and attention.[21] Commonly prescribed ACE inhibitors include donepezil and galantamine.[22] ACE inhibitors increase the availability of the neurotransmitter, and have shown clinical effect is easing the behavioural and memory-related symptoms of Alzheimer's disease.[23] ACE inhibitors represent only a stop-gap treatment, treating the symptoms rather than the underlying pathology which may continue to progress.[24]

1.2.5 Risk factors

Given the substantial burden that dementia represents and the absence of any curative therapies, as detailed in the above sections, the assessment of easily modifiable targets for their utility in the prevention of dementia should be prioritized.[25] To date, a substantial amount of research has been produced examining putative risk factors for dementia.[26–28]

The benefits of a prevention-based approach based on addressing these risk factors are well-studied. Reducing the prevalence of the seven most important risk factors for dementia (obesity, hypertension,[29] diabetes, smoking, physical inactivity, and low educational attainment) by 10-20% per decade is estimated to result in a reduction in dementia prevalence of 8-15% by 2050.[30]

In this context, lipid levels represent a promising target for preventative treatment, due to the ready availability of lipid-modifying treatments which could be repurposed.[31] Determining whether variations in lipid levels are causative for dementia may prove critical in reducing the future burden of the condition.

This thesis will focus on blood lipids as the primary risk factor of interest. The next section provides an overview of blood lipid fractions and therapeutic interventions that modify them, while Section 1.4 provides an overview of the existing evidence for an association between lipids and dementia outcomes.

1.3 Serum lipids

1.3.1 Lipid fractions

The blood lipid profile contains a range of component parts, or fractions. However, this thesis will only consider the two most important fractions, triglycerides (TG) and cholesterol, which are either absorbed from food (exogenous lipids) or produced internally (endogenous lipids).[26]

Triglycerides are the simplest and most common type of lipids, used to store excess calories from food and to move energy around the body.[32] In contrast, cholesterol is primarily used to create cell walls and certain sex hormones.[33] Lipids are not water soluble, and so cholesterol is transported through the blood stream in lipoprotein structures of varying densities. Low-density-lipoprotein cholesterol (LDL-c), commonly known as "bad" cholesterol, acts as an energy conveyor by transporting fat to cells. In contrast, high density-lipoprotein cholesterol (HDL-c) transports cholesterol to the liver to be broken down and excreted.[26]

In addition to the individual fractions, total serum cholesterol (TC) is a commonly-used summary measure to estimate the total amount of lipid present in the blood. The level of TC is derived from measurements of the individual HDL-c, LDL-c and TG levels using the Friedwald formula:[34]

$$TC \approx LDL + HDL + kTG \tag{1.1}$$

where k is 0.20 if measurements are in milligrams per decilitre (*mg/dl*) and 0.45 if measured in millimole per litre (*mmol/l*). Widely used ranges for the acceptable levels of different types of lipids are based on the National Cholesterol Education Program (NCEP)[35], and are outlined in Table 1.2.

Elevated LDL-c in the bloodstream, a condition also known as hypercholesterolemia or hyperlipidaemia,[36] can lead to atherosclerosis,[37] the build-up of fatty deposits in the blood vessels. These deposits constrict blood flow and can lead to vascular complications. Alternatively, part of the deposit can detach from the artery walls, forming a clot that can lead to a heart attack or stroke.[37]

Table 1.2: Classification of blood lipid levels - Category cut-offs for different lipid fractions according to the National Cholesterol Education Program guidelines.[35]

Fraction	Measure (mg/dL)	Classification
LDL cholesterol	<100	Optimal
	100-129	Near/above optimal
	130-159	Borderline high
	160-189	High
	>190	Very high
HDL cholesterol	<40	Low
	>60	High
Triglycerides	<150	Normal
	150-199	Borderline high
	200-499	High
	>500	Very high
Total cholesterol	<200	Desirable
	200-239	Borderline high
	>240	High

1.3.2 Statins

Statins are a commonly prescribed method of lipid regulation.[38] Statins inhibit the conversion of 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) into mevalonate, by competitively binding with HMG-CoA reductase (HMGCR). This conversion is a key rate-limiting step in the cholesterol biosynthesis pathway (see Figure 1.1), enabling statins to effectively reduce the production of LDL cholesterol.

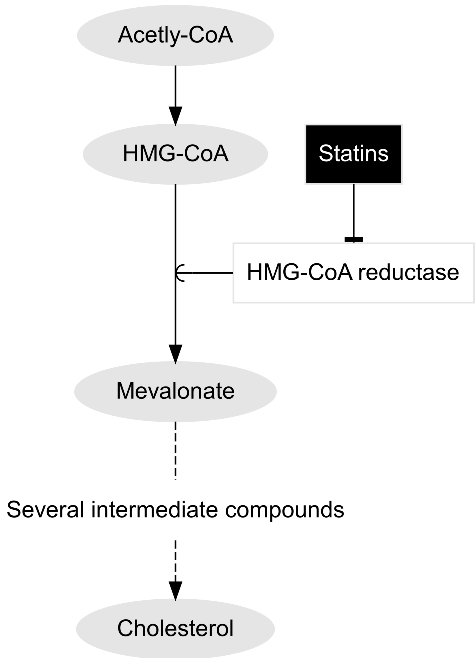

Figure 1.1: Statin mechanism of action - Statins inhibit HMG-CoA reductase which controls the conversion of HMG-CoA to mevalonate. This conversion is the rate-limiting step in cholesterol biosynthesis, and so statin use can reduce the production of cholesterol.

Several statin treatments have been widely available for some time (see Table 1.3). Depending on the statin and dosage prescribed, the average reduction in LDL-c concentrations ranges from 15% with low-intensity regimen (e.g., pravastatin 5 mg/day) up to 60% with a high-intensity regimen (e.g., rosuvastatin 80 mg/day).[38,39] Statins also vary with regard to their lipophilicity (the extent to which they are lipid soluble), affecting their localisation within the body, with hydrophilic statins being concentrated in the liver and lipophilic statins circulating more widely.[40] This may create a divide in the off-target effects of statins with differing lipophilicity, particularly given the ability of lipophilic statins to permeate the blood brain barrier.[41]

Table 1.3: Overview of common statins - There are several commonly prescribed statins used to treat hypercholesterolemia. Their approval date (US), properties and lipid-lowering effect are described here.

Name	Brand name	Year approved	Properties	Lipid-lowering effect
Atorvastatin	Lipitor	1996	Lipophilic	+++
Pravastatin	Lipostat	1989	Hydrophilic	+
Rosuvastatin	Crestor	2003	Hydrophilic	++++
Simvastatin	Zocor	1992	Lipophilic	++

1.3.3 Other lipid regulating agents (LRA)

There are several other interventions that can be used to modify a person's lipid profile, each of which act via different mechanisms. However, in general, these treatments are either used as adjunct (additional) treatments to statin therapy or are used in situations where statins are contra-indicated or not tolerated.

The most commonly used non-statin therapeutic is ezetimibe,[42] which prevents intestinal absorption of cholesterol. However, when used alone, it has a limited LDL-c lowering effect, leading to the creation of combined statin/ezetimibe therapies (both compounds contained in a single pill, as opposed to complimentary treatments).[43]

Fibrates provide a second example of non-statin therapy. They are used to treat hypertriglyceridemia by reducing production of triglyceride carrying compounds in the liver. They are commonly used in patients with mixed hyperlipidaemia if treatment with statins has failed to sufficiently control cholesterol levels.

Finally, PCSK9 inhibitors (or PCSK9i) are a relatively new treatment with strong lipid lowering effects, lauded as a potential alternative to statins.[44] Their mechanism of action is to bind to and inhibit PCSK9, which breaks down LDL-c receptors on the surface of the liver, thus allowing more LDL-c to be internalised and broken down.

Other therapies targeting triglycerides exist, including nicotinic acids[45] and omega-3-fatty acids,[46] but they are far less effective in LDL-c lowering than the therapies described above.

Table 1.4: Summary of available treatments for hyperlipidaemia.

Treatment	Effect	Mechanism of action	Examples
HMG CoA reductase inhibitors (statins)	Lowers LDL-c & TG Raises HDL-c	Inhibits cholesterol biosynthesis pathway in the liver	Atorvastatin, Simvastatin, Pravastatin
Ezetimibe	Lowers LDL-c	Prevents absorption of cholesterol from diet	
Bile acide sequestrants	Lowers LDL-c	Prevents bile acid reabsorption in the gastro-intestinal tract, increasing conversion of cholesterol to bile acids	Colestipol
Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors	Lowers LDL-c	Binds to PSCK9 protein, preventing it from breaking down LDL receptors on hepatic cells, increasing cholesterol uptake	Evolocumab, Alirocumab

1.4 Evidence for the association between blood lipids and dementia

This section provides an overview of the varying sources of evidence on the relationship between blood lipid levels and dementia risk.

1.4.1 Basic science

A role for lipids in the aetiology of dementia is supported by both genetic linkage studies and functional cell biology studies. The generation of the amyloid plaques found in the brains of Alzheimer's patients is cholesterol dependent,[47,48] while the most established genetic risk factor for late-onset dementia, apolipoprotein E ($Apo\mathcal{E}$), is involved in cerebral cholesterol transport. Several other genes involved in cholesterol transport have also been found to be associated with increased AD susceptibility.[49–51]

Despite these results, evidence from the diverse range of epidemiological studies on this topic has been inconclusive.

1.4.2 Observational studies

By far the largest source of evidence on the relationship between blood lipids and dementia outcomes comes from observational designs. Several studies have examined the relationships between concentrations of serum lipids (total cholesterol (TC), LDL-c, HDL-c and triglycerides) and both Alzheimer's disease and vascular dementia. These studies have reported extremely varied results. In some, a high serum cholesterol concentration has been found to be associated with an increase in susceptibility to AD,[52–56] however others have shown no association,[57–60] or a reduced susceptibility.[61,62] With regard to vascular dementia, decreased levels of HDL-c appear to be associated with increased risk,[62] while for LDL-c, studies have reported both positive and negative associations.[62,63]

1.4.3 Randomised controlled trials

In terms of the central research of this thesis, randomised controlled trials (RCTs) of statin therapy can be used to provide indirect evidence on the effect of reducing blood LDL-c levels on dementia risk. However, RCTs may be infeasible if the outcome of interest is one with a long prodromal period, such as dementia (see Section 1.2.1), as they would require extremely long and costly follow-up.[64] It is no surprise then that the two previous trials providing evidence on the effect of statins on dementia risk, identified by a recent Cochrane review,[65] are in fact trials of statins for the prevention of coronary-related outcomes.

While being widely cited, these studies have major limitations that reduce their utility as a source of evidence on the effect of statin treatment in assessing the impact of lipid-lowering treatment on dementia risk. Firstly, the criteria used to determine a dementia outcome are prone to misclassification. One of the trials, the Prospective Study of Pravastatin in the Elderly (PROSPER) trial,[66] reported not on dementia outcomes but on the change in cognitive scores. As alluded to in Section 1.2.2, a "change in score" alone is insufficient to diagnose a dementia outcome. The second trial, the Medical Research Council/British Health Foundation Protection Study,[67] found no effect of simvastatin on dementia (OR: 1.00, 95%CI: 0.61-1.65), but did not report how the outcome was assessed/recorded within the trial.

Additionally, the two trials did not make any effort to assign an underlying pathology to each case, instead reporting an all-cause dementia outcome. As discussed in Section 1.2.1, the different underlying pathologies of dementia have different mechanisms of action, and so it is not guaranteed that the effect of statins would be consistent across them.

Both trials were also limited by the relatively short follow-up period examined. This limited follow-up was to be expected because the primary aim of both trials was to assess the effect of statins on short-term coronary-related outcomes.[66,67] The PROSPER trial had a mean follow-up of 3.2 years, while the MRC/BHF Protection Study estimated risk at 5 years of follow-up. Given the long lag time between non-symptomatic onset of dementia and clinical presentation, it is likely that these durations are insufficient to fully capture the onset of dementia. Finally, as they included only patients at high vascular risk, their generalisability to other settings is limited.[65]

1.4.4 Mendelian randomisation

Newer methodological approaches, such as Mendelian randomisation (MR),[68] have also been used to examine the effect of varying lipid levels on dementia risk. Mendelian randomisation attempts to combat the risk of reverse causation and residual confounding inherent to observational studies by using natural random variation in participants' genomes.[69] In brief, MR uses genetic variants that are both strongly associated with the exposure of interest and are independent from potential confounders to strengthen causal inference.[68] The analytic method relies on several assumptions about the instrumental variable (IV)[70] which are discussed in Section 4.5.3.

Recent MR studies indicated that genetically determined low levels of LDL-c may cause a reduction in AD risk.[71,72] However, the effect was attenuated in sensitivity analyses that exclude the region surrounding the *Apo$\mathcal{E}$* gene, the strongest known risk factor for Alzheimer's disease.[73] Inclusion of *Apo$\mathcal{E}$* variants invalidates the exclusion restriction criteria (Assumption 3, above), as the risk reduction observed may be driven by variants in this region via a pathway independent of lipid levels.

This was supported by further MR studies in which the observed effect attenuated to the null after *Apo$\mathcal{E}$* variants were excluded.[74] Despite the increasing number of MR studies examining this topic, no systematic review of this study design as a source of evidence has been performed.

In summary, multiple sources of evidence exist on the relationship between statins and dementia. In the next section, I introduce the synthesis of diverse sources of evidence as the theoretical framework used in this thesis.

1.5 Theoretical framework: Evidence synthesis

Evidence synthesis is the process of finding and integrating information from several sources to examine a research question.[75] The results of an evidence synthesis exercise can be used to provide a more definitive answer to that question or, failing that, to highlight gaps in the existing evidence base. The ability to identify these gaps is particularly useful in guiding future research to address questions that have yet to be answered. A common type of evidence synthesis exercise is a systematic review, either with or without a meta-analysis.[76]

This thesis seeks to use an evidence synthesis framework to assess the effect of lipid levels, and treatments that influence lipid levels, on dementia outcomes. Specifically, this thesis considers three concepts within the umbrella term of evidence synthesis:

- Inclusion of preprints
- Individual participant data meta-analysis
- Triangulation across evidence sources

These three elements are expanded on below and are used to frame the research presented in the subsequent Chapters.

1.5.1 Inclusion of preprints

The importance of including grey literature, defined as literature not published in peer-reviewed journals,[77] in systematic reviews is widely acknowledged. Meta-research studies have demonstrated that systematic reviews excluding grey literature sources overestimate the effect of interventions.[78–80] Common, well-accepted forms of grey literature include conference abstracts, government reports and theses.[77,81]

However, the role of preprints in evidence synthesis is less well defined. Described by the Committee on Publication Ethics as 'scholarly manuscript[s] posted by the author(s) in an openly accessible platform, usually before or in parallel with the peer review process',[82] preprints serve several purposes. They are used to establish primacy when submitting to a journal where the peer-review process may take several months.[83] In addition, the allow for the rapid dissemination of research findings, as occurred during the COVID-19 pandemic.[84] Finally, they are a source of information on manuscripts that may not have been accepted elsewhere, helping to combat publication bias or the "file-drawer" effect.[85]

One of the major criticisms of using preprints as an evidence source is that they have not yet undergone formal peer review.[86,87] However, this approach assigns substantial weight to peer-review as an indicator of "quality", and is at odds with the acceptance of non-reviewed conference proceedings as an evidence source.[81,88] The argument for including preprints as an evidence source is further strengthened by results that demonstrate preprinted studies seldom change following peer review. Meta-studies of the concordance between preprinted and published studies showed that results were broadly comparable between the two, indicating that while the numerical results may change, the overall interpretation of the results were consistent in the majority of cases.[89–91] This indicates that preprints should be considered a reliable reflection of a given study.

In this thesis, preprints are considered an important source of evidence, in contrast to previous reviews on this topic. However, as with grey literature,[88] there are several logistical problems with carrying out systematic searches in preprint repositories.

As such, to enable the inclusion of preprints in the systematic review described in Chapters 3 & 4, a new tool addressing these issues is presented in Chapter 2.

1.5.2 Individual participant data meta-analysis

Individual participant data (IPD) meta-analyses are commonly considered to be the gold standard in evidence synthesis methodology.[92,93] IPD methods seek to obtain the raw data from each study identified in a systematic review, rather than basing the meta-analysis on summary results extracted from the literature.[92]

In the context of this thesis, if lipids are found to have a causal role in development of dementia, evidence-based preventative strategies would be best informed by identifying the types of individuals who are most likely to receive benefit from treatment with lipid-modifying agents.[94–96] However, if primary studies do not present results stratified by covariates of interest, meta-analyses of summary-level data on this topic often have limited ability to examine research questions related to exposure-covariate interactions.[92] Based on existing evidence, participant age and sex are considered to be of particular interest.[94,97]

An IPD meta-analysis of lipid levels on dementia outcomes would overcome this limitation of summary-level data because access to the raw data allows for an analysis that investigates these interactions.[98] This approach has the added benefit of allowing a common set of inclusion criteria and a common statistical model to be applied across all datasets, potentially eliminating some important causes of heterogeneity.[99]

Despite their advantages, IPD meta-analyses are rarely performed.[100] Factors limiting their uptake include the increased time and effort they require when compared to a summary-level analysis, and the low success rate associated with obtaining the raw data.[101,102] The data underlying primary studies are frequently not publicly available,[103,104] and the availability of data "available on request" from authors declines rapidly over time.[105] Several systematic barriers to open data sharing have been identified[106]. Of particular concern for biomedical IPD analyses are legal issues surrounding the sharing of medical data, motivated by concerns around patient privacy.[107]

In response to these limitations, new collaborative initiatives have developed to enable rapid access to relevant data in a secure supported workshop. The most import in relation to this thesis is the Dementia Platform UK (DPUK),[108] which aims to provide access to several dementia-related datasets via a single simplified application process.

I will attempt to obtain the raw data from relevant primary studies identified by the systematic review presented in Chapters 3 & 4. Any data obtained will be combined with that available from the DPUK portal as part of an IPD meta-analysis in Chapter 6. This will enable the assessment of the effect of lipids on dementia, and whether this relationship is modified by key variables such as participants' age or sex.

1.5.3 Triangulating across study designs

As illustrated in Section 1.4, several diverse epidemiological methods have been used to examine the effect of varying blood lipid levels on dementia risk. Aetiological triangulation is a developing evidence synthesis method that seeks to exploit these differences in study design, and as a result, in underlying bias structures.[109] If several sources of evidence are available and point towards identical conclusions about an exposure-outcome relationship, and these sources are at risk of unrelated biases, this strengthens our confidence in the result. The ideal scenario is where predicted sources of bias are likely to be in competing directions, one to strengthen the effect of the exposure and the other to attenuate it.[109] As such, triangulating these results can provide a middle ground between the competing directions of bias. A triangulation approach can also prove useful in helping to prospectively design new studies that are at risk of different sources of bias to those already observed in the published literature.[110] However, existing methods for triangulation are limited to a qualitative discussion of the different identified results with respect to their biases,[109] an approach which faces issues in interpretability when assessing many results.

To address this limitation, this thesis seeks to develop and apply a novel quantitative triangulation approach to answer causal questions on the effect of blood lipids on dementia outcomes. All existing evidence, regardless of study design, is first identified and assessed for risk of bias by the systematic review presented in Chapters 3 & 4. The existing evidence base is then supplemented by two primary analyses, presented in Chapters 5 and 6. Finally all existing and new evidence is incorporated into the quantitative triangulation framework in Chapter 7.

1.6 Thesis overview

1.6.1 Aim and objectives

The central aim of this thesis was to infer the causal effect of blood lipid levels on dementia outcomes via evidence synthesis methods. The specific research objectives that this thesis seeks to address are:

- To create a tool that allows for the inclusion of health-related preprints in evidence syntheses in a systematic and reproducible manner
- To review all available evidence across multiple diverse study designs to assess the effect of lipids and lipid regulating agents on dementia risk
- To examine whether there is evidence for an effect of lipid-regulating agents on dementia and related outcomes in a large-scale population-based cohort, the Clinical Practice Research Datalink (CPRD)
- To produce evidence on lipid-covariate interactions as part of an IPD meta-analysis
- To propose a generalised framework for the quantitative triangulation across diverse evidence sources

1.6.2 Structure

Chapters are self-contained, presenting the methods and results of that specific research project. The sole exception to this is the systematic review, which due to its size is split across Chapters 3 (Methods) & 4 (Results). Each chapter is bookended by introductory and summary sections which place the methods and results in context. Finally, each chapter is prefaced by a "lay" or plain English summary.

- **Chapter 1:** Background information on dementia and blood lipid levels. This chapter provides an introduction to the topics covered in this thesis and discusses the motivation for the research presented in the following chapters.
- **Chapter 2:** This chapter introduces a new tool, `medrxivr`, which was developed to allow for systematic searches of the health-related preprint repositories.
- **Chapters 3 & 4:** These chapters describe, respectively, the methods and results of a comprehensive systematic review and meta-analysis. This review examined all available evidence on the association of blood lipids and LRA with subsequent risk of dementia.
- **Chapter 5:** This chapter examines the relationship between lipid-regulating agent use and dementia outcomes in the Clinical Practice Research Datalink, a large primary care electronic health record database.
- **Chapter 6:** This chapter describes an individual participant data analysis of three longitudinal cohort studies to describe the relationship between blood lipids and dementia outcomes
- **Chapter 7**: This chapter integrates the evidence identified and produced by the preceding chapters as part of a quantitative triangulation framework.
- **Chapter 8**: This chapter summarise the key clinical and methodological findings of the thesis and discusses their implications for practice. The overall

strengths and weaknesses of this project are discussed in detail, and further avenues of research are suggested.

1.7 Outputs from this thesis

The outputs of this thesis are detailed below, and include peer-reviewed papers, presentations, and open-source evidence synthesis tools.

1.7.1 Contributions to the literature

During the course of this thesis, I have made several contributions to the scientific literature. Those arising from or directly related to the contents of this submission are presented below.

McGuinness L. A.*, Higgins J. P. T., Walker, V. M., Davies, N. M., Martin, R. M., Coulthard, E., Davey-Smith, G., Kehoe, P. G., and Ben-Shlomo, Y. (2021) Association of lipid-regulating drugs with dementia and related conditions: an observational study of data from the Clinical Practice Research Datalink. medRxiv 10.1101/2021.10.21.21265131*

Preprinted manuscript of the analysis of lipid-regulating agents and dementia outcomes in the CPRD, which is presented in Chapter 5.

McGuinness, L. A.*, and L Schmidt. (2020) medrxivr: Accessing and searching medRxiv and bioRxiv preprint data in R. Journal of Open Source Software 5.54 2651. DOI: 10.21105/joss.02651*

A paper introducing the open-source preprint search tool described in Chapter 2. As is common for journal articles describing software, the paper is intentionally short providing only a broad overview of the tool while extensive documentation is available from the project website (see Section 2.1 for more details).

Hennessy, E. A., Acabchuk, R., Arnold, P. A., Dunn, A. G., Foo, Y. Z., Johnson, B. T., Geange, S. R., Haddaway, N. R., Nakagawa, S., Mapanga, W., Mengersen, K., Page, M., Sánchez-Tójar, A. Welch, V., ***and McGuinness L. A.*** *(2021). Ensuring Prevention Science Research is Synthesis-Ready for Immediate and Lasting Scientific Impact. Prevention Science . DOI: 10.1007/s11121-021-01279-8*

The experience of extracting data for the systematic review in Chapters 3 & 4 inspired a practical guide which aims to help primary researchers make their data synthesis-ready. This piece was co-written with Dr. Emily Hennessy (see Acknowledgements in the front materials).

McGuinness, L. A.*, and Higgins J. P. T. (2020) "Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments." Research Synthesis Method). DOI: 10.1002/jrsm.1411*

A publication describing the tool used to visualise the risk-of-bias assessments in Chapters 3 & 4 has been published in Research Synthesis Methods. See Appendix B.2 for more details on this tool. Note that this publication does not describe the recently-developed functionality for producing bias direction plots, as described in Chapter 7.

McGuinness, L. A.*, and Sheppard A. L. 2020. "A Descriptive Analysis of the Data Availability Statements Accompanying Medrxiv Preprints and a Comparison with Their Published Counterparts." PLOS ONE 16(5): e0250887. DOI: 10.1371/journal.pone.0250887*

Using the tool described in Chapter 2, I led a "research-on-research" study to assess the concordance between the openness of data availability statements accompanying a sample of medRxiv preprints and their published counterparts.

For information on additional contributions to the scientific literature not directly related to this thesis, see Appendix A.1.1.

1.7.2 Presentations/Talks

"Identifying and triangulating all available evidence on the effect of blood lipids and statins on dementia outcomes": Poster presentation, Alzheimer's Association International Conference 2021.

"medrxivr: A new tool for searching for and retrieving records and PDFs from the medRxiv preprint repository": Accepted oral presentation abstract, Cochrane Colloquium 2020 (note: event was cancelled due to the COVID-19 pandemic).

"On the shoulders of giants": advantages and challenges to building on established evidence synthesis packages, using the {robvis} package as a case study": Oral presentation, Evidence Synthesis and Meta-Analysis in R Conference (ESMARConf) 2021.

"RoB 2.0: A revised tool to assess risk of bias in randomised trials": Webinar, co-presented with Dr. Theresa Moore as part of the Evidence Synthesis Ireland Methods Series.

1.7.3 Software

medrxvir

An R package that allows users to search and retrieve bibliographic data from the medRxiv[111] and bioRxiv[112] preprint repositories. See Chapter 2 for more details. Install a stable version of the package from the Comprehensive R Archive Network (CRAN), or alternatively install the development version from GitHub, using:

```r
# CRAN version
install.packages("medrxivr")

# Development version
devtools::install_github("ropensci/medrxivr")
```

triangulate

An R package containing functionality to implement the quantitative triangulation approach detailed in Chapter 7. At present, only the development version of the package is available, which can be installed from GitHub using:

```r
# Development version
devtools::install_github("mcguinlu/triangulate")
```

robvis

An R package and associated `shiny` web application that allows users to visualize the results of the risk-of-bias assessments performed as part of a systematic review. See Appendix B.2 for more details. Install a stable version of the package from CRAN, or alternatively install the development version from GitHub, using:

```r
# CRAN version
install.packages("robvis")

# Development version
devtools::install_github("mcguinlu/robvis")
```

1.8 Summary

- In this introductory chapter, I provided background information on the core elements of the central research question and framed the research presented in the context of a theoretical framework of evidence synthesis.
- I also outlined the central aim of this thesis and provided an overview of the individual analyses performed. I described the contributions of this thesis to the field, both in terms of peer-review publications and conference abstracts.
- Finally, I discussed the research tools and software developed to support the analyses performed in this thesis, one of which (the preprint search tool) is introduced more fully in the following chapter.

Why are open source statistical programming languages the best?

Because they R.

— Chris Beely, 2013[113]

2

`medrxivr`: an R package for systematically searching biomedical preprints

Contents

Lay summary

Preprints are copies of academic manuscripts that are posted online in advance of being formally peer-reviewed and published by an academic journal. As part of this thesis, a new software program called `medrxivr` was created to allow researchers to find preprints related to their research in a transparent and reproducible way. Development of this tool was important, as preprints represent a key source of information needed for the research reported in future chapters.

2.1 Introduction

Preprints represent an increasingly important source of scientific information (see Section 1.5.1). As a result, when reviewing the evidence base as part of a systematic review, repositories of preprinted articles should be considered a distinct but complementary information source to databases of published articles. The two key repositories in the health science are bioRxiv, established in 2013,[112] and medRxiv, which launched in 2019 and was designed to replace the "Epidemiology" and "Clinical Trial" categories of bioRxiv.[111]

Searching these preprints as part of the systematic review described in Chapters 3 & 4 was a necessity because many of the existing reviews on the topic of lipids and dementia have not considered this important source of evidence. At the time of writing, however, the bioRxiv and medRxiv websites allow only simple search queries as opposed to the complex searches containing Boolean logic operators (AND/OR/NOT) that information specialists use to query other major databases.[114,115] Additionally, the best available extraction mechanism for obtaining references for all records returned by a search involved going through each record and downloading individual citations one-by-one. As the scale of these preprint databases increase, particularly in light of the massive expansion of the medRxiv repository as a result of COVID-19, this already time-consuming and error-prone method is no longer feasible.

This chapter outlines the development and key functionality of `medrxivr` (version 0.0.5), a tool I created to facilitate the systematic searching of medRxiv and bioRxiv preprints. The factors that necessitated the development of this tool in the context of this thesis are outlined, and the use of `medrxivr` in my own projects and by other researchers is discussed. As the majority of work on this aspect of my thesis is represented by lines of code or online documentation (available at `https://github.com/ropensci/medrxivr` and `https://docs.ropensci.org/medrxivr/` respectively), this chapter is an intentionally short, high-level summary of my work on this project. The GitHub repository for `medrxivr` contains a complete record of the development of this tool, including discussion with other members of the systematic review community.[116]

2.2 Development

2.2.1 Success criteria

I developed the tool to meet three success criteria:[117]

1. reliable, reproducible and transparent search functionality, allowing for Boolean (AND/OR/NOT) operator logic;
2. support for bulk export of references returned to a file type that can be readily imported into a reference manager (e.g.,, *.bib* or *.ris*); and
3. automated retrieval of the full-text PDFs of relevant records.

These criteria were influenced by the need for functionality to perform systematic searches as part of the review presented in the subsequent chapters, discussion with information specialist colleagues about key features, and an informal survey of the evidence synthesis and health librarian communities on Twitter.

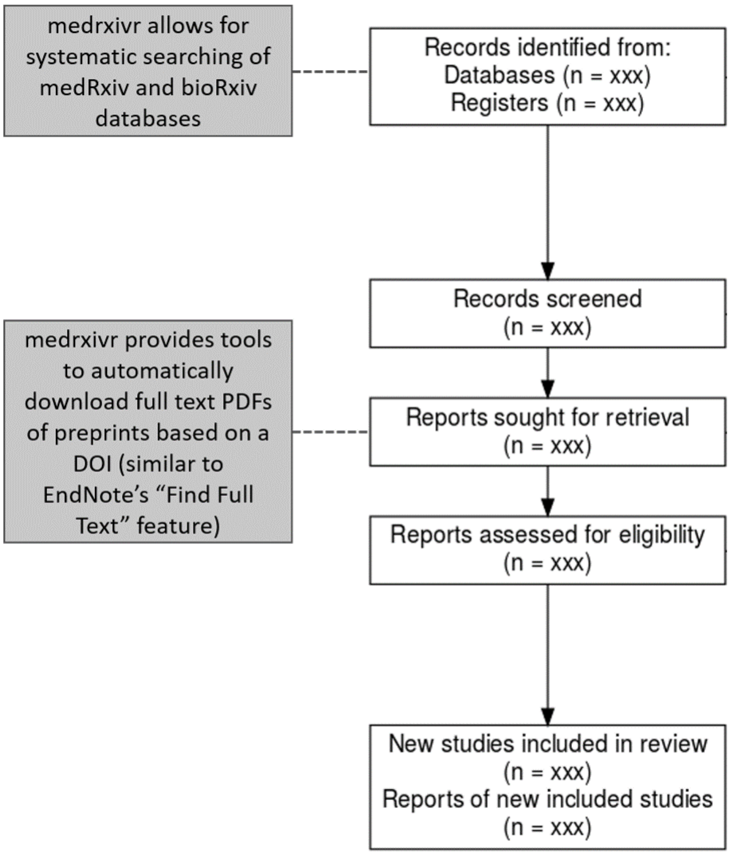

Figure 2.1: Role of `medrxivr` in a systematic review workflow - `medrxivr` allows for systematic searching of biomedical preprints as part of the initial literature searching. Following title and abstract screening, reviewers can then programmatically retrieve a copy of the PDF of included records to facilitate the full-text screening stage (similar to Endnote's "Find Full Text" feature).

2.2.2 Alternative medRxiv/bioRxiv interfaces

Prior to development of this tool, I conducted an audit of existing tools for accessing medRxiv and bioRxiv metadata. While none addresses the success criteria described above, two of these tools are useful in highlighting the additional functionality that `medrxivr` contributes.

The first, a platform called Rxivist[118], allows users to search preprints using keywords. However, the core functionality of the Rxivist platform is focused around exploring the number of times a preprint has been downloaded and/or shared on Twitter, to allow researchers to find the most popular papers related to their topic. Additionally, the search interface[119] does not allow for complex search strategies using Boolean operators.

The second preexisting tool, `search.bioPreprint`, allows users to search for terms across a range of preprint servers, including medRxiv and bioRxiv, but also journals which use a post-publication peer-review process such as F1000Research.[120] However, similar to the Rxivist platform, this tool is designed for researchers aiming to keep up to date with recent developments in their fields rather than systematically assess the entirety of the available literature. As such, the platform only returns the most recent 1,000 records by publication date.

Finally, neither tool provides an easy way to programmatically download a copy of the PDF of relevant preprints as part of the preparation for the full-text screening stage of a systematic review.

2.2.3 Early versions

Work on the `medrxivr` tool began in Summer 2019, and initially consisted of a development of a set of R scripts to allow for searching medRxiv and bioRxiv as part of the systematic search outlined in Chapter 3. Following interest from other researchers in using the *ad-hoc* web-scraping scripts, additional development work took place in 2019/2020, allowing for improved searching and exporting functionality. I released the initial version of the `medrxivr` R package in February 2020.

Early versions of the tool had a reliance on scraping data directly from the repository website. Web-scraping is a fragile mechanism for extracting data, as it is entirely dependent on consistent website design and underlying code structure remaining unchanged.[121,122]. In the case of `medrxivr`, as the medRxiv/bioRxiv websites are regularly updated, ensuring the web-scraping script continued to perform as expected required substantial maintenance work.

However, an application programming interface (API) for the medRxiv and bioRxiv repositories was made public in early 2020 by the institution responsible for managing these preprint repositories, the Cold Springs Harbor Laboratory. This allowed for newer versions of the `medrxivr` package to engage in active "fault prevention" and provide a more robust interface to the data by removing the reliance of web-scraping.[122]

2.2.4 Package infrastructure

I wrote the `medrxvir` package in R using RStudio,[123] and followed development best-practice, including detailed documentation, a robust unit testing framework (99% of all code lines within the package are formally tested across multiple platforms including Windows, MacOS, and Linux), and in-depth code review by two experienced, independent reviewers.

2.3 Usage

The `medrxivr` R package is split into two component parts:

- an interface to the Cold Springs Harbor Laboratory API, which imports medRxiv and bioRxiv metadata into R; and
- a collection of functions for working with the imported metadata, with an explicit focus on searching this data as part of a systematic review or evidence synthesis project.

The standard workflow is to download a copy of all metadata contained in the repository, and then to perform searches on this local copy. This is a workaround as the Cold Springs Harbor Laboratory API does not provide any functionality to search the database.

While the package allows users to interact with and search both medRxiv and bioRxiv metadata, because the process is identical for both, searching the medRxiv database is used as an illustrative example throughout the remainder of this chapter.

2.3.1 Installation

`medrxivr` has been released to the Comprehensive R Archive Network (CRAN), and can be installed with the following code:

```
install.packages("medrxivr")
```

Alternatively, the development version of the package can be installed from GitHub:

```
# install.packages("devtools")
devtools::install_github("ropensci/medrxivr")
```

2.3.2 Importing preprint metadata

Prior to searching the metadata, users must first create a local copy of the database, denoted using `mx_data` below. In `medrxivr`, I have provided two separate but related methods to achieve this (Figure 2.2). The first of these methods, accessed via the `mx_api_content()` function, creates a local copy of all data available from the medRxiv API at the time the function is run.

```
# Get a copy of the database from the live medRxiv API endpoint
mx_data <- mx_api_content()
```

This provides an up-to-the-minute reflection of the medRxiv preprint repository. However, this approach has two limitations. Firstly, because the API returns results as a series of pages limited to 100 records per page, downloading the entire database requires a time-intensive process of cycling through each page. Secondly, the API can become unavailable, either during peak usage times or planned maintenance windows. To address these limitations, I provide a second method of accessing medRxiv data, called via the `mx_snapshot()` function, which allows users to access a maintained static snapshot of the database. Note that due to the size of bioRxiv, only a maintained snapshot of the medRxiv repository is available via `mx_snapshot()`.

```
# Import a copy of the medRxiv data from the snapshot
mx_data <- mx_snapshot()
```

This snapshot is created each morning at 6am using a process known as "git-scraping",[124] whereby the entire database is downloaded using the `mx_api_content()` function and saved as a comma separated value (CSV) file in an online repository (Figure 2.2). Calling `mx_snapshot()` imports this CSV into R, and has the advantage of both faster loading of the data into R (because it is imported as a single file and does not require cycling through the output of the API) and an absence of any reliance on the API. The one limitation of this approach is that the snapshot (by its nature) will not contain details of records added to the database since it was taken. However, given that the number of records added each day is relatively low, this should only pose minor issues.

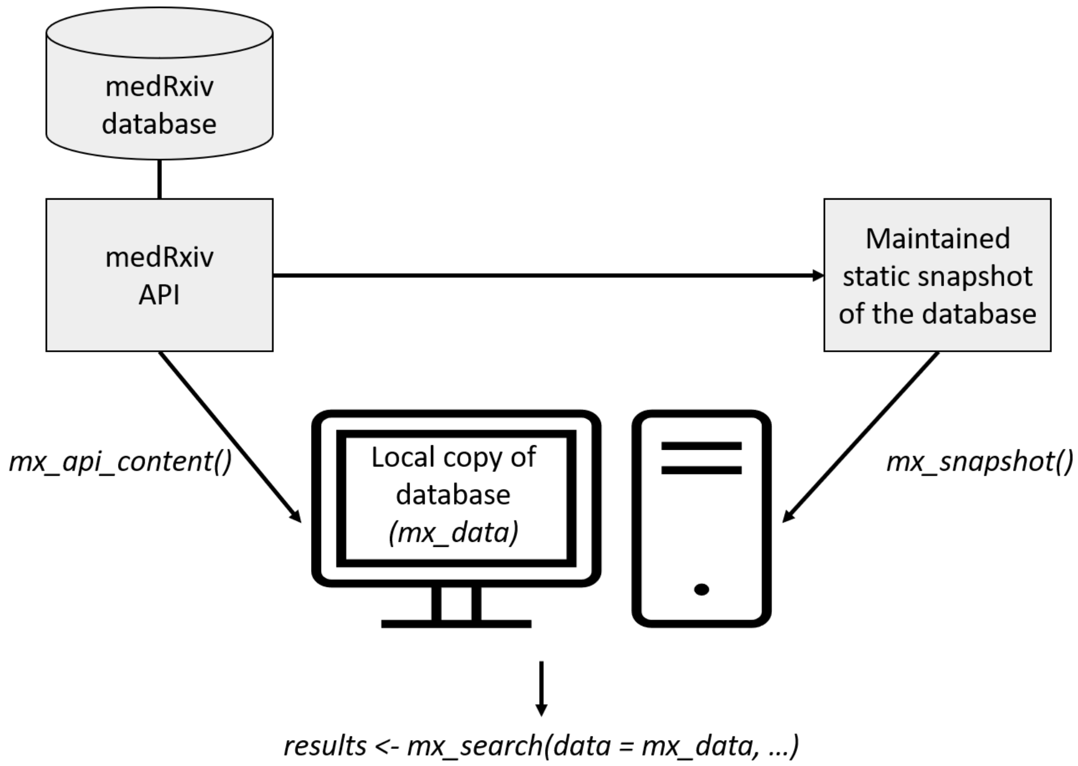

Figure 2.2: Overview of `medrxivr` data sources - Users can either access the API directly via `mx_api_content()`, or can import a maintained snapshot of the database, taken each morning at 6am, via the `mx_snapshot()` function. Note: due to the size of bioRxiv, only a maintained snapshot of the medRxiv repository is available via `mx_snapshot()`.

2.3.3 Performing a search

Once a local copy of the metadata is created, the first step in searching it is to create a search strategy. Search terms to be combined with the OR operator are contained in vectors (`c(...)`), while topics to be combined with the AND operator are contained in lists (`list(...)`).

```r
# Create the search query
topic1  <- c("dementia","alzheimer's")  # Combined with OR
topic2  <- c("lipids","statins")        # Combined with OR

myquery <- list(topic1, topic2)         # Combined with AND
```

For example, when written in standard syntax, the search contained in the `myquery` object above would be: "((dementia **OR** alzheimer's) **AND** (lipids **OR** statins))". There is no limit to the number of search terms that can be included in each topic, nor in the number of topics that can be searched for. Search terms can also contain common syntax used by systematic reviewers and health librarians, including the NEAR operator for the identification of co-localised terms and wild cards which allow for alternate spellings (e.g., "randomi*s*ation" vs "randomi*z*ation").

Once a strategy has been defined, it is passed along with the local copy of the database to the `mx_search()` function.

```r
# Run the search
results <- mx_search(mx_data,
                     myquery)
```

Note that for my example, I took a two-step approach by first creating the full search term `myquery` which is then passed to `mx_search()`. This is not necessary to perform a search, as users can pass terms directly to `mx_search()`:

```r
# Run a search to find all records with "dementia"
results <- mx_search(mx_data,
                     "dementia")
```

2.3.4 Refining a search

An important feature of the `mx_search()` is the `report` functionality, which outputs a structured table showing each search term along with the corresponding number of records.[125]

```
results  <- mx_search(mx_data,
                      myquery,
                      report = TRUE)
```

```
## Found 1 record(s) matching your search.
##
## Total topic 1 records: 224
## dementia: 224
## alzheimer's: 0
##
## Total topic 2 records: 119
## lipids: 90
## statins: 33
```

This is important as part of developing a search strategy,[114] because it allows for the key terms related to each topic to be discovered. It also aids in identifying misspelled or case-sensitive search terms, which will frequently return no results. As an example, in the search presented above, the term "alzheimer's" returns no records. This is expected because "Alzheimer's" is a proper noun and so should be capitalised, but serves to illustrate the usefulness of the reporting function.

In hindsight, the decision to make the search case-sensitive was a poor one because users reported being unaware of this setting when carrying out their search. However, changing the default behaviour of `mx_search()` to be case-insensitive is problematic because it could result in different numbers of hits based solely on which version of the package the user has installed. To address this, `mx_search()` now contains an `autocaps` argument, which when set to `TRUE` will automatically search for both capitalised and uncapitalised versions of the search term.

2.3.5 Exporting to a bibliography file

In line with my second success criteria (Section 2.2.1), one of the key features of the `medrxivr` is the ability for users to easily export the results of their systematic search to a reference manager. While this would seem a likely candidate to be a generic feature, this is one of the key ways in which `medrxivr` is set apart from other preprint search tools. None of tools that I audited provide this feature, nor does the native medRxiv/bioRxiv website search.

The results of our simple search above can be exported to the `medrxiv_export.bib` file using the following code:

```
mx_export(results,
          file = "medrxiv_export.bib",
          report = TRUE)
```

2.3.6 Downloading the PDFs of relevant records

`medrxivr` also allows users to download the full text papers for records that are deemed eligible for full-text screening (see Figure 2.1). `mx_download()` takes the list of included records and saves the PDF for each to a folder specified by the user.

```
mx_download(results,  # Search results, less excluded records
            "pdf/")   # Directory to save PDFs to
```

2.4 Discussion

2.4.1 Reception and future plans

The tool has been well received by the community (as of December 2021, `medrxivr` has been downloaded more than 6100 times), and several use cases have been reported. It has been used to investigate the role of preprints in the response to the 2019 coronavirus outbreak,[126] perform searches of preprints as part of a systematic review,[127,128] and examine how data-sharing behaviour is affected by journal policies (see 1.7).[129]

The package has been accepted into the rOpenSci suite of packages, a collection of "carefully vetted, staff- and community-contributed R software tools that lower barriers to working with scientific data sources on the web".[130] As part of this process, following rigorous peer-review, an associated article introducing the tool was published by the Journal of Open Source Software.[131] The entire review discussion is publicly available and can be viewed online.[132] The tool has also been well received by the open-source community, demonstrated by the engagement of other developers in contributing to important new functionality and suggesting bug-fixes.

Lobbying of the Cold Springs Harbor Laboratory to develop the API to allow for direct searching of the database has been ongoing. This would negate the current need to download a local copy of the relevant preprint database before searching it, which is currently the rate limiting step for performing searches. For example, as of January 2021, downloading a copy of the bioRxiv database takes approximately one hour.

2.4.2 Use cases

In addition to being used to systematically search health-related preprint servers, as illustrated in the systematic review presented in Chapters 3 & 4, `medrxivr` has other uses.

For example, I led a descriptive analysis of the change in data availability statements between preprinted and published versions of the same manuscript, stratified by journal data sharing policy access, underpinned by preprint meta-data provided by `medrxivr`. By comparing the preprinted and published versions of the data availability statement, I could examine the same manuscript - same content, authors and funders - under two different publication policies (preprint server vs peer-review journal). This comparison provides evidence on whether stricter policies which require data sharing as a condition of publication result in increased data availability. The analysis found some evidence that data availability statements more frequently described open data on publication when the journal mandated data sharing, compared to when the journal did not mandate data sharing. This study has since been published,[129] and a copy is included in Appendix B.3.

Secondly, using `medrxivr`, an analysis of the publication rate for medRxiv preprints was performed (see Appendix A.2.1). 87 of the 129 records (67.4%) posted on medRxiv in July 2019 were published by 30th July 2021 (i.e., allowing for a two-year lag between preprint posting and publication). This finding agrees with previous work demonstrating that two-thirds of bioRxiv preprints are published in a peer-reviewed journal within two years of posting.[133] This analysis further illustrates that a substantial number of studies are never formally published but remain accessible as preprints.

In summary, the meta-research/methodological analyses described above illustrate that easy access to medRxiv/bioRxiv metadata has applications beyond the inclusion of preprints in systematic review.

2.4.3 Limitations of `medrxivr`

While searching the medRxiv and bioRxiv databases was crucial for the systematic review element of my thesis, there are some important limitations to note here. A key example is that the tool only searches the available metadata of preprint records (the title, abstract and keywords), rather than the full text of preprints, and so some relevant records might be missed. However, this approach echoes that used by other search platforms such as OvidSP, and while some relevant records may be missed (reduced sensitivity), limiting the search to the metadata fields prevents non-relevant records from being returned (high specificity). A key example of the reduced specificity when searching the full text, identified during development of `medrxivr`, is that a search for “dementia” would return a record where the only occurrence of this term is in the title of one of the references.[134]

There is also the potential that the cross-section of literature posted on medRxiv/bioRxiv is substantially different from those suffering from publication bias (studies or analyses that are not published for a range of reasons including results that are not deemed “novel” or are not statistically significant).[135] This is because simply lowering the barriers to publication may well encourage authors to published “null” results, but due to the effort involved in writing up a distributable manuscript, it is unlikely to completely address the “file drawer” effect.[85]

It is probably too early (and likely too methodologically difficult) to tell whether the increased popularity and acceptance of preprint repositories will have any effect of the availability of research that was not considered “publishable” at other venues.

2.4.4 Role of open-source tools in evidence synthesis

Part of the motivation for creating the `medrxivr` tool was a belief that the development and distribution of open-source scripts and tools should be a fundamental part of evidence synthesis research.[136,137] In the case of `medrxivr`, it is likely that several other evidence synthesists had written personal scripts that have a similar, or related, functionality - in fact, following development of the tool, I identified one other researcher that has done so (Nicholas Fraser, author of the `rbiorxiv` package, which allows for importing medRxiv metadata into R but does not provide search functionality).[138] If these scripts continue to be developed in private and are never shared or publicised, this will inevitably hamper the efforts of the evidence synthesis community, not only in terms of duplication of time and effort but also due to lost opportunities for collaboration.[137] Creating and sharing well-documented packages, the recognised standard for sharing code in R, represents one way to reduce this inefficiency.[139]

2.5 Summary

- In this Chapter, I have introduced a new tool, `medrxivr`, for performing complex systematic searches of the medRxiv and bioRxiv preprint repositories.
- I have outlined the motivation for developing this tool in relation to this thesis - more specifically, that it was used to perform systematic and reproducible searches of key literature sources used in the comprehensive systematic review described in Chapters 3 & 4.
- I have contrasted `medrxivr` with other available interfaces to medRxiv/bioRxiv data to highlight the added functionality it offers. I have also discussed the tool's reception to date, its limitations, and the important role of open-source tools like `medrxivr` in evidence synthesis.

It is surely a great criticism of our profession that we have not organised a critical summary by speciality or sub-speciality, up-dated periodically, of all relevant RCTS.

— Archibald Cochrane, 2000[140]

3

Systematic review of existing evidence on the association between blood lipids and dementia outcomes: Methods

Contents

Lay summary

Systematic reviews are a type of research study that aim to collect and combine all existing evidence to provide the best possible answer to a research question. Well-performed reviews involve multiple steps including: searching for existing studies; assessment of the studies against predefined inclusion criteria; collection of data from each study; and assessment of each study's method and results.

This chapter presents the methods used to perform a systematic review of primary studies that have examined the relationship between the levels of blood lipids (such as cholesterol and triglycerides) and dementia outcomes. In addition, the review included studies that examined the relationship between treatments that change blood lipid levels, such as statins, and dementia outcomes. The results of this systematic review are presented in Chapter 4.

3.1 Introduction

In this chapter, I describe a comprehensive systematic review of the relationship between blood lipid levels (and treatments that modify them) and the subsequent risk of dementia and related outcomes.

This analysis sought to address two specific aims. Firstly, as discussed in the introduction to this thesis (Section 1.4), several diverse forms of evidence on the relationship between lipids and dementia exist. These include randomised controlled trials, observational studies of different design, and Mendelian randomisation studies. However, based on a scoping review of existing literature, no previous evidence synthesis exercise has attempted to examine the association of lipid levels with dementia outcomes across these distinct evidence types. Collating these diverse evidence sources is important because, if the observed association between lipids and dementia is constant across them, it increases our confidence in the association. As such, the primary aim of this analysis was to systematically review all available literature describing prospective analyses, regardless of study design.

Secondly, I explicitly sought to include health-related preprint servers as a potential evidence source in this review, as they are infrequently considered by evidence synthesists but can report relevant unpublished analyses. As a sensitivity analysis to the review presented in this chapter, I sought to quantify the additional evidential value of relevant preprints, making use of the preprint search tool presented in Chapter 2.

Given the size of the review, I have split its reporting across two separate chapters for ease of reading. This chapter details the methodology used, while Chapter 4 presents the results.

3.2 Methods

3.2.1 Protocol

A pre-specified protocol for this analysis was registered on the Open Science Framework platform and is available for inspection.[141] Deviations from the protocol are summarised in Appendix A.3.1.

3.2.2 Contributions

In line with best-practice guidance, secondary reviewers were used to check the accuracy of screening, data extraction and risk-of-bias assessment processes. Due to the scale of the project, this review was performed in conjunction with a team of secondary reviewers (see Acknowledgements in the front matter).

3.2.3 Eligibility criteria

Inclusion criteria

I sought to include studies that examined blood lipid levels as a risk factor for dementia outcomes, defined either as a binary hypercholesterolemia variable or by category/1-standard-deviation increase in a specific lipid fraction. The fractions considered by this review were namely total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides (TG). I also aimed to include studies examining the effect of lipid-regulating agents (LRA) as a source of indirect evidence. LRA are treatments used to modify blood lipids levels, and common examples include statins, fibrates, and ezetimibe.

Eligible study designs were randomised controlled trials of LRA, cohort studies examining blood lipids or LRA, and genetic instrumental variable studies (more commonly known as Mendelian randomisation studies) examining the effect of genetically increased/decreased blood lipid levels.

Eligible studies screened participants for dementia at baseline and excluded any prevalent cases. Alternatively, where no baseline screening was employed, participants were assumed to be dementia free if less than 50 years of age at baseline. Eligible studies defined dementia outcomes according to recognised criteria. Examples of acceptable criteria included the International Classification of Diseases (ICD),[142] the National Institute of Neurological Disorders and Stroke Association-Internationale pour la Recherche en l'Enseignement en Neurosciences (NINDS-AIREN),[13] and the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria.[3] Studies utilising electronic health records were an exception to this, as it was assumed that health care professionals employed their own expertise when entering the outcome into the EHR.

Studies of any duration were included, and no limits were placed on the sample size of included studies. Finally, conference abstracts with no corresponding full-text publication were eligible, and where required, I contacted authors to obtain relevant additional information not available from the abstract. No limitations were imposed on publication status, date, venue or language.

Exclusion criteria

Due to the significant impact of a memory-related outcome such as dementia on exposure recall, case-control studies were excluded, though case-control studies where historical records are used to determine the exposure status were eligible for inclusion. Cross-sectional studies, qualitative studies, case reports/series and narrative reviews were also excluded, as were studies that measured change in continuous cognitive measures (e.g., Montreal Cognitive Assessment (MoCA) score) without an attempt to map these scores to ordinal groups (e.g., no dementia/dementia).[143] Previous systematic reviews were not eligible for inclusion, but their reference lists were screened to identify any potentially relevant articles.

Studies with outcomes not directly related to the clinical syndrome of dementia (e.g.,, neuroimaging) were excluded. Additionally, studies implementing a “multi-domain intervention” where a lipid-regulating agent is included in each arm were excluded. For example, a study examining exercise + statins versus statins alone would be excluded, but a study examining exercise + statins vs exercise alone would be eligible as the effect of statin use can be estimated. Finally, studies using a dietary intervention, for example an omega-3 fatty acid enriched diet, were excluded as it is difficult to disentangle the effect of other elements contained within the diet. Note that this is distinct from studies which delivered a simple tablet-based omega-3 intervention, which would have been eligible for inclusion.

3.2.4 Information sources and search strategy

I systematically searched several electronic bibliographic databases to identify potentially relevant entries (hereafter referred to as "records"). The following databases were searched in June 2019 from inception onwards: MEDLINE, Embase, PsychINFO, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science Core Collection. Given that the contents of the Web of Science Core Collection can vary by institution,[115] the specific databases and date ranges for each database searched via this platform are listed in Appendix A.3.2.

The search strategy used in each database was developed in an iterative manner using a combination of free text and controlled vocabulary (MeSH/EMTREE)[81] terms, incorporating input from an information specialist. The strategy included terms related to lipids, lipid modifying treatments, and dementia, and was designed for use in MEDLINE before being adapted to the other bibliography databases listed. A high-level outline of the strategy is presented in Table 3.1 below and the full search strategies for each database are presented in Appendix A.3.3.

Table 3.1: Summary of systematic search by topic - The full search strategy for each databases searched, including all search terms and the number of hits per term, is presented in Appendix A.3.3.

No.	Concept
1	Dementia
2	Lipids
3	Lipid-modifying treatments
4	1 AND 2
5	1 AND 3
6	4 OR 5
7	Animals NOT (Animals AND Humans)
8	6 NOT 7
9	Observational filter
10	Randomised controlled trial (RCT) filter
11	Mendelian randomisation/Instrumental variable filter
12	OR/ 9-11
13	8 AND 12

For all topics, search queries were comprised of relevant free text & controlled vocabulary terms.

When searching the bibliographic databases, study design filters (Lines 9-11 in Table 3.1) were employed to try to reduce the screening load. I confirmed that the study design filters were not excluding potentially relevant records by screening a random sample of 500 records identified by the main search but excluded by the filters (defined as “8 NOT 12” in Table 3.1).

I also searched clinical trial registries, for example ClinicalTrials.gov, to identify relevant randomised controlled trials. In addition, I searched the bioRxiv and medRxiv preprint repositories using the tool developed in Chapter 2 to identify potentially relevant preprinted studies (see Appendix A.3.4 for the code used to search these preprint repositories).

Grey literature was searched via ProQuest, OpenGrey and Web of Science Conference Proceedings Citation Index, and theses were accessed using the Open Access Theses and Dissertations portal. In addition, the abstract lists of relevant conferences (e.g., the proceedings of the Alzheimer's Association International Conference, published in the journal Alzheimer's & Dementia) were searched by hand. Finally, the reference lists of included studies were searched by hand, while forward and reverse citation searching ("snowballing") was performed using Google Scholar.[144,145]

3.2.5 Study selection

Records were imported into Endnote and de-duplicated using the method outlined in Bramer et al. (2016).[146] In summary, this method uses multiple stages to identify potential duplicates. The initial step involves automatic deletion of records matching on multiple fields ("Author" + "Year" + "Title" + "Journal"), and is followed by manual review of articles with less overlap (e.g., those identified as duplicates based on the "Title" field alone).

Following de-duplication of records, screening (both title/abstract and full-text) was performed using a combination of Endnote and Rayyan. Endnote is a citation management tool,[147] and Rayyan is a web-based screening application.[148] Title and abstract screening to remove obviously irrelevant records was performed, with a random ~10% sample of excluded records being screened in duplicate to ensure consistency with the inclusion criteria. Additionally, I re-screened the same ~10% sample with three-month lag to assess intra-rater consistency.

Similarly, I completed all full-text screening, with a random ~20% being screened by a second reviewer. Additionally, any records I identified as being difficult to assess against the inclusion criteria were also screened by the second reviewer. Reasons for exclusion at this stage were recorded. Disagreements occurring during either stage of the screening process were resolved through discussion with a senior colleague. A PRIMSA flow diagram was produced to document how records moved through the review.[149]

3.2.6 Validation of screening process

Inter- and intra-rater reliability during the screening stages were assessed for a 10% sub-sample of records. Intra-rater reliability involved a single reviewer applying the inclusion criteria to the same set of records while blinded to their previous decisions (i.e., assessment of consistency), while inter-rater reliability involved two reviewers independently screening the same set of records (i.e., assessment of accuracy).

Rater reliability was assessed using Gwet's agreement coefficient ($AC1$).[150] This approach was chosen over other measures such as percent agreement because it accounts for chance agreement between reviewers but does not suffer from bias due to severely imbalanced marginal totals in the same way that Cohen's *kappa* value does.[150] Given the small number of included studies in this review as a proportion of the total number screened, this is a useful characteristic. The formulae used to calculate $AC1$ are given in Appendix A.3.5.

Interpretation of agreement coefficients is a widely debated topic, and while arbitrary cut-off values may mislead readers,[153] they provide a useful rubric by which to assess inter-rater agreement. Here, I used guidelines based on a stricter interpretation of the Cohen's *kappa* coefficient,[154] presented in Table 3.2.

Table 3.2: Ranges for Gwet's $AC1$ - To aid the interpretation of inter-/intra-rater reliability, I used a published set of suggested categories for Gwet's AC1.[154]

Kappa	Interpretation
0 – 0.20	None
0.21 – 0.39	Minimal
0.40 – 0.59	Weak
0.60 – 0.79	Moderate
0.80 – 0.90	Strong
> 0.90	Almost perfect

Intra- and inter-rater reliability was assessed against these cut-offs. If this assessment demonstrated an issue with the screening process (defined as an $AC1$ of less than 0.9), it indicated the need for a larger proportion of records to be dual screened.

3.2.7 Data extraction

Data extraction was performed using a piloted data extraction form. I extracted all data in the first instance, which was subsequently checked for accuracy by a second member of the review team. Extracted items included:

- Article metadata: year of publication, author, journal
- Study characteristics: study location, data source, exposure, outcomes, diagnostic criteria used
- Patient characteristics: age, sex, baseline cognition scores, baseline education scores
- Results: exposure, outcome, effect measure, effect estimate, error estimate, p-value

Grouping multiple reports into studies

As part of the data extraction process, multiple records resulting from a single analysis were included and grouped into single units, hereafter referred to as studies. This was most common in cases where multiple records reported on the same analysis but at different time points. In this case, the result corresponding to the longest follow-up was used. Grouping records into studies builds out the most comprehensive account of a given analysis by incorporating information from all available records.

This was particularly relevant to preprints and published papers reporting the same study, which were not considered to be duplicate records but instead different reports of the same study. This decision was taken due to the potential for the published version to offer some information that the preprint did not, and vice versa.

Combining across groups

In line with best practice, where summary data was presented across two groups (e.g., age at baseline stratified by hypercholesterolemia status), the following approach was used to combine the groups:[155]

$$N = N_1 + N_2 \tag{3.1}$$

$$Mean = \frac{(N_1 M_1 + N_2 M_2)}{(N_1 + N_2)} \tag{3.2}$$

$$SD = \sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1 N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1 M_2)}{N1 + N2 - 1}} \tag{3.3}$$

where N_i, M_i and SD_i denote the number of participants, mean and standard deviation in the ith subgroup, respectively. This approach was implemented in a systematic manner, with the raw group data being extracted and a cleaning script employed to combine the groups for analysis.

Harmonisation of cholesterol measures

Where necessary, lipid levels reported in *mmol/L* were converted in *mg/dL* using the following formula:

$$mg/dL = mmol/L \times Z \tag{3.4}$$

where $Z = 38.67$ when converting total cholesterol, LDL-c and HDL-c measures, and $Z = 88.57$ when converting triglyceride measures.[156] The choice of mg/dL was influenced by the widely-used categories of lipids levels on the mg/dL scale, as shown in Table 1.2 in Section 1.3.1.

Following up with authors

Where additional data not reported by a study were required either for data extraction or risk-of-bias assessment, the corresponding author of the study was contacted. This approach was taken due to the potentially large impact of additional information obtained through contact with study authors on the results of the review.[157]

3.2.8 Risk-of-bias assessment

A key aim of the review presented here is to identify different sources of evidence at risk of a diverse range of biases, and to contrast and compare findings across them (see Section 1.5.3 for an overview of triangulation and Chapter 7 for the results of this analysis). To enable this triangulation exercise, detailed and structured risk-of-bias assessments formed an important part of this review.

There has been a recent movement within the evidence synthesis community away from examining *methodological quality* towards assessing *risk of bias*,[158,159] and thus directly evaluating the internal validity of a study. Internal validity is defined here as the absence of systematic error (or bias) in a study, which may influence its results.[160,161]

This move was prompted by an unclear definition of methodological quality which could include facets such as unclear reporting, in addition to challenges in the comparison of results from different tools. As part of this shift, the focus moved from checklists and score-based tools towards domain-based methods, in which different potential sources of bias in a study are assessed in order. Additionally, the new tools move from assessing bias at the study level to considering each individual numerical result separately. For example, a study may report on the efficacy of an intervention at six months and two years follow-up. In this case, the proportion of missing outcome data may not be an issue at six months but may introduce bias after two years of follow-up. In this case, assigning a single risk-of-bias judgement to the study as a whole would mask the different biases applicable to each unique result.

In this review, domain-based tools were used to assess the risk of bias for each result in each included study. The study-design-specific tools are introduced and discussed in more detail in the following sections.

Randomised controlled trials

Randomised controlled trials were assessed using the RoB 2 tool.[162] This tool assesses the risk of bias across five domains:

- bias arising from the randomisation process,
- bias due to deviations from intended intervention,
- bias due to missing outcome data,
- bias in measurement of the outcome,
- bias in selection of the reported result.

Acceptable judgements for each domain include: “low risk”, “some concerns”, “high risk”. Each of the five domains contains a series of signaling questions or prompts which guide the user through the tool. Once a domain-level judgement for each domain has been assigned, an overall judgement, using the same three levels of risk of bias, is assigned to the result.

Non-randomised studies of interventions/exposures

For non-randomised studies of interventions (NRSI), I used the ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) tool.[159] This tool assesses the risk of bias across seven domains:

- bias due to confounding,
- bias due to selection of participants,
- bias in classification of interventions,
- bias due to deviations from intended interventions,
- bias due to missing data,
- bias in measurement of outcomes, and
- bias in selection of the reported result.

Similar to RoB 2, it has a number of signaling questions which inform the domain-level judgement, with acceptable judgements including "low", "moderate", "serious" and "critical". In the context of the tool, observational studies are assessed in reference to an idealised randomised controlled trial. Under this approach, the (rare) overall judgement of "low" indicates that the results should be considered equivalent to that produced by a randomised controlled trial.

While a risk-of-bias tool for non-randomised studies of exposures (NRSE) is currently under development,[163] it was insufficiently developed at the time the risk-of-bias assessments were performed. Instead, I used a version of the ROBINS-I tool informed by the preliminary ROBINS-E tool (Risk of Bias In Non-randomised Studies – of Exposure), which I had previously applied in a published review.[164] The version had no signaling questions and so judgements, using the same four levels of risk of bias as ROBINS-I, were made at the domain level. The motivation for using this tool above other established tools - such as the Newcastle-Ottowa scale (NOS)[165] - was two-fold. In the first instance, as mentioned in the introduction to this section, using a domain-based tool has distinct advantages over better-developed checklist-type tools including the NOS. Secondly, using a domain-based tool for non-randomised studies of exposures enabled better comparison with risk-of-bias assessments performed for the other study designs considered by this review.

Mendelian randomisation studies

At present, no formalised risk-of-bias assessment tool for Mendelian randomisation studies is available. Assessment of the risk of bias in Mendelian randomisation studies was informed by the tool developed by Mamluk *et al* for use in their own review.[166] This tool was identified through a meta-review of risk-of-bias assessments in systematic reviews of Mendelian randomisation studies,[167] advanced results of which were obtained through personal communication with the authors. A copy of this tool is available in Appendix A.3.6, but in summary, results were assessed for bias arising from weak instruments, genetic confounding, other confounding, pleiotropy and population stratification. Acceptable judgements for each of the five domains in the tool were "low", "moderate" and "high" risk of bias.

Risk of bias due to missing evidence

In addition to assessing the risk of bias within each result contributing to a synthesis, I also assessed risk of bias due to missing evidence at the synthesis level. This assessment examines evidence missing due to selective non-reporting as opposed to the selective reporting of a single result from multiple planned analyses. The assessment was performed using the forthcoming RoB-ME (Risk of Bias due to Missing Evidence in a synthesis) tool.[168] The tool is in development stages, and as part of this review, I piloted the tool and provided feedback to the developers.

3.2.9 Analysis methods

Analysis overview

An initial qualitative synthesis of evidence was performed, summarising the data extracted from studies stratified by study design. Where individual studies were deemed comparable, they were incorporated into a quantitative analysis or "meta-analysis". Results were not combined across different study designs (i.e., RCTs were not combined in a meta-analysis with results from observational studies). The summary effect estimates produced across individual study designs are discussed but are compared and contrasted more fully as part of the triangulation exercise presented in Chapter 7. Similarly, analyses are presented separately for each dementia outcome of interest (all-cause dementia, Alzheimer's disease, vascular dementia).

The range of effect measures presented by studies (odds ratios, risk ratios, hazard ratios, etc.) are not directly interchangeable in the context of systematic review. As such, different reported effect estimates can be one potential problem that precludes a meta-analysis of all studies.[169] However if the outcome is rare, as is the case for dementia outcomes, the estimated odds, risk and hazard ratios will approximate each other.[170] As such, I did not stratify the analyses by reported effect measure.

Random-effects meta-analysis

I used a random-effects model in all meta-analyses.[171,172] Random-effects meta-analysis does not assume one true underlying effect, but rather allows for a distribution of true effects with variance τ^2. The result in the ith study is denoted as y_i. The weight (w_i) assigned to this result is then given as the inverse of the variance of that result (v_i) plus the estimate of between-result variance (τ^2):

$$w_i = \frac{1}{v_i + \tau^2} \tag{3.5}$$

Once the weights are calculated for each result, the overall estimate ($\hat{y}$) and variance ($Var(\hat{y})$) can be estimated:

$$\hat{y} = \frac{\sum y_i w_i}{\sum w_i} \tag{3.6}$$

$$Var(\hat{y}) = \frac{1}{\sum w_i} \tag{3.7}$$

Results included in each meta-analysis were stratified into subgroups on the basis of the overall risk-of-bias judgement. Summary estimates for each subgroup, in addition to an overall effect estimate, are displayed in each forest plot. Additional descriptive statistics are presented, while prediction intervals are shown as a dotted line banding the overall effect estimate. Finally, where at least 10 results are available, a test of subgroup differences between studies at different levels of risk of bias was performed (see subsequent Section 3.2.9).[173] All models were implemented using the `metafor` R package.[174]

Dose-response analyses

Several of the included studies presented data on multiple categories of lipid levels in addition to an overall effect estimate based on a comparison of only two of these categories (e.g., for example, highest vs lowest quartile). While this two-category comparison allows for easy interpretation of the resulting effect estimate, it ignores any potential non-linear relationships between the exposure and outcome, in addition to discarding useful information contained in the interim groups. In order to address this limitation, I performed a dose-response meta-analysis in those studies reporting more than two categories of lipid levels.

Studies were excluded from this analysis if the number of categories was less than three or if the necessary information for synthesis (cut-off points, number of participants and number of events per category) was not available. When the highest reported category was open ended (e.g., LDL-c $\geqslant$ 200 mg/dL), I calculated the category midpoint by assuming the width of the highest category was the same as the one immediately below it. Similarly, when the lowest category was open-ended (e.g LDL-c $\leqslant$ 100 mg/dL), I set the lower boundary for this category to zero (though this is unlikely to occur naturally).

I took a two-stage dose-response meta-analysis approach, where study-specific trends are estimated before being pooled across studies.[175] To estimate within-study trends, a restricted cubic spline model was fitted within each study. This approach allows for a non-linear relationship between lipid levels and dementia, for example a U or J-shaped relationship, where low and high levels of a lipid fraction can have different effects versus the "normal" reference dose.[176,177] Reference doses were defined *a priori* as the cut-off of the "Normal"/"Optimal" categories for each fraction, as detailed in Table 1.2. Under this approach, the reference dose was defined as 200 mg/dL for total cholesterol, 100 mg/dL for LDL-c, 40 mg/dL for HDL-c, and 150 mg/dL for triglycerides.

Restricted cubic spline models use "knots" to separate the data into subsets or "windows", in which the trend is modelled. Further restrictions are then imposed, in that the curves in each window must join up "smoothly" at the knot location, and that the trend is assumed to be linear before the first knot and after the last knot.[178] The locations of the knots in the model were identified using fixed percentiles (5th, 50th, 95th) of the exposure data.[176] Once the within-study trends had been estimated, they were combined in a multivariate random-effects meta-analysis using the restricted maximum likelihood (REML) method.[177,179,180] All dose-response analyses were implemented using the `dosresmeta` R package.[181]

Additional analyses

Where there was evidence of heterogeneity between results included in a meta-analysis, I investigated this further using meta-regression against reported characteristics. *A priori*, I was interested in the effect that the age at baseline, sex and risk-of-bias judgement had on the results. Syntheses with greater than 10 results were assessed for heterogeneity across these covariates.[173] I also investigated the potential for small study effects (of which publication bias is one potential cause) in syntheses with greater than 10 results, both visually using funnel plots and formally using Egger's regression test.[182]

Visualisation of results

Evidence maps are a useful way to explore the distribution of research cohorts included in a systematic review.[183] As part of the initial descriptive synthesis, the location of each individual study contributing to the evidence base was visualised on a world map.

One of the limitations of current risk-of-bias assessment practice in systematic reviews is that they are often divorced from the results to which they refer, and are infrequently incorporated into the analysis.[184,185] In response to this criticism, I developed a new visualisation tool which was designed to allow for the production of "paired" forest plots - a risk-of-bias assessment is presented alongside it's corresponding numerical result - as recommended by the RoB 2 publication.[162] In addition, the risk of bias due to missing evidence in each synthesis, as assessed using the RoB-ME tool, is shown beside the overall summary diamond. This tool was developed as an adjunct to this thesis,[186] and summary of its functionality can be found in Appendix B.2. Unless otherwise stated in the figure, only a single effect measure (hazard ratio/odds ratio/etc.) is represented in a given forest plot.

Assessment of added value of including preprints

Preprints are considered a valuable evidence source within this thesis (see Section 1.5.1). As an adjunct analysis to this review, meta-analyses including a preprint result were re-analysed using a fixed effect model. The weight assigned to the preprinted result was extracted and used to assess the additional evidential value provided to the synthesis by the preprint. In addition, I assessed the impact of including the preprinted results on the summary estimate, using a leave-one-out approach.

Finally, I performed a follow-up analysis, allowing for a two-year lag, to investigate whether included preprints had been subsequently published (in which case preprints provided a snapshot into the future, and a systematic review update would capture the published version of the preprint) or not (in which case preprints provided a distinct evidence source to conventional bibliographic databases).

3.3 Summary

- In this chapter, I have presented the methods underpinning a comprehensive systematic review of the existing literature on the association of dementia incidence with blood lipid levels and lipid-regulating agents.
- I have detailed how this review found, extracted, critically assessed and synthesized the results of existing studies. Additionally, I have highlighted how this review examined the impact of including preprinted results, as enabled by the research tool presented in the previous chapter.
- In the following chapter, I present the results of this review, and detail how the evidence identified is used throughout the remainder of the thesis.

The hundreds of hours spent conducting a scientific study ultimately contribute only a piece of an enormous puzzle. The value of any single study is derived from how it fits with and expands previous work, as well as from the study's intrinsic properties. Through systematic review the puzzle's intricacies may be disentangled.

— Cynthia D Mulrow, 1994[187]

4

Systematic review of existing evidence on the association between blood lipids and dementia outcomes: Results

Contents

Lay summary

Using the methods outlined in the previous chapter, here I present the results of a systematic review of primary studies that have examined the relationship between the levels of blood lipids (such as cholesterol and triglycerides) and dementia outcomes. In addition, I also examined the relationship between treatments that change blood lipid levels, such as statins, and dementia outcomes.

My review included 81 primary studies. I found that statins appear to reduce the risk of all-cause dementia and Alzheimer's disease, but were not associated with risk of vascular dementia. Lipid levels were not associated with any dementia outcome. However, problems with the methods used in some studies included in the review meant that I was less confident in their results. In addition, I found that several results were missing from my analysis as authors decided not to report them.

4.1 Introduction

Following the methods outlined in the previous chapter, I present the results of the comprehensive systematic review here. The use of the evidence identified by the review in future chapters is discussed. Finally, I make recommendations for future methodological work around the inclusion of preprints and Mendelian randomisation studies in evidence synthesis exercises.

4.2 Search results

4.2.1 Initial search and validation of search filters

The database search identified 23,447 records, of which 7,338 were duplicated records. To ensure the accuracy of the study design filters, a random sample of 500 records removed by the filters were screened, and no eligible records were identified. As expected, many of those excluded by the filters were commentaries/educational articles or described basic science studies.

4.2.2 Screening results

Following de-duplication, the titles and abstracts of 16,109 records were assessed for eligibility. Of these, 387 were deemed potentially eligible. The full text records for these records were then accessed and screened.

A PRISMA flow diagram, presented in Figure 4.1, illustrates the movement of articles through the review. To highlight the contribution of preprint archives to the review, the flow diagram delineates between those records captured through databases searches (presented on the left of the diagram) and those captured by the preprint search tool described previously (presented in grey on the right of the diagram).

Common reasons for exclusion at the full-text stage included studies reporting on ineligible exposures (Number of records (N) = 70 ; most commonly an ineligible lipid fraction) or outcomes (N = 67; e.g., change in cognitive scores), or the use of an ineligible study design (N = 56).

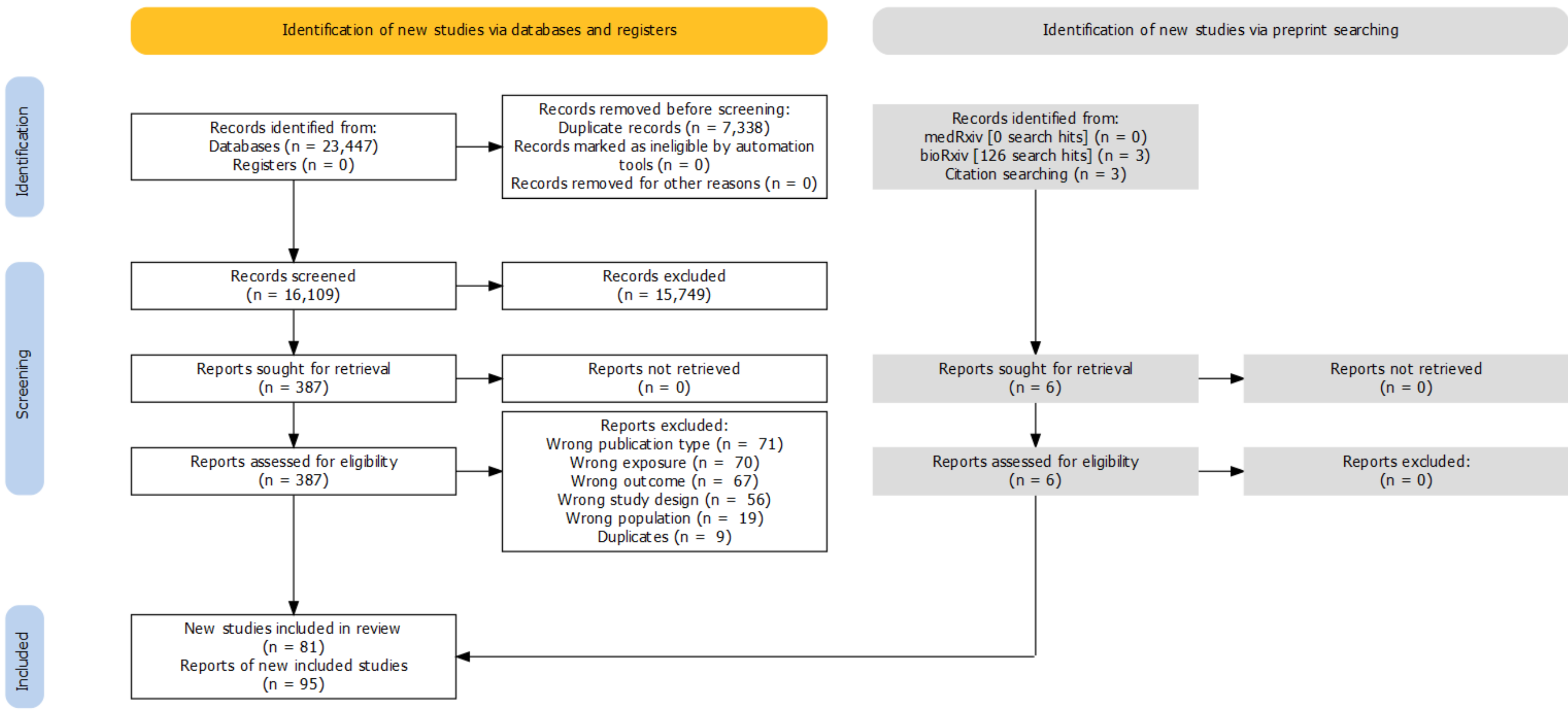

Figure 4.1: PRISMA flow diagram - The diagram illustrates how records moved through the systematic review process. Note that the different contributions of standard bibliographic databases (left) and preprint servers (right) to the review are indicated.

4.2.3 Validation of screening

For the assessment of the intra-/inter-rater reliability, the estimated values of Gwet's agreement coefficient, $AC1$, were interpreted against the categories presented in Table 3.2. For the inter-rater reliability, agreement was "almost perfect" ($AC1 = 0.97$, $kappa = 0.54$, Table 4.1).

Table 4.1: Inter-rater agreement - For a subset of records, the decisions between two independent reviewers were compared. Gwet's $AC1$ was calculated from this data to assess inter-rater reliability, indicating high accuracy ($AC1 = 0.97$).

		Initial screening decision		
		Exclude	**Include**	**Total**
Second reviewer decision	**Exclude**	1244	9	1253
	Include	26	22	48
	Total	1270	31	1301

Those records which were excluded in the initial screening but were included by the second reviewer (N =26, Table 4.1) were investigated. This discrepancy between the two reviewers was explained in all cases by differing interpretations of the inclusion criteria, most commonly around the definition of cognitive decline versus dementia and of eligible lipids fractions.

Similarly, for intra-rater reliability, agreement was "almost perfect" ($AC1 = 0.99$, $kappa = 0.65$, Table 4.2).

Table 4.2: Intra-rater agreement - For a subset of records, the decisions between the same reviewer with three-month lag were compared. Gwet's $AC1$ was calculated from this data to assess intra-rater reliability, indicating high consistency ($AC1 = 0.99$).

		Initial screening decision		
		Exclude	**Include**	**Total**
Same reviewer decision (with 3 month lag)	**Exclude**	1266	14	1280
	Include	4	17	21
	Total	1270	31	1301

In both cases, the discrepancy between the $AC1$ and *kappa* coefficients illustrates the sensitivity of *kappa* to imbalanced marginals, caused in this sample by a large imbalance towards exclusion.[188]

4.2.4 Characteristics of included studies

Following full-text screening, 81 unique studies (described across 95 reports) met the criteria for inclusion in this review.[53–62,67,71,72,74,189–255] Table 4.3 presents a summary of the characteristics of each study.

The majority of included studies described non-randomised analyses, with the only two included randomised controlled trials (the Heart Protection Study/British Heart Foundation trial[67] and the JUPITER trial[189]) both reporting on the effect of statin use on incidence of all-cause dementia in older adults. A similarly small number of Mendelian randomisation studies were identified, several of which employed a two-sample approach using summary statistics from the same published genome wide association studies (GWAS). This leads to complications in the synthesis of these estimates due to the potential for double counting (see Section 4.3.2).

Of the 31 non-randomised studies examining lipid-regulating agents (LRA), all examined statin use while a small number also reported on other non-statin agents such as fibrates (N = 2; 6.5%). In the 43 non-randomised studies of exposure, hypercholesterolemia (N = 19; 44.2%) and total cholesterol levels (N = 21; 48.8%) were the most frequently reported risk factors.

In terms of outcomes, the vast majority of studies examined either all-cause dementia (N = 59; 72.8%) or Alzheimer's disease (N = 51; 63%), with only a small proportion examining vascular dementia (N = 15; 18.5%). Some other outcome classifications such as vascular-component or mixed dementia were also investigated but were much rarer.

Table 4.3: Characteristics of included studies - The characteristics of studies included in this review, stratified by study design, are presented below. Note that three studies reported on multiple analytical designs within a single study report (Beydoun 2011,[193] Reitz 2010,[213] and Benn 2017[74]), and these have been duplicated across the relevant sub-sections. Preprinted studies are denoted using an asterisk.

Study	Location	N	Age at baseline	Female (%)	Exposures	Outcomes	Diagnostic criteria
Randomised controlled trials							
HPS 2002[67]	United Kingdom	20536	>70	24.8	Simvastatin	Dementia	NR
JUPITER 2009[189]	Multiple	17902	66 (median) 60-71 (range)	38	Rosuvastatin	Dementia	NR
Non-randomised studies of interventions							
Ancelin 2012[190]	France	7056	NR	67	Fibrate; Statin	Dementia; AD	DSM-IV; NINCDS-ADRDA
Arvanitakis 2008[191]	United States	929	74.9 (NR)	68.7	Statin	AD	Consortium to Establish a Registry for Alzheimer's Disease (CERAD)
Bettermann 2012[192]	United States	3069	78.6 (3.3)	46.2	Non-statin LRA ; Statin	Dementia; AD; Vascular component	Consensus panel - criteria not reported
Beydoun 2011[193]	United States	1604	57.6 (18.4)	38.5	Statin	Dementia	DSM-III-R
Chao 2015[194]	Taiwan	256265	73.2 (7.4)	50.3	Statin	Non-vascular dementia	ICD-9
Chen 2014[195]	Taiwan	18100	67 (8.6)	47.9	Statin	Dementia; AD; Non-AD	ICD-9
Chitnis 2015[196]	United States	8062	74.47 (9.21)	53.04	Statin	Dementia	ICD-9
Chou 2014[197]	Taiwan	33398	>60	53.9	Statin	Dementia; AD; VaD; Non-vascular dementia	ICD-9
Chuang 2015[198]	Taiwan	123300	54 (13)	49.1	Statin	Dementia	ICD-9
Cramer 2008[199]	United States	1674	70 (6.8)	58	Statin	Dementia/CIND	DSM-IV
Gnjidic 2016[200]	Sweden	2056	>60	NR	Statin	Dementia	DSM-IV
Haag 2009[201]	Netherlands	6992	69.4 (9.1)	60	Non-statin LRA ; Statin	AD	NINCDS-ADRDA

Table 4.3: Characteristics of included studies - The characteristics of studies included in this review, stratified by study design, are presented below. Note that three studies reported on multiple analytical designs within a single study report (Beydoun 2011,[193] Reitz 2010,[213] and Benn 2017[74]), and these have been duplicated across the relevant sub-sections. Preprinted studies are denoted using an asterisk. *(continued)*

Study	Location	N	Age at baseline	Female (%)	Exposures	Outcomes	Diagnostic criteria
Hendrie 2015[202]	United States	974	76.6 (4.9)	69.7	Statin	Dementia; AD	DSM-IV; Consortium to Establish a Registry for Alzheimer's Disease (CERAD)
Hippisley-Cox 2010[203]	United Kingdom	2004692	46 (14)	51	Statin	Dementia	EHR codelist
Jick 2000[204]	United Kingdom	1364	50-89	61	Non-statin LRA ; Statin	Dementia	EHR codelist
Li 2004[206]	United States	2356	75.1 (6.1)	59.8	Non-statin LRA; Statin	Dementia; AD	DSM-IV; NINCDS-ADRDA
Li 2010[205]	United States	3392	75 (6.2)	59	Statin	AD	NINCDS-ADRDA
Liao 2013[207]	NR	5221	NR	NR	Statin	Dementia	NR
Liu 2019[208]	Taiwan	2012	74 (7.5)	NR	Statin	Dementia	ICD
Pan 2018[209]	Taiwan	14807	65 (13)	43	Statin	Dementia	ICD-9
Parikh 2011[210]	United States	377838	75.53 (6.07)	2	Statin	Dementia	ICD-9
Rea 2005[211]	United States	2798	NR	NR	Non-statin LRA ; Statin	Dementia; AD; Mixed; VaD	NINCDS; NINCDS-ADRDA; Combination; State of California Alzheimer's Disease Diagnostic and Treatment Centers
Redelmeier 2019[212]	Canada	28815	76 (NR)	61.3	Statin	Dementia	ICD-9
Reitz 2004[213]	United States	1168	78.4 (6.2)	68.3	Statin	VaD; AD	Cohort criteria; NINCDS-ADRDA
Smeeth 2009[214]	United Kingdom	729529	50 (NR)	40-81	Statin	Dementia; AD; Non-AD	EHR codelist
Solomon 2010[215]	Finland	17597	68 (5.8)	57	Statin	Dementia	EHR codelist

Table 4.3: Characteristics of included studies - The characteristics of studies included in this review, stratified by study design, are presented below. Note that three studies reported on multiple analytical designs within a single study report (Beydoun 2011,[193] Reitz 2010,[213] and Benn 2017[74]), and these have been duplicated across the relevant sub-sections. Preprinted studies are denoted using an asterisk. *(continued)*

Study	Location	N	Age at baseline	Female (%)	Exposures	Outcomes	Diagnostic criteria
Sparks 2008[216]	United States	2068	75 (3.8)	54	Statin	AD	NINCDS-ADRDA
Szwast 2007[217]	United States	1416	77.3 (5.3)	69.3	Statin	Dementia	DSM-IV
Yang 2015[218]	Taiwan	45973	82 (5.3)	48	Fibrate; LRA (exlc. statin + fibrates); Statin	Dementia	ICD-9
Zamrini 2004[219]	United States	3397	73 (NR)	0	Statin	AD	ICD-9
Zandi 2005[220]	United States	3308	NR	NR	Non-statin LRA; Statin	Dementia; AD	DSM-III-R; NINCDS-ADRDA
Non-randomised studies of exposures							
Ancelin 2013[221]	France	7053	74 (5.3)	61.1	Hypercholesterolemia	AD; Dementia	NINCDS-ADRDA; DSM-IV
Batty 2014[222]	United Kingdom	103764	47.3 (18.1)	55	Non-HDL-c; Hypercholesterolemia	Dementia	ICD
Benn 2017[74]	Denmark	111194	56 (median) 46-66 (range)	55	LDL-c	AD; VaD; Dementia	ICD; ICD-10
Beydoun 2011[193]	United States	1604	57.6 (18.4)	38.5	TC	Dementia	DSM-III-R
Bruce 2017[223]	Australia	217	63.6 (8.4)	45.6	HDL-c; TC; TG	Dementia	NR
Chiang 2007[224]	Taiwan	785	58 (7.4)	41.4	TC; TG	Dementia; AD; VaD	ICD-9; NR
Dodge 2011[225]	United States	822	71.6 (4.7)	64.4	Hypercholesterolemia	Dementia; AD	DSM-III-R; Consortium to Establish a Registry for Alzheimer's Disease (CERAD)
Forti 2010[226]	Italy	749	73 (6.1)	53	Hypercholesterolemia; TG	Dementia; AD; VaD	DSM-IV; NINCDS-ADRDA; NINCDS-AIREN
Gottesman 2017[227]	United States	15407	54.2 (5.8)	55	TC	Dementia	Combination

Table 4.3: Characteristics of included studies - The characteristics of studies included in this review, stratified by study design, are presented below. Note that three studies reported on multiple analytical designs within a single study report (Beydoun 2011,[193] Reitz 2010,[213] and Benn 2017[74]), and these have been duplicated across the relevant sub-sections. Preprinted studies are denoted using an asterisk. *(continued)*

Study	Location	N	Age at baseline	Female (%)	Exposures	Outcomes	Diagnostic criteria
Gustafson 2012[228]	Sweden	NR	NR	100	TC	AD	NR
Hayden 2006[229]	United States	3308	74.0 (6.4)	58.2	Hypercholesterolemia	Dementia; AD; VaD	DSM-III-R; NINCDS-ADRDA; NINCDS-AIREN
Kimm 2011[230]	South Korea	848505	53 (9.3)	42.2	TC	AD; VaD; Dementia	ICD-10
Kivipelto 2001[231]	Finland	1499	50.4 (6.0)	62	Hypercholesterolemia	AD	NINCDS-ADRDA
Kivipelto 2005[53]	Finland	1449	50.6 (6.0)	62	Hypercholesterolemia	Dementia	DSM-IV
Kuo 2015[232]	Taiwan	67066	62.1(11.4)	48.4	Hypercholesterolemia	Dementia	ICD-9
Li 2005[57]	United States	2141	74.9 (5.9)	60.5	HDL-c; TC	Dementia; AD	DSM-IV; NINCDS-ADRDA
Mainous 2005[58]	United States	6558	NR	NR	Hypercholesterolemia	Dementia; AD	ICD-9
Mielke 2005[59]	Sweden	382	NR	70	TC; TG	Dementia	DSM-III-R
Mielke 2010[61]	France	1460	38-60 (range)	100	Hypercholesterolemia; TC	Dementia; AD	DSM-III-R; NINCDS-ADRDA
Mielke 2012[233]	United States	99	74 (2.5)	100	HDL-c; TC; TG	Dementia; AD	DSM-IV; NINCDS-ADRDA
Muller 2007[234]	United States	542	NR	NR	HDL-c; TG	Dementia; AD	DSM-IV; NINCDS-ADRDA
Noale 2013[235]	Italy	5632	71.3(5.3)	56.3	Hypercholesterolemia; TG	Dementia	DSM-III-R
Notkola 1998[236]	Finland	444	40-59 (range)	0	Hypercholesterolemia	AD	Combination
Peters 2009[237]	Multiple	3336	>80	60.4	HDL-c; TC	Dementia	DSM-IV
Raffaitin 2009[238]	France	7087	73.4 (4.9)	61	Hypercholesterolemia; TG	Dementia; AD; VaD	DSM-IV; NINCDS-ADRDA; Combination
Rantanen 2017[239]	Finland	3309	42 (median) 39–46 (range)	0	TC; Hypercholesterolemia	Dementia; AD; VaD	NR

Table 4.3: Characteristics of included studies - The characteristics of studies included in this review, stratified by study design, are presented below. Note that three studies reported on multiple analytical designs within a single study report (Beydoun 2011,[193] Reitz 2010,[213] and Benn 2017[74]), and these have been duplicated across the relevant sub-sections. Preprinted studies are denoted using an asterisk. *(continued)*

Study	Location	N	Age at baseline	Female (%)	Exposures	Outcomes	Diagnostic criteria
Reitz 2004[213]	United States	1168	78.4 (6.2)	68.3	HDL-c; LDL-c; Non-HDL-c; TC; TG	VaD; AD	Cohort criteria; NINCDS-ADRDA
Reitz 2010[62]	United States	1130	75.7(6.3)	65.7	HDL-c; LDL-c; TC	AD	NINCDS-ADRDA
Ronnemaa 2011[240]	United States	2268	49.6 (0.6)	0	Hypercholesterolemia	AD; VaD; Dementia	NINCDS-ADRDA; ADDTC; DSM-IV
Schilling 2017[54]	France	9294	73.8 (5.3)	61	HDL-c; LDL-c; TC; TG	Dementia; AD; Mixed	DSM-IV; NINCDS-ADRDA; NINCDS-AIREN
Solomon 2007[241]	Finland	1449	50.4 (6.0)	62.1	Hypercholesterolemia	Dementia	NR
Solomon 2009[55]	United States	9844	43 (1.7)	54	TC	AD; VaD	ICD-9
Strand 2013[242]	Norway	48793	42.6 (4.3)	49	TC	Dementia; AD	ICD
Su 2017[243]	United Kingdom	212085	NR	NR	NR	NR	NR
Svensson 2019[244]	Japan	781	54.1 (5.6)	NR	HDL-c; Hypercholesterolemia	Dementia	DSM-IV
Tan 2003[60]	United States	1026	76.1 (5.3)	63	TC	AD	NINCDS-ADRDA
Tynkkynen 2016[245]	Finland	13725	48.4 (13.3)	51.6	HDL-c	Dementia; AD	ICD-10
Tynkkynen 2018[246]	Multiple	22623	57 (9.2)	47	HDL-c; LDL-c; TC; TG	Dementia; AD	ICD-10
Wang 2012[247]	Taiwan	1230400	60 (13)	52	Hypercholesterolemia	AD	ICD-9
Whitmer 2005[56]	United States	8845	68 (2.6)	53.7	Hypercholesterolemia	Dementia	ICD-9
Yamada 2009[248]	Japan	1637	>60	100	NR	NR	NR
Yoshitake 1995[249]	Japan	828	74 (5.9)	59.5	HDL-c; LDL-c; TC; TG	VaD; AD	NINCDS-AIREN; NINCDS-ADRDA
Zimetbaum 1992[250]	United States	350	79 (median) 75-85 (range)	64.5	HDL-c; LDL-c; TC; TG	Dementia	DSM-III-R

Table 4.3: Characteristics of included studies - The characteristics of studies included in this review, stratified by study design, are presented below. Note that three studies reported on multiple analytical designs within a single study report (Beydoun 2011,[193] Reitz 2010,[213] and Benn 2017[74]), and these have been duplicated across the relevant sub-sections. Preprinted studies are denoted using an asterisk. *(continued)*

Study	Location	N	Age at baseline	Female (%)	Exposures	Outcomes	Diagnostic criteria
Mendelian randomisation studies							
Andrews 2019[251,256] *	GLGC + IGAP	54162	Not applicable	Varied by GWAS	HDL-c; LDL-c; TC; TG	AD	Varied by GWAS
Benn 2017[74]	Copenhagen General Population Study/ City Heart Study; GLGC + IGAP	111194; 54162	Not applicable	55; Varied by GWAS	HMGCR; LDL-c; PCSK-9	AD; VaD; Dementia	EHR codelist; Varied by GWAS
Burgess 2017[252]	ADGC	21165	Not applicable	Varied by GWAS	HDL-c; LDL-c; TG	AD	Varied by GWAS
Larsson 2017[71]	GLGC + IGAP	54162	Not applicable	Varied by GWAS	LDL-c	AD	Varied by GWAS
Mukherjee 2013[253]	GLGC + IGAP	54162	Not applicable	Varied by GWAS	HDL-c; LDL-c; TG	AD	Varied by GWAS
Ostergaard 2015[72]	GLGC + IGAP	54162	Not applicable	Varied by GWAS	HDL-c; LDL-c; TC; TG	AD	Varied by GWAS
So 2017[254] *	GLGC + IGAP	54162	Not applicable	Varied by GWAS	HMGCR	AD	Varied by GWAS
Zhu 2018[255,257] *	GLGC + IGAP	54162	Not applicable	Varied by GWAS	HDL-c; LDL-c; TG	AD	Varied by GWAS

* Denotes preprinted study.
Abbreviations: AD - Alzheimer's disease; ADGC - Alzheimer's Disease Genetics Consortium DSM - Diagnostic and Statistical Manual (Roman numerals indicate edition); EHR - Electronic code list; ICD - International Classification of Disease (numbers indicate edition); IGAP - International Genomics of Alzheimer's Project GLGC - Global Lipid Genetics Consortium HDL-c - high density lipoprotein cholesterol; LDL-c - low density lipoprotein cholesterol; NINCDS-ADRDA - National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINCDS-AIREN - National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences; NR - Not reported; TC - total cholesterol; TG - triglycerides; VaD - vascular dementia.

Three included reports were preprinted (denoted in the Table 4.3 using an asterisk),[254,256,258] one of which had subsequently been published and was captured by the primary literature search.[255] All three included preprints were obtained from the bioRxiv preprint server and all described a Mendelian randomisation analysis.

As illustrated in Figure 4.2, the majority of reports described studies conducted in high-income countries, with the most highly represented region being North America. Of interest, several of the included studies were conducted in Taiwan (N = 10; 12.35%), all but one of which made use of the Taiwan National Health Insurance database.

Figure 4.2: Geographical distribution of study cohorts - The country or countries of origin for the studies included in the review are shown. Note that the majority of included studies were performed in westernised countries, predominantly in Europe and North America.

Overall, the reporting of included studies was poor, particularly for non-randomised studies of lipids and LRA. Several studies did not report baseline characteristics such as the proportion of women in the study cohort. Additionally, some omitted important details on reported characteristics (e.g., the study reported the mean but not the standard deviation of baseline age).

Finally, there were several eligible studies reported as conference abstracts that did not present numerical results. These reports were included in the analysis to enable assessment of risk of bias due to missing evidence (see Section 3.2.8).

4.3 Primary analyses

In the following sections, analyses are grouped first by outcome (all-cause dementia, Alzheimer's disease and vascular dementia) and are then further stratified by exposure category (lipids, lipid regulating agents).

4.3.1 All-cause dementia

Lipids

Across all outcomes, lipid levels were categorised in a number of ways. The most common categorisation was hypercholesterolemia at baseline, defined most frequently as a total cholesterol measurement of greater than 6.5 mmol/L.

Eleven studies reported on the association of hypercholesterolemia with all-cause dementia and provided weak evidence for an effect (HR: 1.11, 95%CI: 0.97-1.27, Figure 4.3).

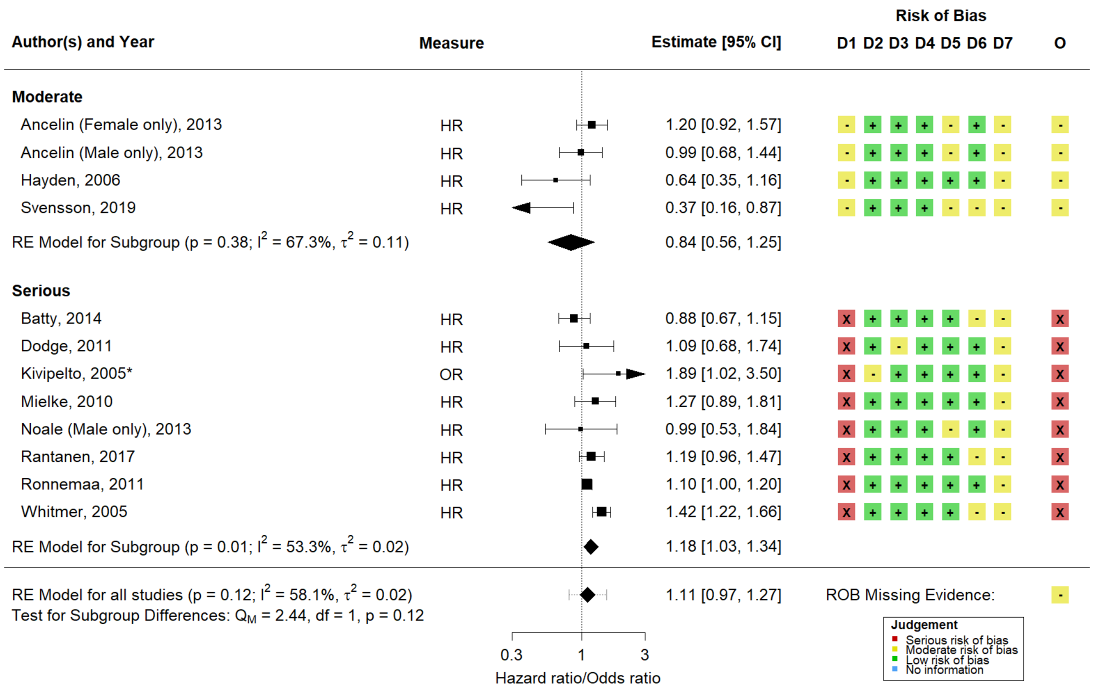

Figure 4.3: Random-effects meta-analysis of hypercholesterolemia on all-cause dementia - Non-randomised studies examining the association of hypercholesterolemia with all-cause dementia were synthesised using a random-effects meta-analysis. Subgroup estimates, stratified by overall risk-of-bias level, are also presented. D1-D7 and O refer to the seven risk-of-bias domains and single overall judgement in the ROBINS-E tool, while the risk of bias due to missing evidence is shown beside the overall summary diamond.

Several studies analysed individual lipid fractions by estimating the risk of dementia per 1 standard deviation increase in that fraction (Figure 4.4). Weak evidence for an effect on all-cause dementia was found for total cholesterol (N = 5; HR: 0.97, 95%CI: 0.88-1.07), LDL-c (N = 2; HR: 0.97, 95%CI: 0.86-1.08), HDL-c (N = 4; HR: 1.05, 95%CI: 0.96-1.14) and triglycerides (N = 3; HR: 0.90, 95%CI: 0.74-1.09).

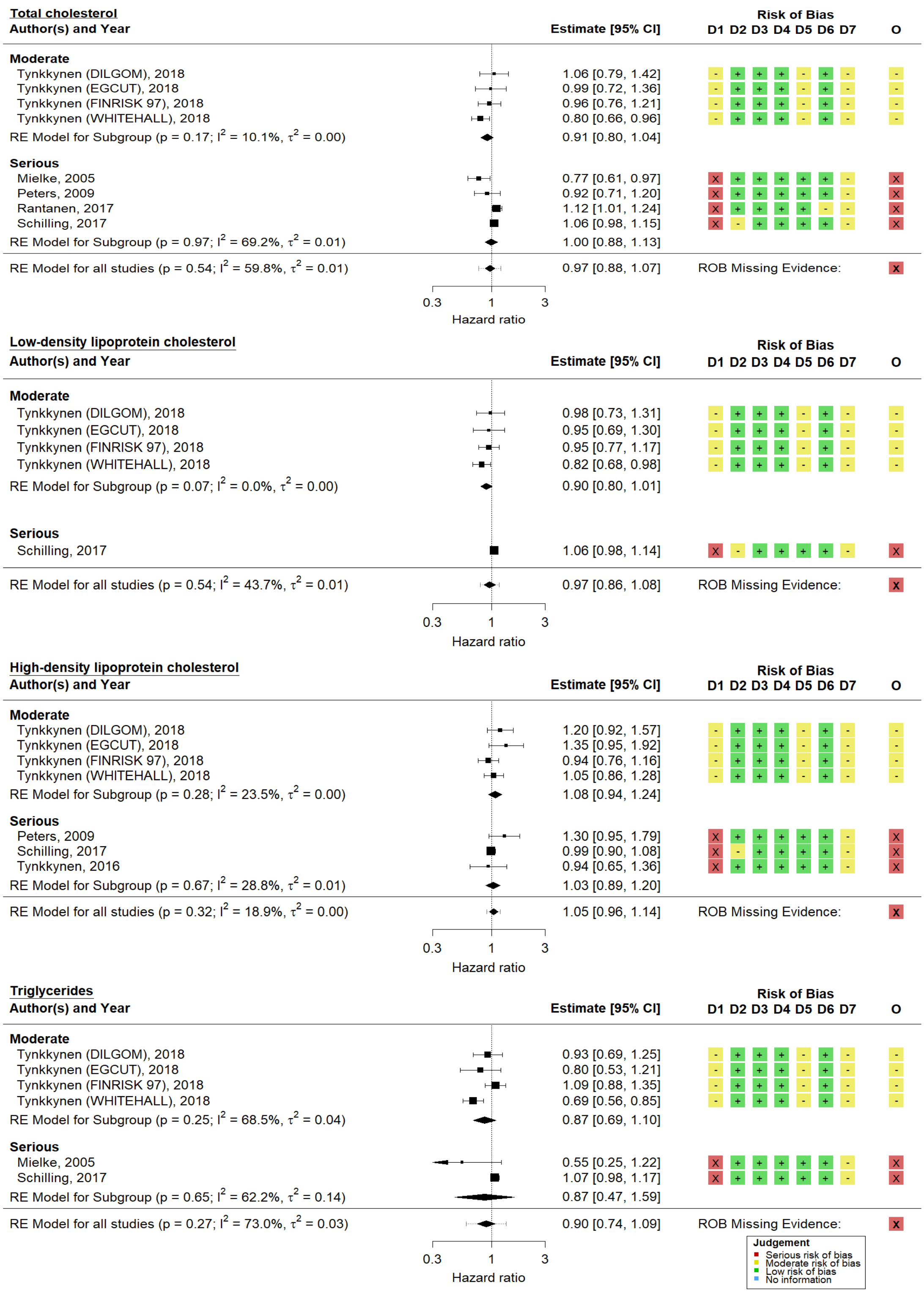

Figure 4.4: Random-effects meta-analysis of lipids on all-cause dementia - Non-randomised studies examining the association of four lipid fractions (total cholesterol, HDL, LDL, and triglycerides) with all-cause dementia risk, standardised per 1-SD increase, were synthesised using a random-effects meta-analysis. D1-D7 and O refer to the seven risk-of-bias domains and single overall judgement in the ROBINS-E tool, while the risk of bias due to missing evidence is shown beside the overall summary diamond. Note that Tynkkyen *et al*[246] reported results from multiple cohorts and these are presented separately.

Finally, there were no identified Mendelian randomisation analyses examining the effect of lower lipid levels, as determined by any genetic instrument, on all-cause dementia risk.

Statins

The two randomised controlled trials identified provided weak evidence (OR: 1.07, 95%CI: 0.70-1.66) of an effect on statin use on all-cause dementia risk (Figure 4.5).

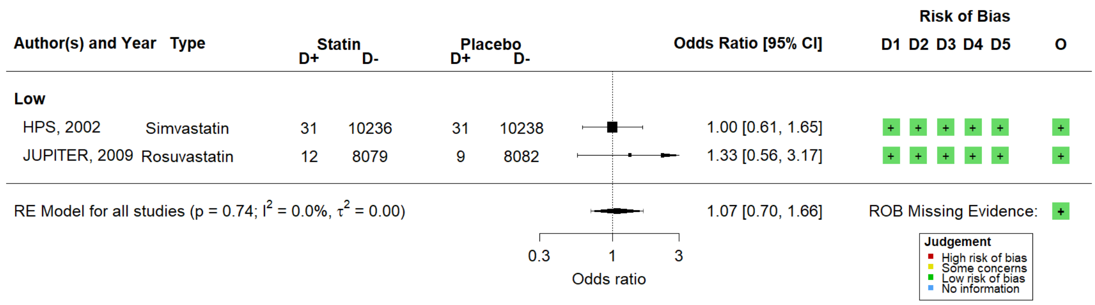

Figure 4.5: Random-effects meta-analysis of statins on all-cause dementia in RCTs - Randomised controlled trials examining the effect of statin use on all-cause dementia risk were synthesised using a random-effects meta-analysis. D1-D5 and O refer to the five risk-of-bias domains and single overall judgement in the RoB2 tool, while the risk of bias due to missing evidence is shown beside the overall summary diamond.

In contrast, a meta-analysis of 18 prospective observational studies provided some evidence of a protective effect of statin use on all-cause dementia risk (HR: 0.75, 95%CI: 0.67-0.84, Figure 4.6).

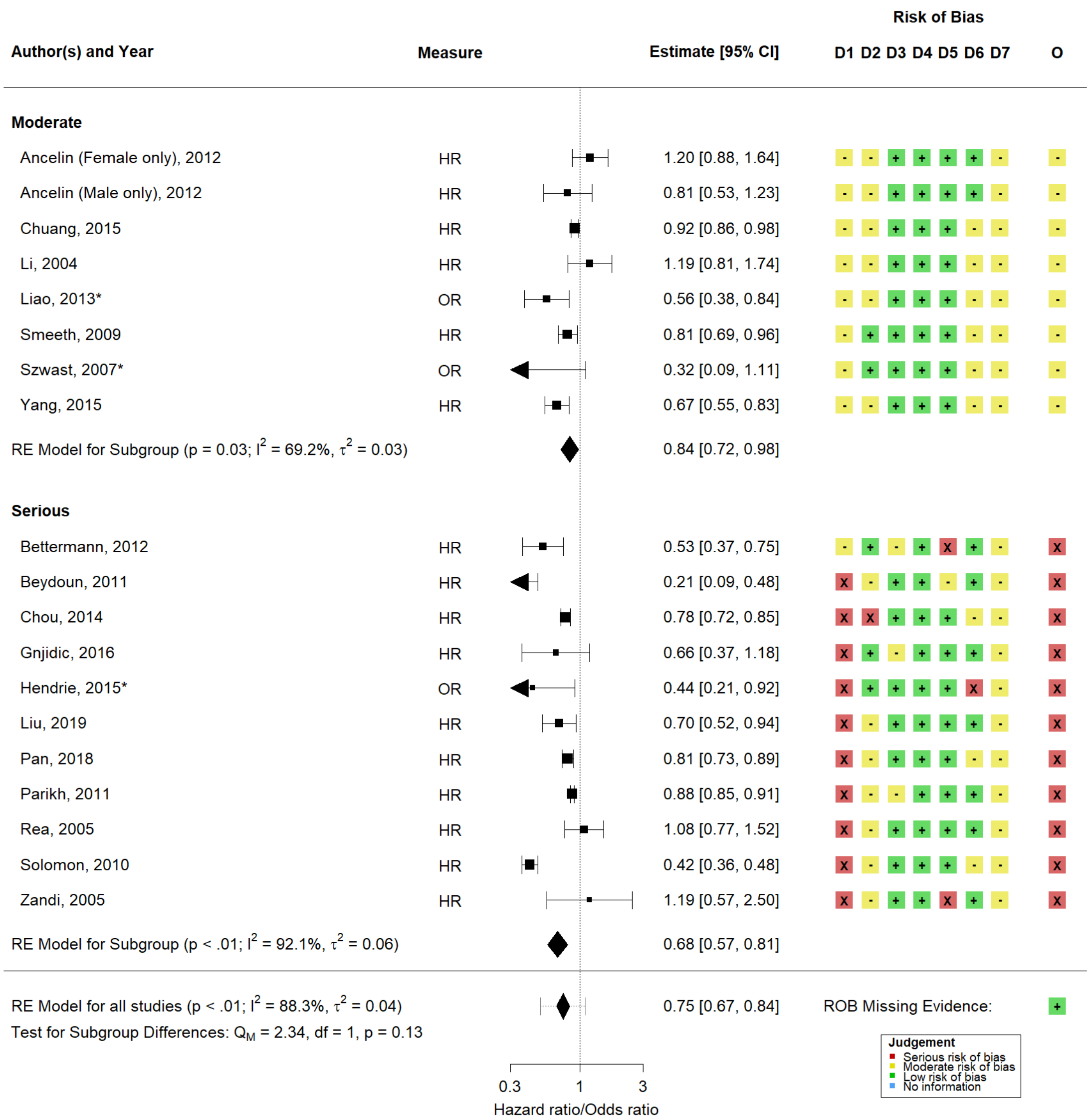

Figure 4.6: Random-effects meta-analysis of statins on all-cause dementia - Non-randomised studies examining the association of statin use with all-cause dementia were synthesised using a random-effects meta-analysis. Subgroup estimates, stratified by overall risk-of-bias level, are also presented. D1-D7 and O refer to the seven risk-of-bias domains and single overall judgement in the ROBINS-I tool, while the risk of bias due to missing evidence is shown beside the overall summary diamond.

Finally, a single Mendelian randomisation analysis was identified examining the effect of lowered LDL-c levels on the risk of all-cause dementia via genetic inhibition of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), emulating statin treatment (see Section 1.3.2 for more details of the statin mechanism of action).

This analysis provided weak evidence for an effect (RR: 0.90, 95%CI: 0.29-2.81).

Fibrates

Two studies examined the effect of fibrate use on all-cause dementia and found weak evidence for an effect (HR: 0.89, 95%CI: 0.75-1.07, Figure 4.7).

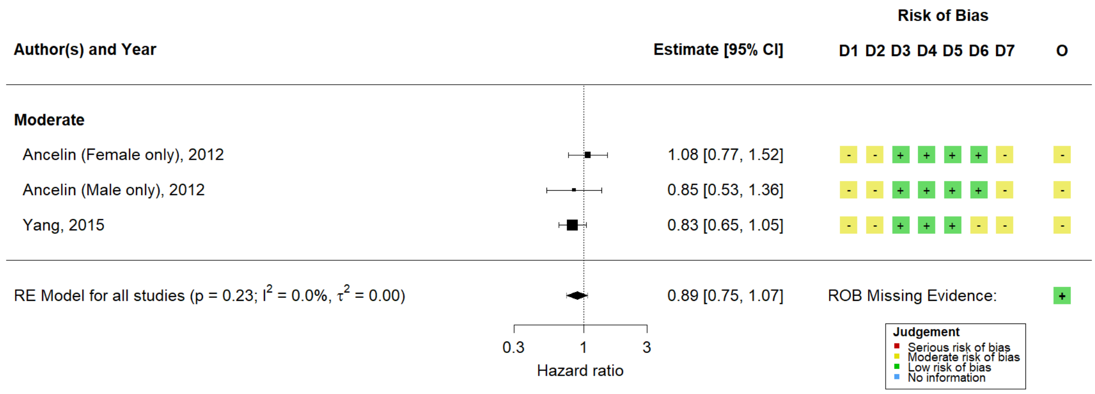

Figure 4.7: Random-effects meta-analysis of fibrates on all-cause dementia - Random-effects meta-analysis of non-randomised studies examining the effect of fibrate use on all-cause dementia. D1-D7 and O refer to the seven risk-of-bias domains and single overall judgement in the ROBINS-I tool, while the risk of bias due to missing evidence is shown beside the overall summary diamond.

4.3.2 Alzheimer's disease

Lipids

Eight studies reported on the association of hypercholesterolemia with Alzheimer's disease and provided weak evidence for an effect (HR: 0.89, 95%CI: 0.70-1.12, Figure 4.8)

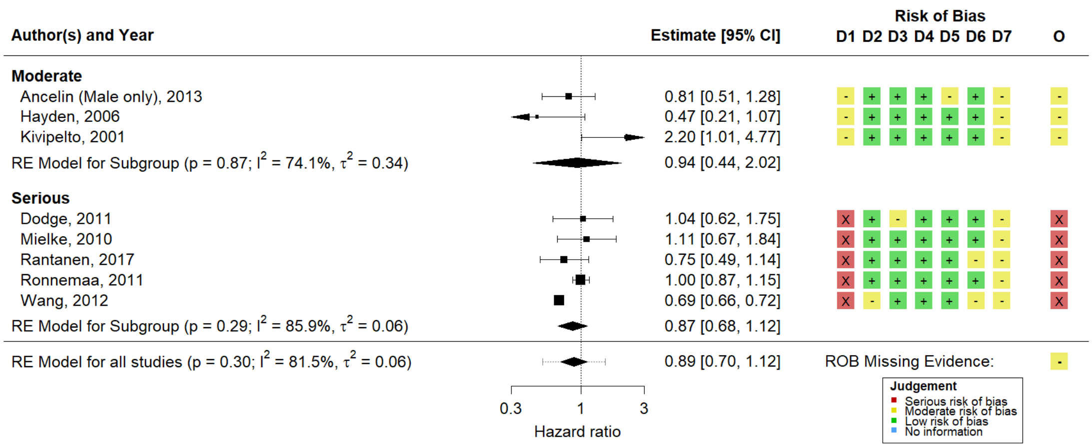

Figure 4.8: Random-effects meta-analysis of hypercholesterolemia on Alzheimer's disease - Non-randomised studies examining the association of hypercholesterolemia with Alzheimer's disease were synthesised using a random-effects meta-analysis. Subgroup estimates, stratified by overall risk-of-bias level, are also presented. D1-D7 and O refer to the seven risk-of-bias domains and single overall judgement in the ROBINS-E tool, while the risk of bias due to missing evidence is shown beside the overall summary diamond.

Similarly to all-cause dementia, several studies analysed individual lipid fractions by estimating the risk of dementia per 1 standard deviation increase in that fraction (Figure 4.9). Weak evidence for an effect on all-cause dementia was found for total cholesterol (N = 5; HR: 1.01, 95%CI: 0.94-1.09), LDL-c (N = 3; HR: 1.06, 95%CI: 0.98-1.16), HDL-c (N = 4; HR: 0.99, 95%CI: 0.91-1.07) or triglycerides (N = 3; HR: 1.00, 95%CI: 0.84-1.18).

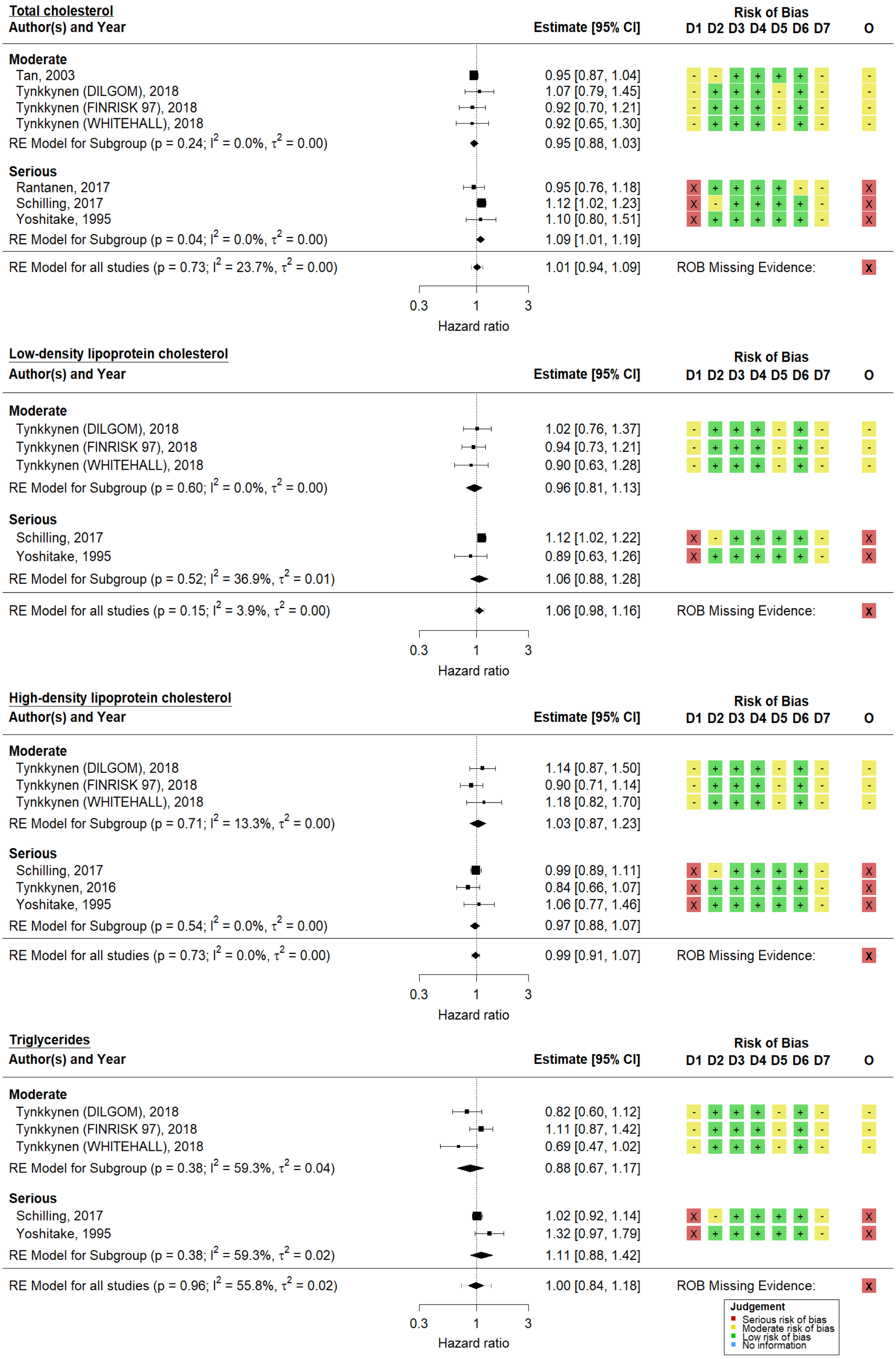

Figure 4.9: Random-effects meta-analysis of association of lipid fractions with Alzheimer's disease - D1-D7 and O refer to the seven risk-of-bias domains and single overall judgement in the ROBINS-E tool, while the risk of bias due to missing evidence is shown beside the overall summary diamond. Note that Tynkkyen *et al*[246] reported results from multiple cohorts and these are presented separately.

Finally, there were several identified Mendelian randomisation studies examining the effect of genetically lowered LDL-c on Alzheimer's disease risk (Figure 4.10). However, all of these studies took a two-sample approach, making use of summary statistics from the International Genomics of Alzheimer's Project (IGAP) consortium and the Global Lipid Genetics Consortium (GLGC). Synthesis of these results would result in a falsely precise estimate caused by multiple counting of the same participants, and as a result, no meta-analysis of these studies was performed. However, across each analysis using varying number of single nucleotide polymorphisms (SNPs), no evidence for an effect was observed (Figure 4.10).

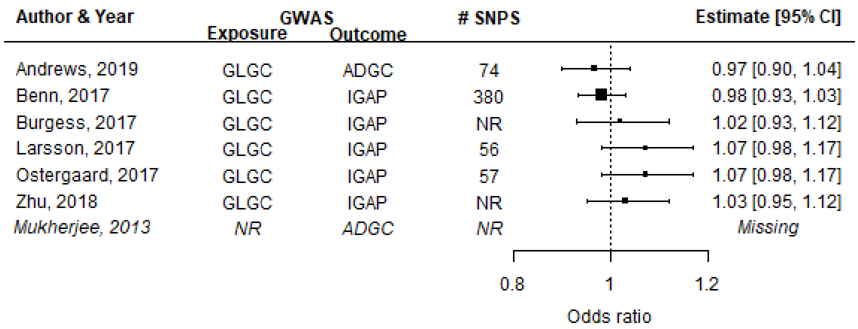

Figure 4.10: Summary of duplication across two-sample Mendelian randomisation studies - Several Mendelian randomisation studies used summary statistics from the Global Lipid Genetics Consortium (GLGC) and the International Genomics of Alzheimer's Project (IGAP). Note that the Alzheimer's Disease Genetics Consortium (ADGC) is a sub-cohort within IGAP.

Statins

There were no randomised trials of the use of statins or any other lipid regulating agents on Alzheimer's disease, though several observational studies examined this association and provided evidence for a protective effect (N = 13; HR: 0.78, 95%CI: 0.66-0.93; Figure 4.11).

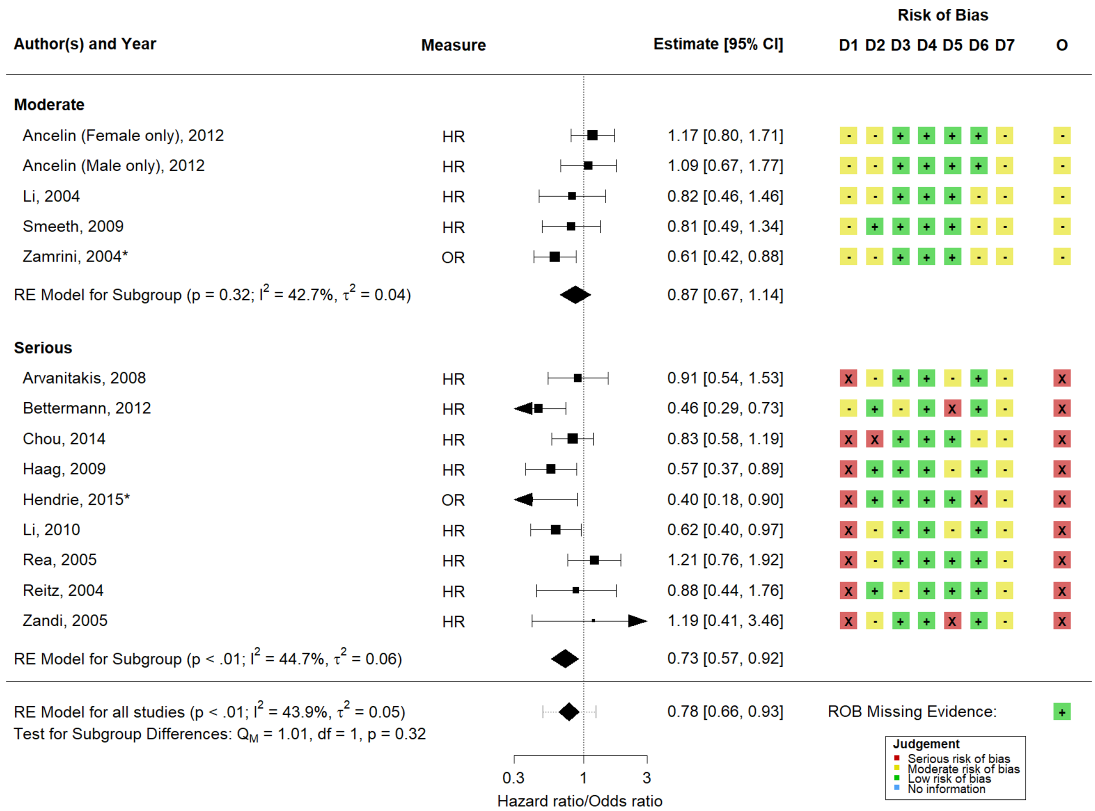

Figure 4.11: Random-effects meta-analysis of statins on Alzheimer's disease - Non-randomised studies examining the association of statin use with Alzheimer's disease were synthesised using a random-effects meta-analysis. Subgroup estimates, stratified by overall risk-of-bias level, are also presented. D1-D7 and O refer to the seven risk-of-bias domains and single overall judgement in the ROBINS-I tool, while the risk of bias due to missing evidence is shown beside the overall summary diamond.

Two Mendelian randomisation studies looked at lipid-lowering specifically as a result of HMGCR inhibition, mediated by SNPs in the gene (rs172338484 and rs12916).[74,254] The first used a one sample approach (SNP-exposure and SNP-outcome associations are estimated using the same dataset) in a large Copenhagen-based cohort, while the second made use of summary level data obtained from the GLGC (SNP-exposure) and the IGAP (SNP-outcome). Meta-analysis of these estimates provided weak evidence of an effect (RR: 0.76, 95%CI: 0.51-1.14, Figure 4.12).

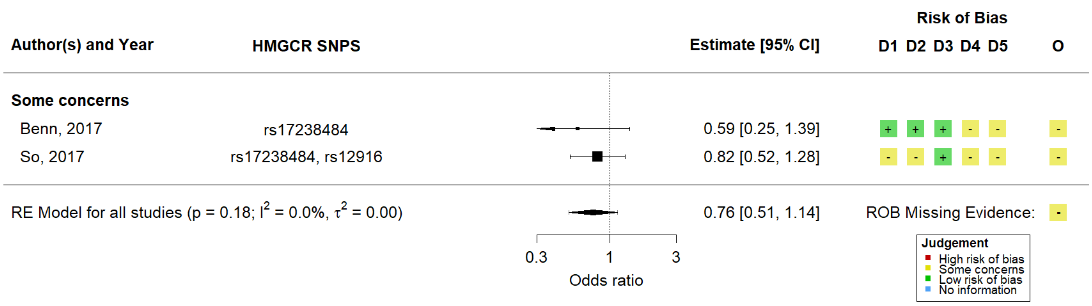

Figure 4.12: Random-effects meta-analysis of HMGCR inhibition on Alzheimer's disease - Mendelian randomisation studies examining the association of genetically lowered LDL-c via HMGCR inhibition with Alzheimer's were synthesised using a random-effects meta-analysis. D1-D5 and O refer to the five risk-of-bias domains and single overall judgement in the Mamluk *et al* tool, while the risk of bias due to missing evidence is shown beside the overall summary diamond.

4.3.3 Vascular dementia

Lipids

As noted in Section 4.2.4 above, there was substantially less literature available on the association of the risk factors of interest with vascular dementia. Three studies reported on the association of hypercholesterolemia with vascular dementia and provided weak evidence for an effect (HR: 1.20, 95%CI: 1.00-1.44, Figure 4.13).

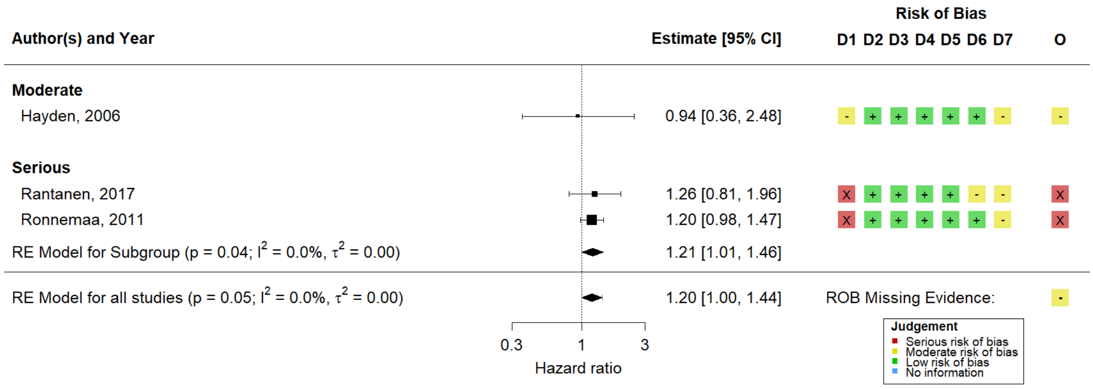

Figure 4.13: Random-effects meta-analysis of hypercholesterolemia on vascular dementia - Non-randomised studies examining the association of hypercholesterolemia with vascular dementia were synthesised using a random-effects meta-analysis. Subgroup estimates, stratified by overall risk-of-bias level, are also presented. D1-D7 and O refer to the seven risk-of-bias domains and single overall judgement in the ROBINS-E tool, while the risk of bias due to missing evidence is shown beside the overall summary diamond.

Few studies investigated the effect of individual lipid fractions on vascular dementia. Only for total cholesterol was there greater than one result reported (Figure 4.14), and a meta-analysis of these results found weak evidence for an effect (N = 2; HR: 1.05, 95%CI: 0.79-1.41). A single study provided evidence on the other three fractions.[249] This analysis similarly found minimal evidence of an effect of LDL-c (HR: 1.12, 95%CI: 0.83-1.51), HDL-c (HR: 0.83, 95%CI: 0.60-1.14) or triglycerides (HR: 1.00, 95%CI: 0.75-1.34) on vascular dementia.

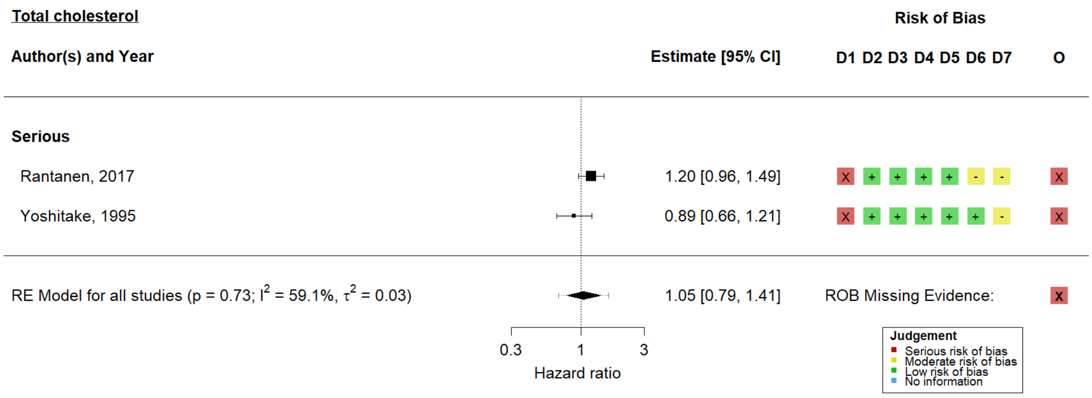

Figure 4.14: Random-effects meta-analysis of total cholesterol on vascular dementia - Non-randomised studies examining the association of total cholesterol with vascular dementia risk, standardised per 1-SD increase in the lipid fraction, were synthesised using a random-effects meta-analysis. D1-D7 and O refer to the seven risk-of-bias domains and single overall judgement in the ROBINS-E tool, while the risk of bias due to missing evidence is shown beside the overall summary diamond.

Finally, no Mendelian randomisation analyses examining the effect of genetically determined lipid levels on vascular dementia risk were identified.

Statins

There were no available randomised trials of statin use for the vascular dementia outcome. Three prospective cohort studies examined statin use and vascular dementia, though meta-analysis of these studies provided weak evidence for an effect (N = 3; HR: 0.99, 95%CI: 0.79-1.25; Figure 4.15).

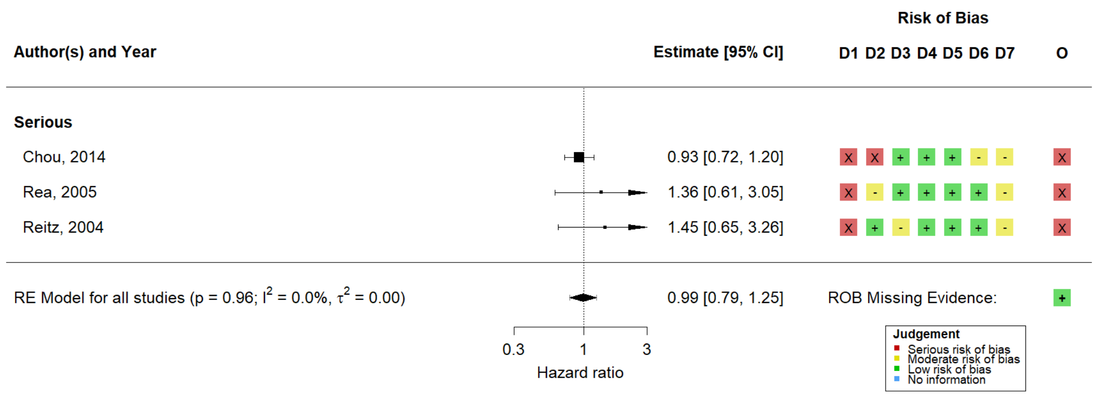

Figure 4.15: Random-effects meta-analysis of statins on vascular dementia - Non-randomised studies examining the association of statin use with vascular dementia were synthesised using a random-effects meta-analysis. Subgroup estimates, stratified by overall risk-of-bias level, are also presented. D1-D7 and O refer to the seven risk-of-bias domains and single overall judgement in the ROBINS-I tool, while the risk of bias due to missing evidence is shown beside the overall summary diamond.

A single Mendelian randomisation analysis was identified that examined the effect of genetically lowered LDL-c levels via HMGCR inhibition on the risk of vascular dementia, which provided some evidence for an effect (RR: 0.44, 95%CI: 0.21-0.91).

4.3.4 Risk of bias

As shown in the "paired" forest plots in the above sections, the risk-of-bias assessments are presented alongside their corresponding numerical result. This section presents only a brief summary of the biases observed in each study design, as detailed discussion of the sources and directions of bias in each result is presented in Chapter 7.

For the two randomised controlled trials, both were judged to be at low risk of bias. In contrast, many of the non-randomised studies of statin use were at serious risk of bias primarily due to poor controlling for confounding, immortal time bias, and missing outcome data. Similarly, non-randomised studies of exposures suffered from incomplete adjustment for potentially important confounders, and concerns over the selection of the reported result from among several analyses (e.g., examination of lipids as a binary or continuous variable). Finally, bias was introduced into Mendelian randomisation studies via the potential for horizontal pleiotropy and population stratification.[70]

Following best practice, any result judged to be at critical risk of bias should be excluded from any quantitative analysis.[159] Three observational studies were excluded on this basis, predominantly due to a lack of adjustment for any potentially important confounders (i.e., the study reported unadjusted estimates).[58,232,236]

The risk of bias due to missing evidence in each synthesis is shown beside the overall summary diamond in each "paired" forest plot presented above. For randomised controlled trials and non-randomised studies of interventions, the risk of bias due to missing evidence was assessed to be minimal. However, there was substantial evidence that results were selectively reported in studies examining the effect of lipid fractions on dementia outcomes (Figures 4.4, 4.9 and 4.14).

In the three analyses with greater than 10 results (Figures 4.3, 4.6 and 4.11), stratification by overall risk-of-bias level did not demonstrate a difference between the "Serious" and "Moderate" risk of bias groups. The result of the test for subgroup differences is shown in the bottom left of the forest plots for these three meta-analyses.

4.4 Additional analyses

4.4.1 Dose response meta-analysis of lipid levels

There were 13 studies initially considered eligible for the dose-response meta-analysis, as they appeared to provide data on risk of dementia outcomes across several categories of lipid exposure. However, following data extraction, five were excluded as they did not report all of the information needed for the analysis. Most commonly, the cut-off measures for each category were missing.

Across the remaining eight studies, a sufficient number of results (n $\geqslant$ 3) were identified only for the total cholesterol-Alzheimer's, LDL-Alzheimer's, and total cholesterol-dementia strata. This analysis provided weak evidence for a non-linear effect of lipid levels on dementia outcomes, and Figure 4.16 illustrates this for the total cholesterol-Alzheimer's strata. Similar figures for the other analysed lipid-outcome strata are presented in Appendix A.4.3.

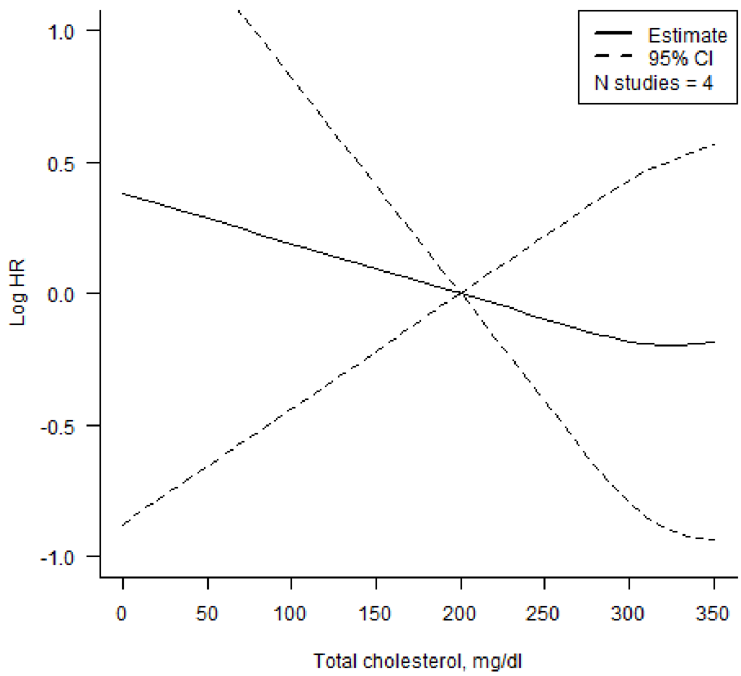

Figure 4.16: Dose-response meta-analysis of total cholesterol on Alzheimer's disease - Non-randomised studies examining the association of lipids levels with Alzheimer's disease across several categories or "doses" of exposure were synthesised using a dose response meta-analysis. The reference dose was defined *a priori* as 200 *mg/dL*, the cut-off of the "Normal"/"Optimal" category for total cholesterol as detailed in Table 1.2.

4.4.2 Heterogeneity and publication bias

There was evidence of heterogeneity in several of the meta-analysis performed, as indicated by a high I_2 statistic. I_2 represents the percentage of variability in the results included in a synthesis that is due to heterogeneity rather than chance.[259] The I_2 value for each analysis are provided in the forest plots above.

Investigation of potential sources of heterogeneity was complicated by two factors. In the first instance, a minority of meta-analysis (3 out of 18, 17%) included 10 or more results, the recommended minimum required for meta-regression. Secondly, poor reporting of baseline characteristics of interest precluded the use of several results in a meta-regression analysis.

Only for the sex covariate were sufficient number of results available to enable meta-regression. Across the three meta-analyses examined, the percentage of females in the study cohort was not related to the observed effect estimate ($p = 0.85$ for hypercholesterolemia/all-cause dementia, Figure 4.3; $p = 0.76$ for statins/all-cause dementia - Figure 4.6; $p = 0.17$ for statins/Alzheimer's disease - Figure 4.11).

Similarly, assessment of small-study effects, for which publication bias could be one potential reason, was limited to these three meta-analyses including 10 or more results. However, there was weak evidence for the presence of small-study effects in each analyses assessed (see Appendix A.4.2).

4.4.3 Added evidential value of including preprints

As shown in the PRISMA flow diagram (Figure 4.1), the number of hits returned by preprint searching was not substantial (bioRxiv = 256, medRxiv = 0). From these hits, three preprinted reports of eligible studies were included in the review, of which two described unique studies not captured by the main search.[254,256]

One preprint (So *et al*[254]) provided additional evidential value in a single meta-analysis (5.6% of the 18 meta-analyses performed in this chapter). This meta-analysis of Mendelian randomisation studies examined the effects of lipid-lowering via HMGCR mutations on incidence of Alzheimer's disease (Figure 4.12). To assess the evidence added to the meta-analysis through inclusion of the preprint, the data was re-analysed using a fixed-effect model. Examination of the weight assigned to each result in the analysis illustrated that a large proportion (78%) of the weight is given to the preprinted result. However, the inclusion of the preprinted study did not have a substantial impact on the result of the meta-analysis (RR: 0.76, 95%CI: 0.51-1.14) compared with that reported by the single published study (RR: 0.59, 95%CI: 0.25-1.39), other than slightly increasing the precision.

The other two preprints identified[256,258] reported on the effect of LDL-c on Alzheimer's disease using data from GLGC and IGAP. As illustrated in Figure 4.10, these consortia were previously analysed in several published reports, and so these preprints did not add new information to the evidence base.

For one of the three preprints identified, the published version of the preprint was captured by the main search. Investigation of the publication status of the two unpublished preprints found that, allowing for a two-year lag (i.e., up to July 2021), only one had been subsequently published.[251,256]

4.5 Discussion

This review presented a summary of the available evidence on the association of lipids and LRA with subsequent risk of dementia outcomes. This discussion seeks to summarise the key findings in terms of literature sources and results as reported. A detailed comparison across the evidence sources, exposure measures and sources of bias reported here is presented as part of the triangulation exercise in Chapter 7.

4.5.1 Summary of findings

There was some indication of a protective effect of statins on all-cause and Alzheimer's disease dementia when looking solely at observational studies. This finding was not supported by evidence from the two available RCTs, or by studies that emulated statin treatment using a genetic proxy. This suggests that these findings may be a result of differing exposure windows (e.g., mid-life lipid lowering in non-randomised studies versus life-course lipid exposure in Mendelian randomisation studies and late-life lipid reduction in RCTs) or alternatively due to biases within the non-randomised studies.

Across dementia outcomes, the majority of studies were non-randomised studies of lipids or lipid regulating agents. This distribution of evidence between analytical designs is to be expected. Randomised controlled trials of dementia are particularly challenging, as the follow-up made necessary by the long latency period of the condition makes trials logistically difficult and financially expensive. Similarly, Mendelian randomisation is a comparatively new study design, and studies employing it in relation to dementia outcomes only appear in the evidence base in recent years, as illustrated in Figure 4.17. This recent increase is likely driven by the availability of summary genome wide association studies (GWAS) that form the basis of the two-sample Mendelian randomisation approach.

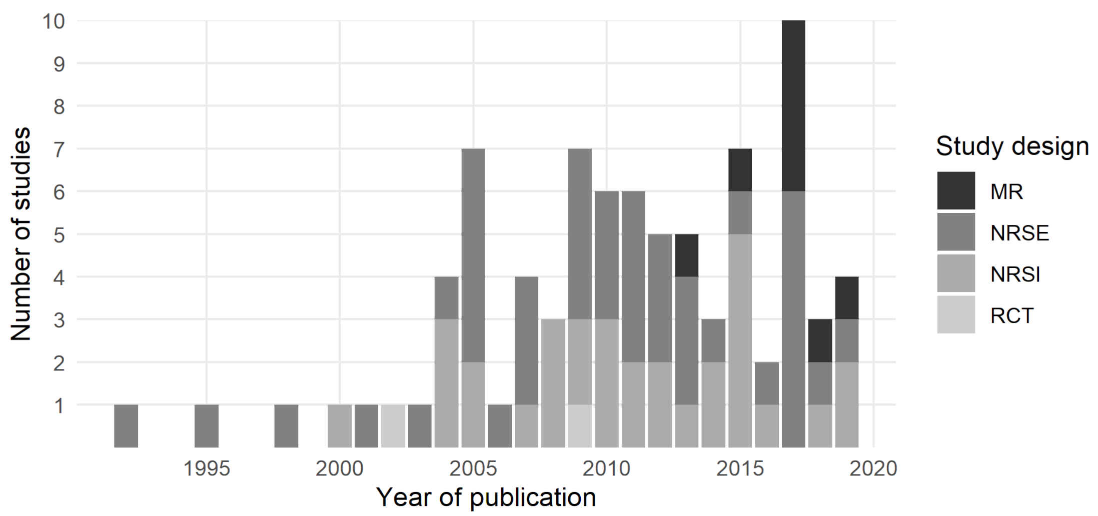

Figure 4.17: Study designs by year of publication - Included studies across all dementia outcomes are shown grouped by study design and year of publication. Note that Mendelian randomisation studies only begin to appear in the evidence base much later than other study designs.

A central finding of this review is the absence of studies examining vascular dementia as an outcome, most noticeable when comparing the evidence base for statins in dementia/Alzheimer's (Figures 4.6 & 4.11) with that available for vascular dementia (Figure 4.15). This is particularly interesting given that lipids and statins are strongly related to the prevention of vascular disease. A potential explanation for this observation may be publication bias or the "file-drawer effect",[85] though small-study effects (of which publication bias is one potential cause)[182] could not be investigated for this outcome due to the small number of available results. Similarly, only one Mendelian randomisation study examined this outcome, likely due to the absence of vascular dementia GWAS which precludes a two-sample approach.

Of note, this review did not include the commonly cited PROSPER RCT, which examined the effect of pravastatin on cardiovascular disease risk and reported on cognitive measures as one of several secondary outcomes.[260] While widely cited in relation to the effect of statins on dementia risk and included in the Cochrane review of RCTs on this topic,[65] the trial reported solely on the change in a range of cognitive measures (MMSE, Stroop test, Picture-Word Learning test and others) over follow-up rather than a binary dementia outcome. As such, this trial did not meet the inclusion criteria for this review.

Risk of bias across the individual results was generally high. The expected impact of these biases on the results are discussed in more detail in Chapter 7. Of particular interest to this chapter, however, was the high risk of bias due to missing evidence observed for observational studies of lipid levels. In many cases, estimates were known to be missing from meta-analyses due to preferential reporting of significant results, leading to high risk of bias due to missing evidence. These missing estimates were most commonly identified through differing descriptions of the same analysis in conference abstract versus the final publication.[248,261] In addition, some authors stated outright that non-significant results were not reported (e.g., "The other lipid variables not significantly associated with dementia and Alzheimer's disease ... were not reported in the table.").[221] However, as all identified missing results are likely to be non-significant, they would not be expected to have a substantial impact on their respective meta-analyses (which provided weak evidence of an effect of lipid levels on dementia outcomes) beyond increasing the precision of the summary estimate.

Finally in terms of generalisability, despite a large proportion of the included studies being conducted in the westernised countries (Figure 4.2), the applicability of the results to other populations is aided by the inclusion of several studies which made use of data from the Taiwan National Health Insurance database.

4.5.2 Comparison with previous reviews

While conducting this review, I identified several previous systematic reviews of this topic.[262–266] However, to my knowledge, this review is the first to use established domain-based assessment tools (for example, the RoB 2 tool for randomised controlled trials)[162] to assess the risk of bias in included studies. The majority of the highly cited reviews on this topic either do not formally consider risk of bias in the observational studies they include,[262,267] or use a non-domain-based assessment tool (e.g., the Newcastle-Ottowa Scale).[265]

I identified one previous review of Mendelian randomisation studies examining risk factors for Alzheimer's disease. However, this review was conducted prior to the majority of Mendelian randomisation studies included in this review being published. In addition, this previous review extracted the results of analyses which did not account for SNPs in the *Apo*$\mathcal{E}$4 genetic region (see the following section for a discussion of the bias this introduces).

Despite these differences in time scales and methodology, the duplication of work across systematic reviews (including this one) is substantial. In retrospect, an alternative approach to conducting a further systematic review from scratch, known as an umbrella review or review-of-reviews,[268,269] could have been employed. This study design uses other systematic reviews rather than primary studies as the unit of analysis. Furthermore, it would have enabled more efficient identification of a comprehensive set of primary studies relevant to this clinical question. Having defined this set, the methods which set this review apart could then have been applied.

4.5.3 Inclusion of Mendelian randomisation studies

One of the particular strengths of this review is the inclusion and critical assessment of Mendelian randomisation studies as a source of evidence.

Mendelian randomisation is a powerful analytical technique, using natural variation in participants' genomes to identify causal links between a genetically determined risk factor and an outcome, given that the three core assumptions detailed in Figure 4.18 are valid. These assumptions are namely that:

1. the genetic variant associates with the risk factor of interest (relevance assumption);
2. the variant-exposure association has no unmeasured confounders (independence assumption);
3. the variants affect the outcome only through their effect on the risk factor of interest (exclusion restriction assumption).

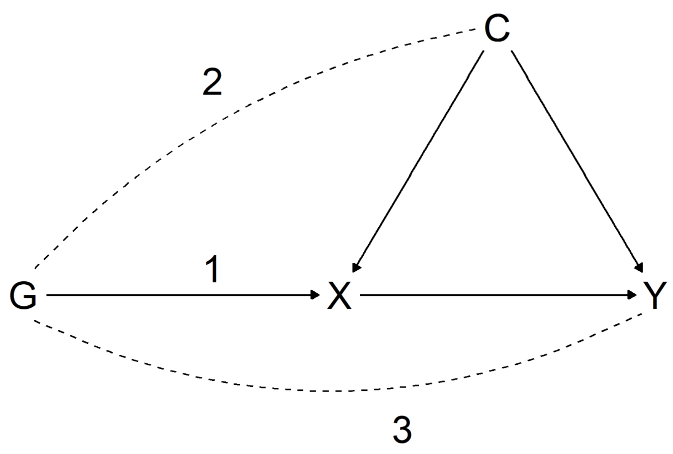

Figure 4.18: Summary of the assumptions in Mendelian randomisation analyses - Mendelian randomisation analyses make three key assumptions: (1) *relevance* - the genetic variant associates with the risk factor of interest; (2) *independence* - the variant-exposure association has no unmeasured confounders; and (3) *exclusion restriction* - variants affect the outcome only through their effect on the risk factor of interest (i.e., there is no horizontal pleiotropy).

However, inclusion of Mendelian randomisation as an acceptable study design in this review was complicated by a number of factors. Firstly, this study design is relatively new, particularly when compared to randomised trials or cohort studies. Figure 4.17 demonstrates that Mendelian randomisation studies only begin to appear in the evidence base much later than NRSE/NRSI, likely due to the limited availability of large scale GWAS datasets needed for two-sample Mendelian randomisation analyses. As such, the process and tools for systematically assessing this study design are not as well developed. A key example of this is the absence of validated search filters for Mendelian randomisation studies. This limitation is further complicated by the varying terminology used to describe the method, particularly in the early years of its application, which led to me including general terms for instrumental variable analyses in my search.

Additionally, there is currently no widely used risk-of-bias assessment tool for Mendelian randomisation studies. While a recent commentary provided a checklist for interpreting Mendelian randomisation studies, this includes reporting items in their quality checklist.[70] Reporting quality is an important consideration for

Mendelian randomisation studies, as reflected by the recent release of the STROBE MR reporting guidelines,[270] but is a separate issue to bias as discussed in Section 3.2.8. Similarly, a previous review of Mendelian randomisation studies used the Q-Genie tool which was designed to assess the quality of GWAS included in a meta-analysis.[271] While this tool assesses the underlying GWAS used, it does not address the additional methodological considerations of the Mendelian randomisation analysis itself. For this review, I used the best available author-devised tool, sourced from a recent review of systematic reviews of Mendelian randomisation studies.[167]

As a further stumbling block, Mendelian randomisation lends itself to the analysis of multiple exposure-outcome comparisons as part of a single study, particularly when using a two-sample summary data design. This is particularly relevant to the consideration of bias due to missing evidence. As an example, through snowballing (forwards and backwards citation chasing) and other measures, I identified at least one relevant Mendelian randomisation study that had not been captured by the search strategy.[71] This study examined lipid fractions as one of many risk factors for Alzheimer's disease, though the search would not have been expected to find this study given the absence of any lipid-related keywords in the title or abstract. Studies examining multiple risk factors such as this can introduce bias into a systematic review, as it is commonly only those risk factors with a statistically significant result that are reported in the abstract and so are captured by a systematic search. These studies are described as "unknown unknown's" in the context of the RoB-ME tool and are considered to be particularly challenging (as opposed to an analysis that was insufficiently reported to be included in the statistical analysis, or the "known unknown's").

In better-resourced reviews, a broader search (e.g., "risk factor" AND "dementia" AND "Mendelian randomisation") followed by manual review of studies that examined multiple risk factors would be advisable. This was not feasible in the context of this review, given the large number of records to be screened even when using study design filters (N = 16,109). Additionally, the value of methods that support traditional bibliographic database searches, such as snowballing and communication with relevant topic experts, should not be underestimated.

One item of particular interest is the attenuation of any effects identified by Mendelian randomisation studies following the adjustment for/exclusion of genetic variation in the *Apo$\mathcal{E}$4* gene region. As discussed in the introduction to this thesis (see Section 1.4.1), an increasing number of *Apo$\mathcal{E}$4* alleles is a major independent risk factor for Alzheimer's disease and so violates the exclusion restriction criteria of Mendelian randomisation studies (Figure 4.18). In all cases, excluding variants in the *Apo$\mathcal{E}$* region attenuates the observed effect to the null. A clear example of this is Benn *et al* (2017), where *Apo$\mathcal{E}$* variants were not sufficiently identified and excluded, leading the published paper to report a protective effect of LDL-c on Alzheimer's (RR: 0.83, 95%CI: 0.75-0.92).[74] Following several rapid responses, the data was re-analysed to exclude a larger area around *Apo$\mathcal{E}$* which attenuated the finding to the null.[272]

4.5.4 Inclusion of preprints

As highlighted in Section 1.5.1, this review explicitly sought to synthesize all available evidence, irrespective of publication status (preprinted vs. published). Using the tool described in Chapter 2.1, two preprint servers related to health and biomedical sciences were searched as part of this review. The small number of studies returned by the preprint searches (or the absence of any relevant hits in the medRxiv database - see the PRISMA flow diagram in Figure 4.1) is largely due to the timing of the preprint searches. The searches for this review were performed in mid-July 2019, but the medRxiv repository, an offshoot of the Epidemiology and Clinical Trials categories of the bioRxiv preprint server, only registered its first preprint 25th June 2019. As such, at the point it was searched, the medRxiv database contained only a very small number of records (N = 148; Figure 4.19).

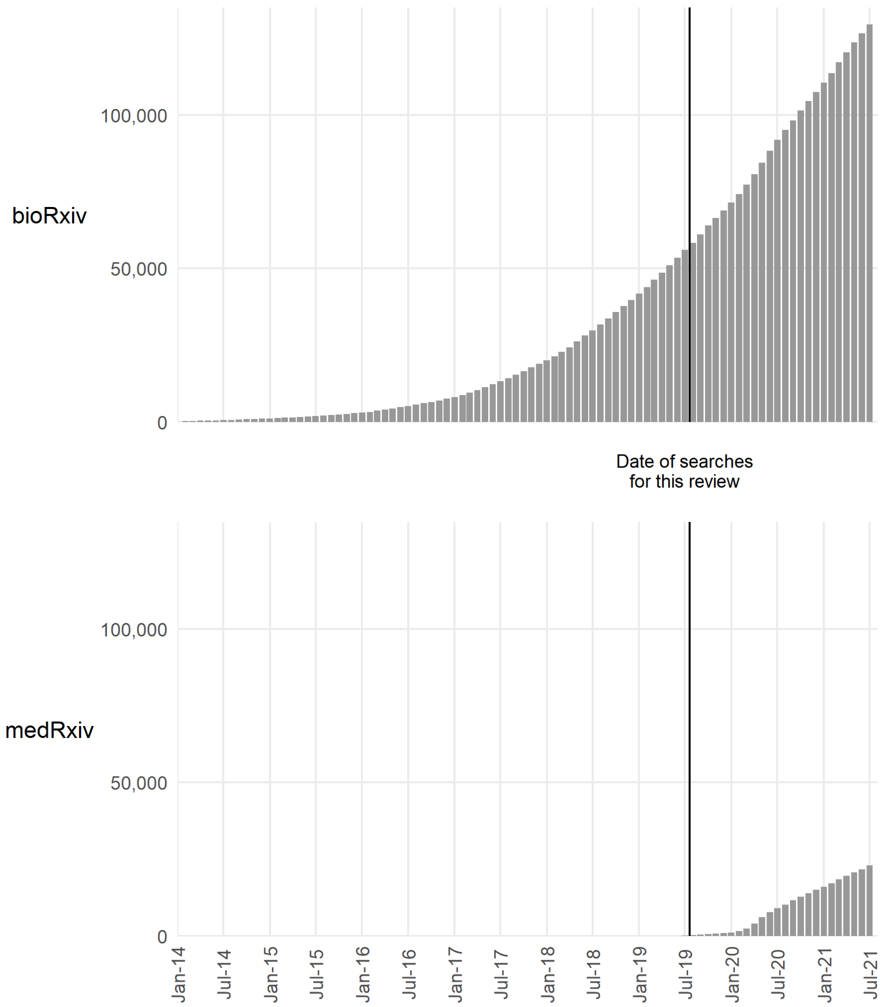

Figure 4.19: Growth of preprint repositories over time - Given the relative sizes of the preprint repositories at the time the searches for this review were conducted (bioRxiv N = 56,007, medRxiv N = 148), the number of hits returned by each is expected.

Three relevant preprints from bioRxiv were identified. Of note, all three described a Mendelian randomisation study, potentially indicating that more biologically-focused study designs are over-represented in the bioRxiv repository. The added evidential value of including these preprints was described in Section 4.4.3 and indicated that results available only via preprinted reports can contribute additional evidence to a meta-analysis. However, the scale of this contribution is questionable. Preprinted evidence was incorporated into only a single meta-analysis in this review, and inclusion of the preprinted result did not substantially impact the summary effect estimate.

Of the three identified preprints, two were subsequently published as of July 2021. This fits well with the analysis presented in Chapter 2 that, allowing for a two-year lag, approximately two-thirds of preprints are published. It also illustrates the dual advantages of preprinted reports to evidence synthesis exercises. Firstly, preprints provide an advance snapshot of the literature, capturing articles that will eventually be published but were not available at the time of the main search. For example, one eligible preprint in this review was initially posted on bioRxiv in July 2019[256] and was subsequently published in 2021 following peer-review.[251] Secondly, inclusion of preprints allows for results that may never be formally published to be included in an evidence synthesis exercise, as is the case with a second preprint included in this review.[254] Both of these aspects illustrate that inclusion of preprints is a necessity if the aim is to find all relevant literature on a topic at the time of searching.

Recently, inclusion of preprints in systematic reviews has become significantly more widespread. This is largely due to the role of preprint servers, in particular medRxiv, as a key evidence dissemination venue during the early stages of the COVID-19 pandemic.[84] How well this adoption of preprints will transfer to other less-urgent topics, where the speed of research does not put the same focus on preprinted articles, is currently unknown.

4.5.5 Open data sharing

As discussed in Section 4.4.1, many primary studies did not report important information required for the dose-response meta-analysis, and so could not be included in this analysis. This limitation was compounded by the expected low response rate to requests for further information from primary authors. Contacting authors is worthwhile, because it can substantially change the conclusion of a systematic review[273] and is not too costly to systematic reviewers.[274] However, a preferable option is that the authors of primary studies readily deposit all relevant study data at the point of publication.

Based on my experience of extracting data for this review, I co-authored a guidance article to aid primary prevention scientists in preparing and sharing their data so that it can easily be incorporated into an evidence synthesis exercise, using a trial of mindfulness interventions as a case study.[275] A copy of this publication is available in Appendix B.3. In an attempt to apply my own guidance, I have invested a substantial amount of time and effort into making the data obtained by this review openly available to other researchers, via a GitHub repository.

4.5.6 Strengths and limitations

Strengths

There are several aspects where this review is distinct from those already available in the published literature. While several reviews of this research topic exist,[262–265] the overlap between the list of studies included in each is not complete. As part of this review, I have not only performed an original search of primary literature databases but have also screened the reference lists of comparable reviews to ensure no relevant study has been omitted.

Secondly, this review employed a structured approach to risk-of-bias assessment using a domain-based tool. This represents an important strength of this review, as the detailed risk of bias assessments are used to inform the quantitative triangulation analysis presented in Chapter 7.

Thirdly, as discussed at length in the section above, in contrast to other available reviews and enabled by the tool described in Chapter 2, this review systematically searched health-related preprints.

Finally, as a secondary element, I used this review to pilot new research synthesis methodologies, in particular a new visualisation approach for risk-of-bias assessments and a forthcoming tool for assessing the risk-of-bias due to missing evidence.

Limitations

A primary limitation of this review is the fact that only a sample of records were dual screened at the title/abstract and full-text stages is a potential limitation, because there is a chance that some eligible records could have been excluded. However, evidence from assessments of inter- and intra-rater reliability indicate that this is not a major concern. Additionally, the search date of the study (July 2019) is a further limitation, in that more recently published studies are not included in this analysis.

One particular limitation with regards to the risk-of-bias assessment is the fact that the ROBINS-E assessments were performed using an adapted version of the ROBINS-I tool. This meant that there were no signaling questions to guide the domain-level risk-of-bias assessments, which may have influenced the accuracy with which the judgements were assigned. However, there is no published empirical evidence supporting the need for signaling questions. Additionally, a previous assessment of inter-rater reliability in domain-bases risk-of-bias tools found that, even with the use of signaling questions, reviewers' assessment of bias can vary substantially.[276]

A final limitation is the potential for missing evidence on the basis of the results. Evidence for this limitation came from the ROB-ME assessments and was supported by empirical evidence that some studies containing relevant results were missed by the search (see Section 4.5.3 above for a fuller discussion of this issue with respect to Mendelian randomisation studies). Unfortunately, this is probably a common limitation across all systematic reviews, based on the way in which increased search sensitivity must be balanced with a manageable workload.

4.6 Summary

- In this chapter, I presented the results of a comprehensive systematic review of existing evidence on the association between lipid levels and dementia use. The review included both direct (studies that examined lipid levels directly) and indirect (studies examining lipid regulating agents such as statins) forms of evidence. In contrast to previous reviews, I also included preprinted evidence, facilitated by the research tool introduced in Chapter 2.

- I found no consistent relationship between lipids or lipid-regulating agents and dementia across different evidence sources. However, there was some indication of a protective effect of statins on all-cause and Alzheimer's disease dementia in non-randomised studies of interventions.

- The findings from this review are used throughout the subsequent chapters. In Chapter 5, this summary of the evidence guided the choice of analysis approach, ensuring that the new analysis was at risk of a different source of bias and provided evidence on an under-studied outcome (vascular dementia). In Chapter 6, prospective cohorts identified by the review were contacted in an attempt to obtain individual participant data. Finally, the results identified here are used as a key source of evidence for the triangulation exercise presented in Chapter 7.

When dealing with human beings controlled experiments frequently prove to be impracticable, so for a scientific basis for our assumptions we turn to past history to reconstruct the suspected causal chain of events - and then our statistical troubles may begin.

— Harold F. Dorn, 1953[277]

5

Primary analysis of lipid-regulating agents and dementia outcomes in the CPRD

Contents

Lay summary

Electronic health record (EHR) databases are large collections of medical data, used to manage patient administration and care. Under these systems, whenever a patient attends their GP, their clinical data is recorded in a central database using a standardised coding system. These databases have several advantages over traditional methods of data collection, including the number of people they contain and the relatively low cost of data collection. This is particularly important when studying diseases such as dementia, which may begin to develop in patients long before symptoms are seen.

This analysis makes use of the Clinical Practice Research Datalink (CPRD), which contains the electronic medical records of more than 3 million people from general practices across England. Using this data, the analysis presented in this chapter examined whether lipid-regulating agents (treatments which change lipid levels) affect the risk of all-cause dementia and related outcomes (Alzheimer's disease, vascular dementia and other dementias).

Little evidence for an effect of lipid-regulating agents on the risk of Alzheimer's disease was found, with the exception of a slightly increased risk in those prescribed a certain type of lipid-regulating agent called fibrates. In contrast, I found an increased risk of vascular and other (i.e., non-Alzheimer's) dementia was associated with lipid-regulating agent use.

This increased risk in outcomes with a vascular element (e.g., vascular dementia) is unexpected and is very likely to be due to the presence of bias in my analysis. This bias, called "confounding by indication", is caused when those who are prescribed a statin are more at risk of vascular dementia for a range of reasons, which makes it appear as if statins are harmful. Despite this limitation, the analysis provides an important source of information which will be used in later chapters.

5.1 Introduction

In this chapter, I present an analysis of a large population-based electronic health record (EHR) dataset to investigate the relationship between lipid-regulating agent (LRA) use and dementia outcomes. The analysis aims to address two important limitations of the current evidence base as identified by the systematic review presented in Chapters 3 & 4.

Firstly, it explicitly examines vascular dementia as an outcome. The systematic review presented in the previous chapter identified an evidence gap around the effect of lipid-regulating agents on the risk of vascular dementia. As triangulation exercises require as many diverse sources of evidence as possible, this analysis provides an additional source of information on this outcome.

Secondly, and in a similar vein, the analysis intentionally takes a different analytical approach to that most commonly used to examine the effect of statins on dementia as identified by the systematic review. Specifically, this involved a concerted effort to address immortal time bias through use of a Cox proportional hazards analysis, incorporating a time-varying treatment indicator.[278] By employing this approach, the analysis provides an evidence source at risk of a distinct bias, making it useful to the triangulation exercise presented in Chapter 7.

This chapter represents an extended version of a preprinted manuscript, a copy of which is available in Appendix B.3.

5.2 Methods

5.2.1 Study protocol

An *a priori* protocol for this study was published,[279] and amendments to this are recorded in Appendix A.5.1.

5.2.2 Data source

Previously known as the General Practice Research Database, the Clinical Practice Research Datalink (CPRD) is a large population-based EHR database.[280] The database has been collecting primary care data from participating practices across

England since 1987.[281,282] It contains the records of more than 10 million primary care patients in England and is broadly representative of the UK population in terms of age, sex and ethnicity.[280,283]

To avoid the ambiguity of interpreting free-text clinical notes and to allow for easy analysis of the resulting data, the CPRD primarily collects data using a predefined coding system known as Read codes.[284] All clinical events, including test results and diagnoses, can be identified by a specific Read code. The codes use a nested approach (see Table 5.1), with the initial characters defining broad diagnostic topics (e.g., Eu... - Mental and behavioural disorders), while subsequent characters provide additional information on the specific condition diagnosed (e.g., Eu001 - Dementia in Alzheimer's disease with late onset).

Table 5.1: Example of CPRD Read code hierarchy - Broad topics are specified using the initial two alpha-numeric characters of the Read code, while subsequent characters are used to define specific conditions and context. The example shown illustrates how "Dementia in Alzheimer's disease with late onset" (*Eu001*) is nested under the top-level of "Mental and behavioural disorders" (*Eu...*).

Level	Read code	Term
1	E....	Mental disorders
2	Eu...	Mental and behavioral disorders
3	Eu0..	Organic mental disorder
4	Eu00.	Dementia in Alzheimer's disease
5	Eu001	Dementia in Alzheimer's disease with late onset

The index events, exposures and outcomes used in this analysis were identified using predetermined code lists, which are available for inspection from the repository accompanying this analysis (data/code availability is discussed in Section 5.4.4).

5.2.3 Cohort definition

This analysis included all patients registered at a participating practice between 1 January 1995 and 29 February 2016 who had a flag for “research quality” data (as defined by the CPRD). Records pre-dating the 1995 cut-off were provided as part of the original CPRD extract obtained for this analysis. However, these older records were excluded from the analysis because data quality and reliability are thought to be higher after this date.[285] Additionally, individuals with less than 12 months of continuous records prior to cohort entry were excluded, making the effective start date of the cohort 1 January 1996.

Participants were included in the study cohort if their record contained any of the following index events:

- a Read code for a diagnosis of hypercholesterolemia or related condition;
- a Read code for prescription of a lipid-regulating agent (such as statins);
- a total cholesterol test result of >4 mmol/L; or
- an LDL-c test result of >2 mmol/L.

The blood lipid cut-offs were based on NIHR-recommended levels at the time the protocol was written. These index events allowed me to define a population of participants who were either at risk of hypercholesterolemia, as indicated by the elevated total or LDL cholesterol test results, or had already been diagnosed with it, as indicated by a diagnostic code/related prescription.

The index date for a participant was defined as the date where the first relevant code or test result was recorded on their clinical record, and participants were followed up until the earliest of:

- an outcome of interest;
- death;
- end of follow-up (29 February 2016);
- last registration date with their GP practice; or

- the last CPRD collection date for their practice.

Participants were ineligible for the cohort if they were less than 40 years of age (because these patients are less likely to be prescribed a LRA), had less than 12 months of "research quality" data, were simultaneously prescribed more than one lipid-regulating agent (due to the difficultly of assigning these to a single exposure group), or were diagnosed with an outcome of interest before or on the date of the index event (i.e., had less than one full day of follow-up).

5.2.4 Exposures

I considered seven lipid-regulating drug classes based on groupings in the British National Formulary,[286] namely: statins, fibrates, bile acid sequestrants, ezetimibe, nicotinic acid groups, ezetimibe and statin (representing one treatment containing both drugs, rather than the two classes being prescribed concurrently), and omega-3 fatty acid groups.

A participant's drug class was assigned based on their first recorded prescription, and any drug switching was ignored in an effort to mimic an intention-to-treat approach. I did however examine how often the initial drug class altered according to one of three criteria:

- **stopped**: defined as the last prescription of the primary class being followed by at least six months of observation;
- **added**: defined as a second drug class being prescribed before the last prescription of the initial class; and
- **switched**: defined as a second drug class being prescribed after the last prescription of the initial class.

5.2.5 Outcomes

I considered five outcomes as part of this analysis: probable Alzheimer's disease, possible Alzheimer's disease, vascular dementia, other dementias, and a composite all-cause dementia outcome. When two or more outcomes were coded in a participant's clinical record, a decision tree was used to differentiate between them (Figure 5.1). The diagnosis date of the outcome was determined by the first record of a relevant code.

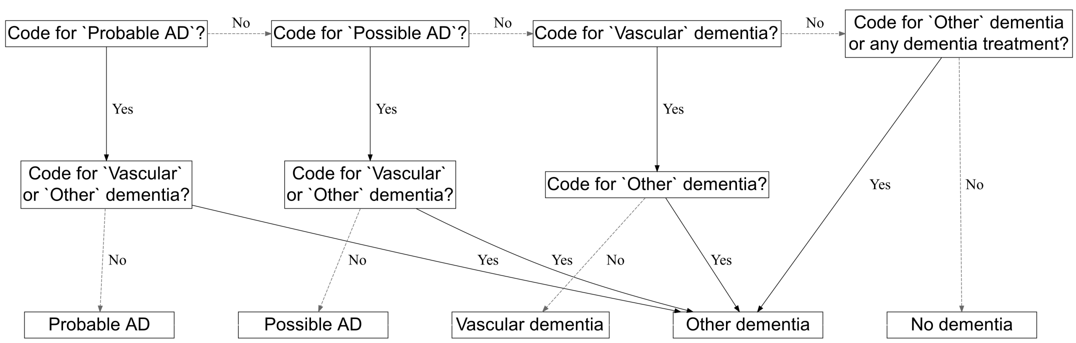

Figure 5.1: Decision tree for assigning dementia subtypes - Based on the presence of specific Read codes in the patient's record, a decision tree was used to classify dementia subtypes ("Probable" or "Possible" Alzheimer's disease, vascular dementia, and other dementia). Note that an outcome of "probable" or "possible" Alzheimer's disease (AD) requires the absence of any vascular outcome codes.

5.2.6 Covariates

A range of additional variables were included in the analysis. These covariates were adjusted for in the analysis in an attempt to address the different distributions of potential confounding factors between those who were prescribed a lipid-regulating agent and those who were not. These are discussed in detail below and summarised in Table 5.2.

Table 5.2: Definitions of covariates adjusted for in the analysis - The code lists used to define the majority of these covariates were originally created for use in a previously published analysis.[287] while others were built on or adapted from previous published work.[288–290]

Covariate	How was the covariate defined?
Previous history of coronary arterial disease	Presence of one or more relevant Read codes on record.
Previous history of coronary bypass surgery	Presence of one or more relevant Read codes on record.
Previous history of cerebrovascular disease (including stroke)	Presence of one or more relevant Read codes on record.
Chronic illness, including cancer and arthritis	Charlson index implemented using Read code lists.[288] Code lists based on those by Taylor et al.[289]
Socioeconomic position	2010 English Index of Multiple Deprivation (IMD) at the twentile level, where 1 represents the least deprived and 20 the most deprived.
Consultation rate	Calculated by dividing the total number of clinic visits by the length of the patient record prior to the index date to give an average annual rate.
Alcohol status	Recorded value (current, former or never).
Smoking status	Most recent of recorded value (current, former or never) or Read code indicating a recorded value. Code lists based on those by Wright et al.[290]
Body Mass Index	Recorded value if available, or a calculated value using the last recorded height and weight measurements. Measurements taken before the age of 25 were excluded to ensure adult measurements were used.
Peripheral arterial disease	Presence of one or more relevant Read codes on record.
Hypertension	Presence of one or more relevant Read codes on record.
Baseline total cholesterol	Continuous value recorded as test result ("enttype==163 & test_data1==3")
Baseline LDL cholesterol	Continuous value recorded as test result ("enttype==177 & test_data1==3")
Chronic kidney disease	Presence of one or more relevant Read codes on record.
Type 1 Diabetes	Presence of one or more relevant Read codes on record.
Type 2 Diabetes	Presence of one or more relevant Read codes on record.

Demographic covariates adjusted for included age and gender. Age in years was calculated at date of entry into the cohort, using the 1st of January of a patient's birth year (the exact date of birth was not provided by CPRD), and was adjusted for via its use as the time axis for the Cox model (see Section 5.2.10). Socioeconomic status was proxied using the Index of Multiple Deprivation (IMD) 2010. The IMD draws on seven domains (income; employment; education, skills and training; health and disability; crime; barriers to housing and services; living environment) to create an overall deprivation score for each of 32844 statistical geography areas in England. To help preserve patient privacy, IMD score is only available from the CPRD in twentiles, with 1 indicating the least deprived and 20 indicating the most deprived. Smoking and alcohol use was determined at index, and usage was categorised as current, former, or never.

Body mass index (a summary measure calculated as $\frac{weight}{height^2}$), baseline total cholesterol and baseline LDL cholesterol measures were obtained, using the last recorded value prior to the index date. A variable indicating grouped year of entry into the cohort (<=2000, 2001-2005, 2006-2010, >2010) was included to allow for changes in prescribing trends across the lifetime of the cohort. To assess healthcare utilisation, I adjusted for the average annual number of consultations between the beginning of a patient's data and their entry into the cohort.

Finally, presence of a range of related conditions at baseline were accounted for, including cardiovascular disease, coronary bypass surgery, coronary artery disease, peripheral arterial disease, hypertension, chronic kidney disease, and Type 1 and Type 2 diabetes. In addition to adjusting for these covariates individually, a Charlson co-morbidity index (CCI) score was calculated for each participant. The CCI is a weighted index that uses presence and severity of a number of conditions to enable adjustment for the general health of a participant in terms of their mortality risk.[291] The conditions considered under the index are: AIDS; cancer; cerebrovascular disease; chronic pulmonary disease; congestive heart disease; dementia; diabetes; diabetes with complications; hemiplegia; metastatic tumour; mild liver disease; moderate liver disease; myocardial infarction; peptic ulcer disease; peripheral vascular disease; renal disease; and rheumatological disease. Inclusion of this index allowed me to adjust for the general health of patients included in the analysis.

Code lists for all covariates can be found in the archived data repository accompanying this analysis (see Section 5.4.4).

5.2.7 Missing data

Missing data are a recognised problem in electronic health records databases.[292] These databases are created from administrative data, collected primarily for the purposes of patient management and care rather than academic research.

In this analysis, missing data was handled using a multiple imputation approach.[293] Variables with missing observations were identified for inclusion in the imputation model. Nominal variables with missing values were modelled using multinomial logistic regression, while continuous variables were modelled using linear regression. As per best practice, all variables used in the analytic model, including the outcome, were included in the imputation model.[294] Using the MICE (Multiple Imputation by Chained Equations) command in STATA 16,[295] 20 imputed datasets were created.

Missing data was only considered problematic for variables where a numerical test result was expected (e.g., BMI), or where a code existed for the absence of the condition (e.g., categorical smoking status). This approach was necessary because absence of a code for other treatments or conditions (e.g., statin use or dementia) was assumed to indicate absence of the treatment/condition rather than being considered missing.[292]

5.2.8 Estimation methods

A Cox proportional hazards (PR) model was used to estimate the effect of statins on dementia outcomes. Cox PR models are defined in general terms as:

$$h(t) = h_o(t) \times exp(b_1x_1 + b_2x_2 + ... + b_px_p) \tag{5.1}$$

where:

- t is the survival time;
- $h(t)$ is the hazard function;
- $x_1, x_2, ..., x_p$ are the covariates which determine the hazard function, while $b_1, b_2, ..., b_p$ are the coefficients for each covariate; and
- $h_o(t)$ is the baseline hazard - when all x_i are zero, the $exp()$ function resolves to 1.

A Cox PR model was chosen for this analysis as it inherently accounts for the length of time participants spend in each exposure group. Using this approach, time-at-risk can be properly attributed to the appropriate exposure group, thus mitigating the impact of immortal time bias. This is discussed in detail in the following section.

5.2.9 Immortal time bias and time-varying treatment indicators

Immortal time bias describes two distinct but related types of bias, considered here in relation to statin use (Figure 5.2). The first presentation, the selection bias aspect (Panel A), occurs when time prior to statin initiation is excluded leading to the statin and control groups being followed up from different time points.[296] The unexposed group are followed from the date of an index event (e.g., diagnosis of hypercholesterolemia), while the statin group is followed from date of a statin initiation. In this scenario, the time between the index event and statin initiation is missing, and any events that occur in the exposed group prior to the prescription will be inappropriately excluded from the analysis.

The second presentation of immortal time bias is as a type of misclassification bias (Panel B, Figure 5.2). It occurs when the exposure time and events prior to statin initiation are inappropriately assigned to the statin group.

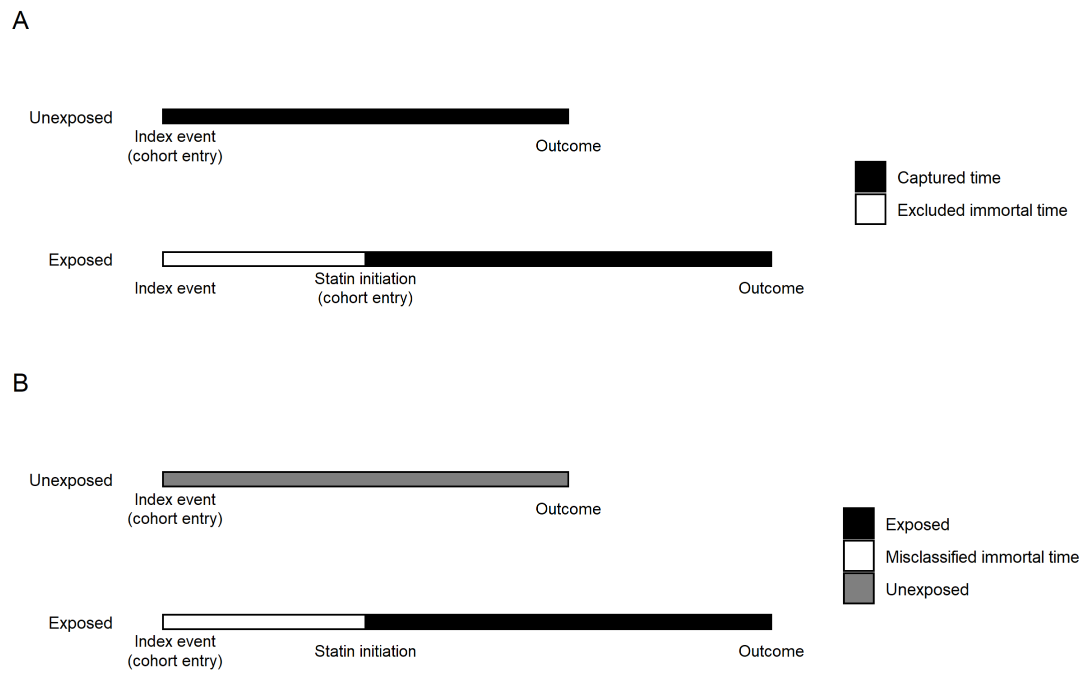

Figure 5.2: Immortal time bias - The two presentations of immortal time bias are illustrated. Panel A shows the selection bias presentation, where time prior to a statin exposure is excluded from the analysis and outcomes in this time period are lost. Panel B shows the misclassification presentation, there time (and events) prior to statin exposure is incorrectly assigned to the exposed group.

This second presentation appears to be common in the existing literature on the relationship of statins and dementia. Several of the studies included in the systematic review performed as part of this thesis were identified as being at risk of immortal time bias following formal risk of bias assessment using the ROBINS-I tool (see Section 4.3.4).

Following a recommended approach to address the second form of immortal time bias, I employed a time-varying treatment indicator to correctly allocate time-at-risk to the exposed and unexposed groups.[296] Under this approach, all patients are followed from a common index date, defined as earliest of:

- date of raised cholesterol test results;
- date of hypercholesterolemia diagnosis; or
- date of LRA prescription.

Patients start in the unexposed group and contribute time-at-risk until they are prescribed a lipid-regulating agent, at which point they move into the exposed group. Note, patients for whom prescription of a lipid-regulating agent was the index event only contribute time to the exposed group (i.e., they enter the cohort and move into the exposed group on the same day).

5.2.10 Time axis

As part of a Cox proportional hazard model, there is the option to use either absolute time in cohort or participants' age as the time scale of interest.[297–299] A model using age as the time axis inherently accounts, or adjusts, for participants age as a potential confounder of the exposure-outcome relationship. As such, the analyses presented all used age as the time axis.

5.2.11 Sensitivity analyses

The primary analysis examined the effect of a lipid-regulating agent on dementia risk, stratified by outcome and drug class. To assess the robustness of the results, a number of sensitivity analyses were performed. These are described in the following sections.

Complete case vs imputed data

Using multiple imputation to handle missing data is an alternative to a "complete case" approach,[300] where participants missing any covariate are dropped from the dataset. As a recommended sensitivity analysis,[301] I performed and compared the results of both methods, to investigate the impact of multiple imputation on the results.

Control outcomes

In addition to the primary outcomes of interest (described in Section 5.2.5), I extracted data on three additional control outcomes. The inclusion of control outcomes in observational analyses are a useful technique to assess the strength of uncontrolled confounding,[302] and these outcomes are usually classed as either "negative" or "positive" outcomes.

Negative outcomes are defined as those without a likely causal path between the exposure and outcome (see Figure 5.3 for a directed acyclic graph, or DAG, describing an ideal negative outcome). Conversely, positive control outcomes are those with a known causal association with the exposure of interest, ideally sourced from large well conducted randomised controlled trials. Positive control outcomes are also useful in observational epidemiology because if the analysis can reproduce a known result for the control outcome, confidence in the result for the outcome of interest is increased. Due to the wealth of data available on statins as a lipid-regulating agent, I chose three control outcomes in reference to this drug class: back pain (negative control), ischemic heart disease (positive protective control), and Type 2 diabetes (positive harmful control).

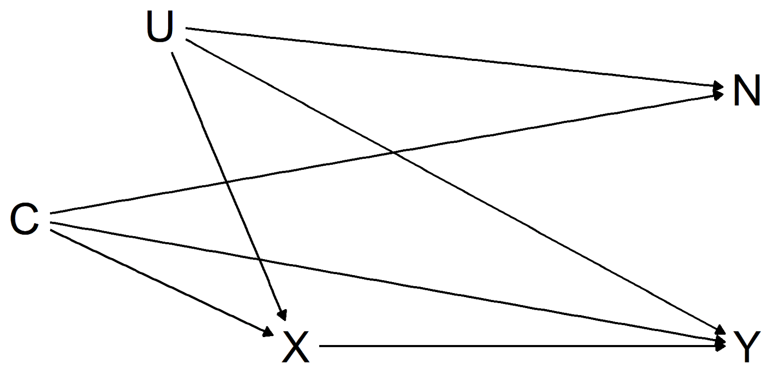

Figure 5.3: Causal diagram for an ideal negative outcome - The directed acyclic graph shows the relationship between the exposure X, outcome Y, confounders (measured C and unmeasured U) and an ideal negative outcome N. Note the absence of any arrow between X and N. In this scenario, any association observed between X and N is due to the presence of uncontrolled confounders U (assuming C has been adjusted for).

Despite observational analyses suggesting a link between statins and muscular pain (as opposed to more serious complications such as myopathy),[303] an effect was not observed in either systematic reviews of adverse events of statin use[38] or N-of-1 trials explicitly exploring the association of statin use with muscle pain.[304] Based on this evidence, I used muscular backpain as a negative control outcome in this analysis. Under this approach, if statin use is found to be associated with muscular backpain in this analysis, this suggests the presence of residual confounding and reduces my confidence in the results for the dementia outcomes.

Similarly, incident ischemic heart disease and Type 2 diabetes were included as protective and harmful positive control outcome, respectively. The protective effect of lipid-lowering via statins on the risk of ischemic heart disease is well-established,[38] while there is growing evidence for an increased risk of Type 2 diabetes with statin use.[38,305,306] Similar to the negative outcome, if the analysis strategy can reproduce these known associations, this will provide evidence that potential confounders have been sufficiently adjusted for.

Impact of additional covariates

To observe the effect of adjusting for additional covariates, I ran two additional models unadjusted except for: (a) age; and (b) age and gender. The results of these models were then compared the results with the fully adjusted model.

Sensitivity cohorts

Two sensitivity cohorts were also created. The first stratified by year of entry into the cohort in an attempt to assess for time period effects. The second removed participants who may have been pregnant (coded as under 55) to assess the robustness of the estimates, as statins are contraindicated in pregnancy.[307]

Statin properties

As detailed in the introduction, the properties of statins may be important due to the ability of lipophilic statins to cross the blood brain barrier (see Section 1.3.2).[41] As such, I expected that any effects of statins on dementia outcomes would be stronger in the lipophilic versus the hydrophilic statin subgroup. To investigate this, I further stratified the statin exposure group into lipophilic (Atorvastatin, Lovastatin, Simvastatin, Cerivastatin) and hydrophilic (Pravastatin, Rosuvastatin, Fluvastatin) statins.

Impact of using different code lists for defining dementia outcomes

To explore the impact of the code lists used to define dementia outcomes, I created alternative Alzheimer's disease and non-Alzheimer's dementia outcomes using code lists from a published study by Smeeth *et al.*[214] The intended purpose of this analysis was to assess the robustness of my results to the choice of code list.

This published analysis used a propensity matching approach to estimate the association of statins with a range of outcomes in The Health Improvement Network database, an alternative source of English electronic health records which has substantial overlap with the CPRD.[308] The code lists used in this analysis were obtained through correspondence with the authors of that study, and are available for inspection (see Section 5.4.4).

5.3 Results

5.3.1 Patient characteristics

Of the 3,179,733 participants included in the extract, 1,684,564 met the inclusion criteria (Figure 5.4), with a total follow-up of 10,835,685 patient years at risk.

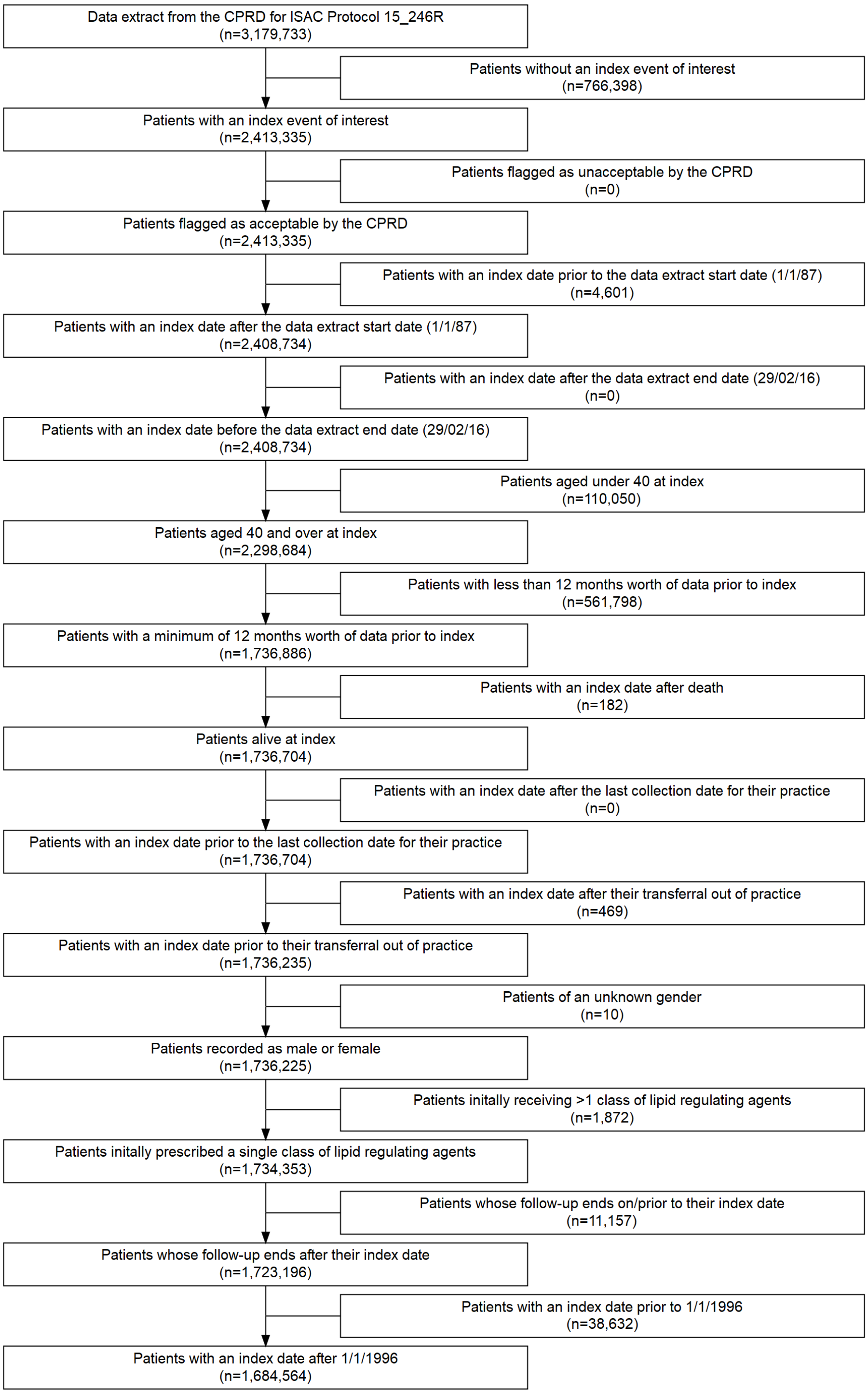

Figure 5.4: Attrition of CPRD participants - Patients were excluded from the study cohort for several reasons, and the number of patients excluded as each eligibility criterion was applied is shown above. Note that the largest cause of attrition was the absence of an index event of interest.

The median participant age at index was 57 years (inter-quartile range (IQR): 48-67 years) and participants were followed up for a median of 5.9 years (IQR: 2.7-9.7 years). During follow-up, an all-cause dementia diagnosis was recorded for 41,830 patients (12,647 probable AD, 9,954 possible AD, 8,466 vascular dementia, 10,763 other dementias).

The number of events, time-at-risk and crude rates for each drug class, tabulated by dementia outcome, are shown in Table 5.3. A substantial majority (98.1%) of participants prescribed a lipid-regulating agent were prescribed a statin. I excluded the "Ezetimibe and statins" (N =127) and "Nicotinic acid groups" (N = 165) classes from subsequent class-based subgroup analyses based on the extremely small number of participants in these groups. Note that the "Ezetimibe and statins" treatment group represent those prescribed a single treatment containing both ezetimibe and statins, rather than those where the two treatments were prescribed concurrently.

Table 5.3: Crude rates, stratified by outcome and drug class of interest - The number of events, years at risk and crude rates per 100,000 participant-years-at-risk stratified by dementia outcome and drug class of interest are presented below.

	Any dementia			Possible AD			Probable AD			Vascular dementia			Other dementia		
Exposure Group	**Events**	**PYAR**	**Rate** *	**Events**	**PYAR**	**Rate** *	**Events**	**PYAR**	**Rate** *	**Events**	**PYAR**	**Rate** *	**Events**	**PYAR**	**Rate** *
No LRA (unexposed)	18,608	5,872,717	317	6,368	5,818,047	109	4,790	5,808,285	82	2,637	5,800,964	45	4,813	5,811,594	83
By drug class															
Statins	22,920	4,871,568	470	6,190	4,758,526	130	5,086	4,747,237	107	5,773	4,753,437	121	5,871	4,755,258	123
Omega-3 FAGs	19	8,034	236	4	7,927	50	4	7,925	50	7	7,950	88	4	7,938	50
Fibrates	141	38,003	371	49	37,102	132	35	36,983	95	21	36,835	57	36	37,001	97
Ezetimibe	32	6,604	485	8	6,429	124	5	6,393	78	7	6,425	109	12	6,444	186
BAS	106	36,370	291	28	35,808	78	33	35,808	92	19	35,726	53	26	35,768	73
Ezetimibe + Statins †	0	986	-	0	986	-	0	986	-	0	986	-	0	986	-
NAG	4	1,403	-	0	1,379	-	1	1,382	-	2	1,391	-	1	1,389	-
Total	41,830	10,835,686	386	12,647	10,666,205	119	9,954	10,644,999	94	8,466	10,643,714	80	10,763	10,656,378	101

* Crude rate per 100,000 participant-years-at-risk

† One treatment containing both drugs, rather than the two classes being prescribed concurrently

Abbreviations: AD - Alzheimer's disease; BAS - Bile acid sequestrants; LRA - Lipid regulating agent; NAG - Nicotinic acid groups; Omega-3 FGs - Omega-3 Fatty acid groups; PYAR - Participant-years-at-risk.

Table 5.4: Patient characteristics by drug class - Summary statistics are presented as "% (N)" unless otherwise specified in the variable name.

	Whole Sample	None	Statins	Bile acid sequestrants	Ezetimibe	Fibrates	Omega-3 Fatty Acid Groups
Sample size (N)	1,684,564	1,087,704	585,528	5,396	763	3,889	992
Year of cohort entry (median)	2006	2007	2004	2005	2004	2001	2005
Female	53.0% (893174)	56.2% (610950)	47.1% (276043)	66.4% (3585)	54.5% (416)	38.6% (1500)	52.6% (522)
Age at cohort entry (median)	57	54	62	57	60	58	56
CAD	0.4% (7133)	0.1% (589)	1.1% (6465)	0.1% (6)	0.9% (7)	1.4% (53)	1.3% (13)
CBS	0.3% (5699)	0.1% (682)	0.8% (4926)	0.1% (4)	0.4% (3)	2.0% (78)	0.6% (6)
CVD	2.1% (34899)	1.1% (11619)	3.9% (22977)	1.6% (86)	2.6% (20)	4.4% (170)	1.7% (17)
Charlson (ever > 0)	30.6% (516135)	25.1% (272642)	40.7% (238403)	42.5% (2292)	41.7% (318)	50.8% (1976)	40.4% (401)
IMD-2010 (median)	9	8	9	8	9	10	10
Consultation rate (mean/SD)	5.4 (5.4)	5.0 (5.0)	6.2 (6.1)	8.6 (7.4)	7.4 (6.6)	7.1 (6.2)	8.0 (8.0)
Alcohol (ever)	85.9% (1447151)	86.6% (941648)	84.7% (496110)	82.8% (4468)	84.0% (641)	82.9% (3223)	82.0% (813)
Smoking (ever)	51.1% (861355)	47.1% (511826)	58.6% (343074)	55.2% (2978)	57.5% (439)	60.2% (2341)	53.7% (533)
BMI (mean/SD)	27.0 (5.3)	26.7 (5.2)	27.7 (5.3)	26.8 (5.8)	28.1 (5.7)	29.0 (5.2)	26.9 (5.5)
PAD	0.7% (12613)	0.4% (4039)	1.4% (8424)	0.9% (47)	0.9% (7)	1.9% (75)	1.0% (10)
Hypertension	16.0% (269804)	11.5% (124604)	24.4% (143101)	12.8% (692)	23.9% (182)	25.8% (1002)	15.7% (156)
Total cholesterol (mean/SD)	5.7 (10.1)	5.5 (6.4)	6.2 (15.3)	5.3 (1.3)	7.1 (26.5)	6.4 (5.6)	5.6 (1.6)
LDL cholesterol (mean/SD)	3.6 (4.9)	3.4 (5.3)	4.0 (3.7)	3.1 (1.0)	3.9 (1.1)	3.3 (1.8)	3.2 (1.0)
CKD	0.1% (1295)	0.1% (740)	0.1% (545)	0.1% (6)	0.1% (1)	0.0% (0)	0.3% (3)
Type 1 Diabetes	0.2% (4037)	0.1% (785)	0.5% (3196)	0.3% (14)	1.0% (8)	0.8% (31)	0.1% (1)
Type 2 Diabetes	2.9% (48557)	1.1% (11797)	6.1% (35941)	2.3% (123)	5.4% (41)	15.8% (614)	2.8% (28)

Note: The 'Nicotinic acid groups' (n=165) and 'Ezetimibe and Statins' (n=127) subgroups are not shown, but are included in the whole sample column
Abbreviations: BMI - Body mass index; CAD - Coronary arterial disease; CBS - Coronary bypass surgery; CKD - Chronic kidney disease; CVD - Cardiovascular disease; IMD - Index of multiple deprivation; LRA - Lipid regulating agent; PAD - Peripheral arterial disease; SD - Standard deviation.

The distribution of baseline characteristics across the remaining seven drug classes can be seen in Table 5.4. Note due to the experimental design, the median year of entry is expected to be later for those not prescribed an LRA. This is because the unexposed group is more likely to include those who entered into the cohort towards the end of study window, and so had less follow-up time in which to be prescribed an LRA.

The stopping, addition and switching of drug classes was common across all drug classes (Table 5.5).

Table 5.5: Summary of treatment change - The number of participants who stopped, switched or added treatments was calculated, stratified by initial LRA type.

	Whole Sample	**Statins**	**Bile acid sequestrants**	**Ezetimibe**	**Ezetimibe & Statins**	**Fibrates**	**Nicotinic acid groups**	**Omega-3 Fatty Acid Groups**
Stopped	6.9% (115899)	19.1% (111798)	56.1% (3028)	19.7% (150)	12.6% (16)	12.3% (478)	44.8% (74)	35.8% (355)
Added	1.6% (27441)	4.4% (25990)	3.6% (192)	19.0% (145)	3.9% (5)	21.6% (841)	3.6% (6)	26.4% (262)
Switched	0.9% (14935)	2.0% (11996)	11.3% (612)	34.6% (264)	64.6% (82)	44.0% (1713)	45.5% (75)	19.5% (193)

Definitions: Stopped - last prescription of the primary drug class followed by at least six months of observation with no further prescriptions; Added - second drug class prescribed before the last prescription of the initial class; Switched - second drug class being prescribed after the last prescription of the initial class.

5.3.2 Missing data

Full covariate information was available for 450,234 participants (26.7%). Six key variables had some missing data: IMD 2010 score was missing for 625,788 participants (37.1%) because it is only recorded for English practices; alcohol status was missing for 269,526 participants (16%); smoking status was missing for 84,424 participants (5%); BMI, or a calculated BMI from height and weight measurements, was missing for 266,672 participants (15.8%); baseline total cholesterol was missing for 119,675 participants (7.1%); and baseline LDL cholesterol was missing for 787,289 participants (46.7%).

5.3.3 Primary analysis

The results of the primary analysis using the fully adjusted Cox proportional hazards model with participant age as the time scale are presented for each drug/outcome combination in Figure 5.5.

For each outcome, the overall "Any drug class" estimate was driven by the statin subgroup, based on its large size relative to the other drug classes.

Analysis	Participants	Events	Hazard ratio
Any dementia			
Any drug class	1,684,564	41,830	1.17 (1.14 to 1.19)
Statins	1,673,232	41,528	1.16 (1.14 to 1.19)
Omega-3 Fatty Acid Groups	1,088,696	18,627	0.75 (0.47 to 1.21)
Fibrates	1,091,593	18,749	1.28 (1.08 to 1.52)
Ezetimibe	1,088,467	18,640	1.37 (0.94 to 1.98)
Bile acid sequestrants	1,093,100	18,714	0.95 (0.77 to 1.16)
Probable AD			
Any drug class	1,655,381	12,647	0.98 (0.94 to 1.01)
Statins	1,644,262	12,558	0.98 (0.94 to 1.01)
Omega-3 Fatty Acid Groups	1,076,441	6,372	0.54 (0.20 to 1.44)
Fibrates	1,079,261	6,417	1.52 (1.13 to 2.03)
Ezetimibe	1,076,203	6,376	1.16 (0.58 to 2.33)
Bile acid sequestrants	1,080,782	6,396	0.78 (0.53 to 1.15)
Possible AD			
Any drug class	1,652,688	9,954	0.97 (0.93 to 1.01)
Statins	1,641,580	9,876	0.97 (0.93 to 1.01)
Omega-3 Fatty Acid Groups	1,074,863	4,794	0.50 (0.16 to 1.54)
Fibrates	1,077,669	4,825	1.11 (0.79 to 1.56)
Ezetimibe	1,074,622	4,795	0.58 (0.19 to 1.81)
Bile acid sequestrants	1,079,209	4,823	0.98 (0.67 to 1.43)
Vascular dementia			
Any drug class	1,651,200	8,466	1.81 (1.73 to 1.89)
Statins	1,640,114	8,410	1.81 (1.73 to 1.90)
Omega-3 Fatty Acid Groups	1,072,713	2,644	1.83 (0.82 to 4.09)
Fibrates	1,075,502	2,658	1.29 (0.83 to 2.02)
Ezetimibe	1,072,471	2,644	2.33 (1.11 to 4.89)
Bile acid sequestrants	1,077,042	2,656	1.24 (0.78 to 1.97)
Other dementia			
Any drug class	1,653,497	10,763	1.19 (1.15 to 1.24)
Statins	1,642,388	10,684	1.19 (1.15 to 1.24)
Omega-3 Fatty Acid Groups	1,074,886	4,817	0.66 (0.25 to 1.76)
Fibrates	1,077,693	4,849	1.34 (0.96 to 1.87)
Ezetimibe	1,074,652	4,825	1.88 (1.01 to 3.50)
Bile acid sequestrants	1,079,225	4,839	0.93 (0.62 to 1.39)

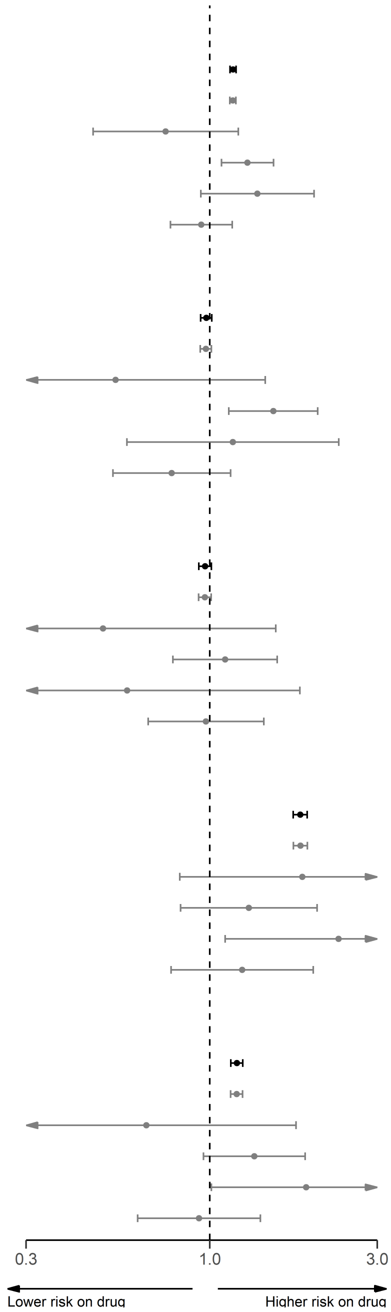

Figure 5.5: Results from primary analyses of CPRD data - Effect estimates obtained from the fully-adjusted time-varying model with participant age as the time scale, stratified by lipid-regulating agent and dementia outcome.

Alzheimer's disease

My results show little evidence was found for an effect of lipid-regulating agents on probable (HR:0.98, 95%CI:0.94-1.01) and possible (HR:0.97, 95%CI:0.93-1.01) Alzheimer's disease when compared to no treatment, with the sole exception of fibrates on probable Alzheimer's disease (HR:1.52, 95%CI:1.13-2.03).

Non-Alzheimer's disease dementias

In contrast to the findings for Alzheimer's disease outcomes, an association between lipid-regulating agents and an increased risk of a subsequent diagnosis of vascular dementia (HR:1.81, 95%CI:1.73-1.89) or other dementias (HR:1.19, 95%CI:1.15-1.24) was observed. Again this effect was driven mainly by the statin subgroup, but there was some evidence that ezetimibe was associated with an increased risk of vascular (HR:2.33, 95%CI:1.11-4.89) and other (HR:1.88, 95%CI:1.01-3.5) dementia.

All-cause dementia

For the composite all-cause dementia outcome, I found treatment with a lipid-regulating agent was associated with a slightly increased risk (HR:1.17, 95%CI:1.14-1.19), which lies between the associations for the Alzheimer and non-Alzheimer dementia outcomes as would be expected. There was also some evidence that fibrates were associated with increased risk of all-cause dementia (HR:1.28, 95%CI:1.08-1.52).

5.3.4 Sensitivity analyses

The results of the sensitivity analyses are described in the following sections.

Complete case versus imputed data

In almost all cases, the use of imputed data resulted in a marginal attenuation of the effects observed when using a complete case analysis. It should be noted that due to the large amount of missing data (e.g., 787,289 participants (46.7%) were missing a baseline LDL cholesterol measure), the number of participants included in the complete case analysis was substantially smaller than that included when using imputed data. In this case, though the overall position of the effect estimates does not change substantially when using the imputed dataset, there is a noticeable gain in power.[293]

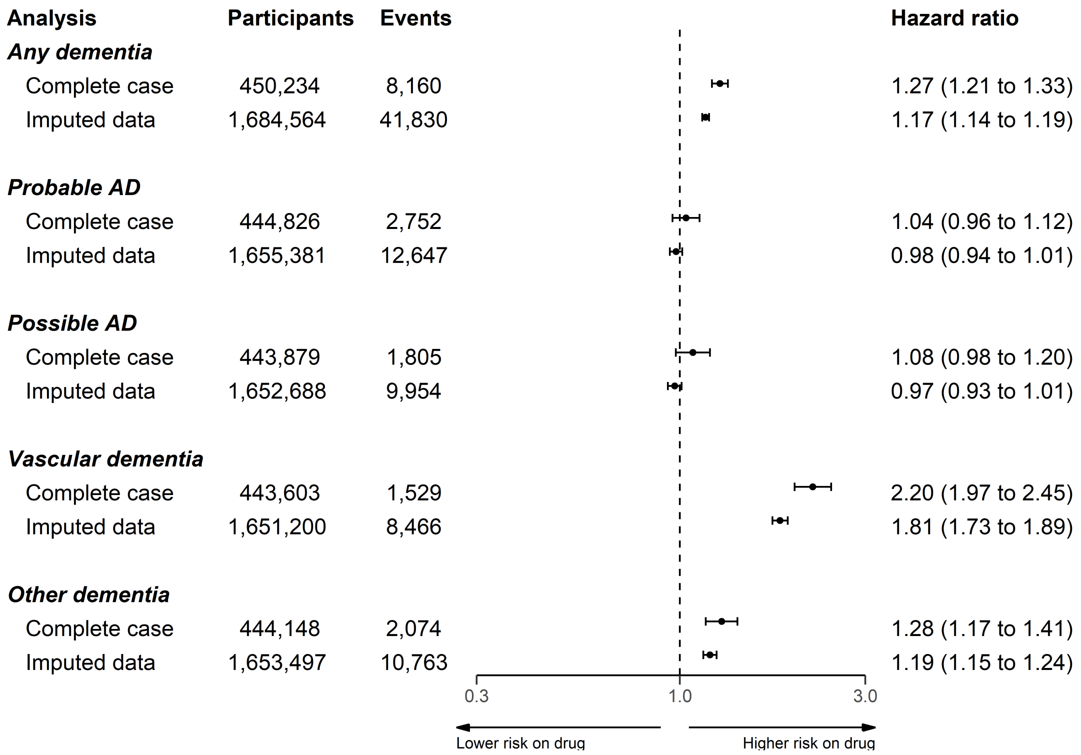

Figure 5.6: Sensitivity analysis: complete case vs. imputed data - Comparison of analyses using the complete case versus imputed cohorts, indicating broad agreement between the two approaches. Note that the analyses using imputed data gave more precise estimates due to the low proportion of patients with complete covariate data.

Control outcomes

The fully adjusted model was also used to estimate the effect of treatment with a statin on three control outcomes: back pain (negative), ischemic heart disease (positive protective) and Type 2 diabetes (positive harmful). The results of this analysis are presented in Figure 5.7.

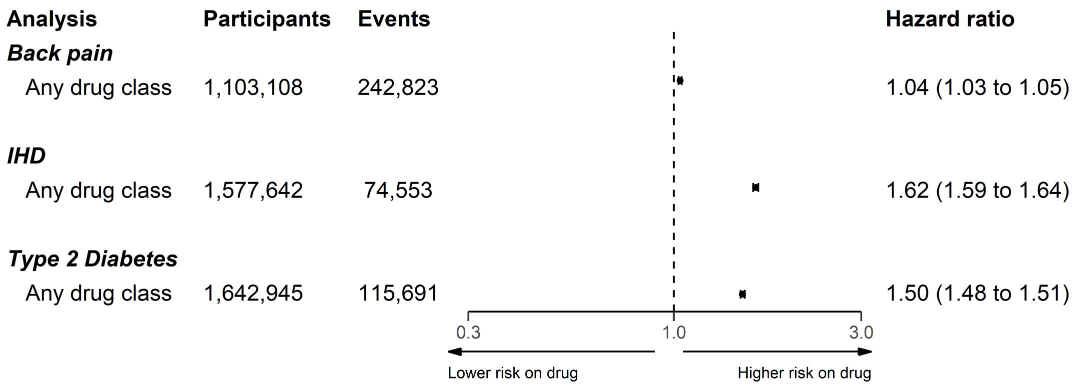

Figure 5.7: Sensitivity analysis: control outcomes - Effect estimates obtained from the fully-adjusted time-varying model with participant age as the time scale for three control outcomes: backpain (negative), ischemic heart disease (positive protective), and diabetes (positive harmful).

For the negative control, there was some evidence that treatment with a statin was associated with an increased risk of back pain (HR: 1.04, 95%CI: 1.03-1.05), suggesting there may be some residual confounding. However, statin prescription was also associated with a substantially increased risk of ischemic heart disease (HR: 1.62, 95%CI: 1.59-1.64) and Type 2 diabetes (HR: 1.50, 95%CI: 1.48-1.51).

Impact of additional covariates

The results of three models adjusted for age only, age and sex, and full covariates respectively, are presented in Figure 5.8. These models were used to estimate the impact of adjustment for additional covariates. Note that obtaining a completely unadjusted model is not possible because age was used in the Cox model as the time scale.

Adjustment for additional covariates beyond age and sex had a limited impact on the observed effect estimates, with the exception of the probable AD outcome. In this case, adjustment for the full set of covariates attenuated the protective effect observed when adjusting only for age and sex to the null.

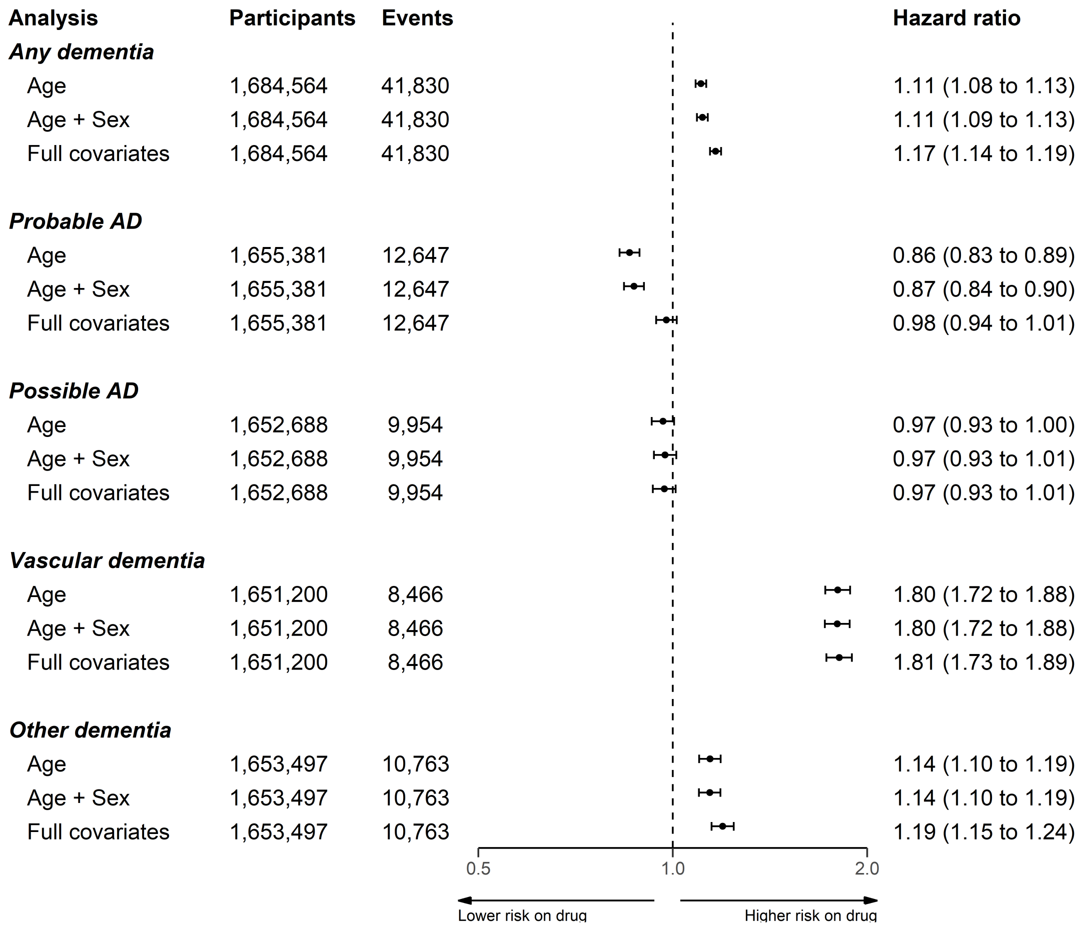

Figure 5.8: Sensitivity analysis: covariate comparison - The results obtained using three different sets of covariates (age only, age + sex, all covariates) are shown for each dementia outcome. Note that the x-axis cutoffs (0.5,2) are different compared to other plots (0.3,3) to enable greater comparison between the different models.

Sensitivity cohorts: Entry year

When stratifying based on year of entry to the cohort, I observed no variation in risk by time period in any subgroup except for probable Alzheimer's disease (Figure 5.9).

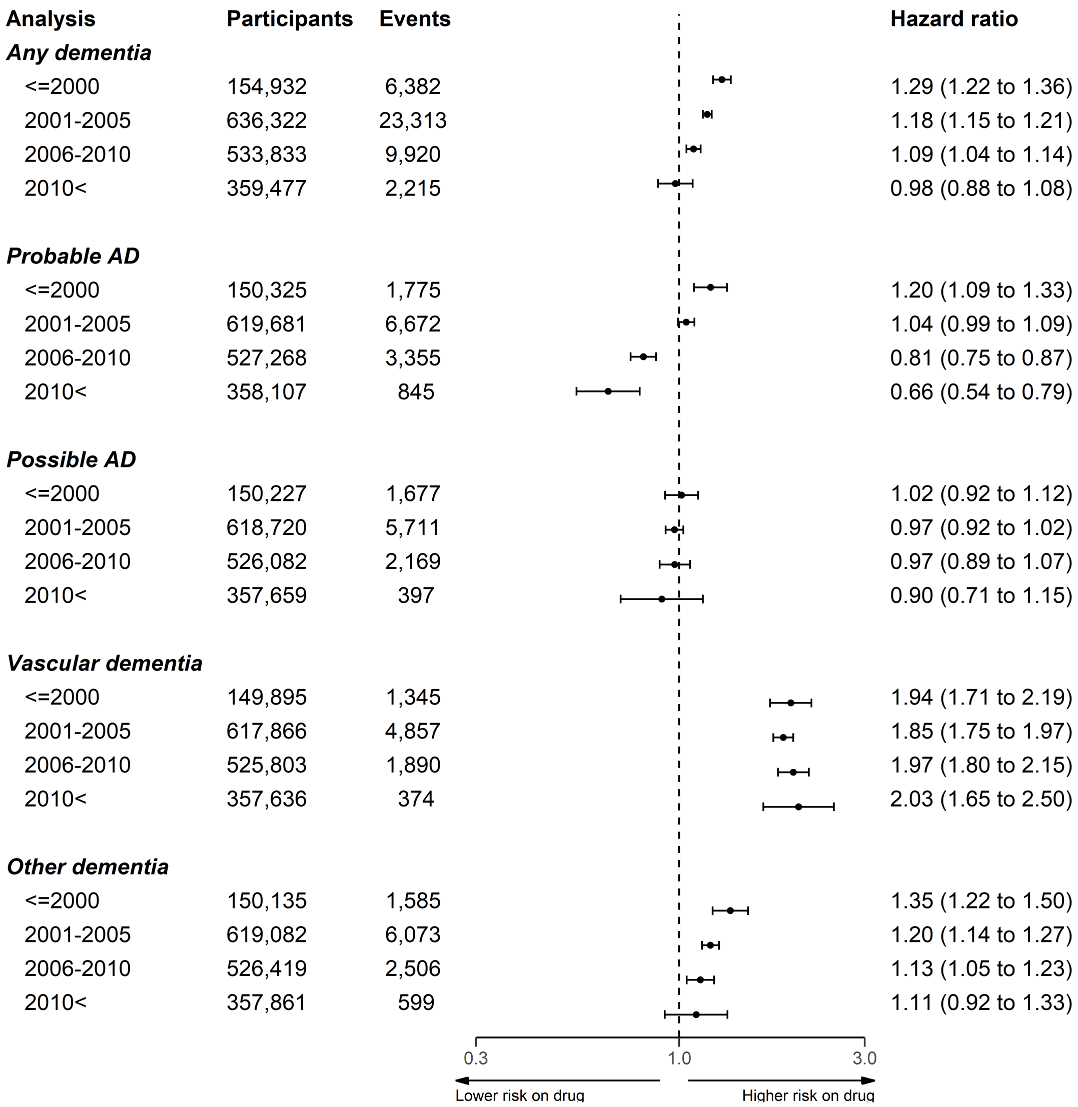

Figure 5.9: Sensitivity analysis: year of entry - Effect estimates, obtained from the fully-adjusted time-varying model with participant age as the time scale, for the association of the any LRA class with the probable AD outcome, stratified by grouped year of cohort entry.

On the assumption that this variation could be caused by changes in the frequency of probable AD diagnoses in the cohort over time, I performed a *post-hoc* investigation of the frequency of each dementia outcome by year of entry (Table 5.6). While the frequency of outcomes declines in more recent strata, likely due to the limited follow-up inherent to these groups, this decline in frequency is relatively constant across the dementia subtypes.

Table 5.6: Dementia diagnoses by year of entry - As part of a *post-hoc* investigation of the time period effect observed in the probable AD outcome, the frequency of dementia diagnoses by grouped year of cohort entry was calculated.

Year of cohort entry	No dementia	Probable AD	Possible AD	Vascular dementia	Other dementia	Total
<=2000	148550 (95.9%)	1775 (1.1%)	1677 (1.1%)	1345 (0.9%)	1585 (1.0%)	154932
2001-2005	613009 (96.3%)	6672 (1.0%)	5711 (0.9%)	4857 (0.8%)	6073 (1.0%)	636322
2006-2010	523913 (98.1%)	3355 (0.6%)	2169 (0.4%)	1890 (0.4%)	2506 (0.5%)	533833
2010<	357262 (99.4%)	845 (0.2%)	397 (0.1%)	374 (0.1%)	599 (0.2%)	359477
Total	1642734 (97.5%)	12647 (0.8%)	9954 (0.6%)	8466 (0.5%)	10763 (0.6%)	1684564

Sensitivity cohorts: Pregnancy

In the second sensitivity cohort, removing patients who may have been pregnant (coded as aged 55 and under at index) from the analysis had minimal effect on the effect estimates (Figure 5.10).

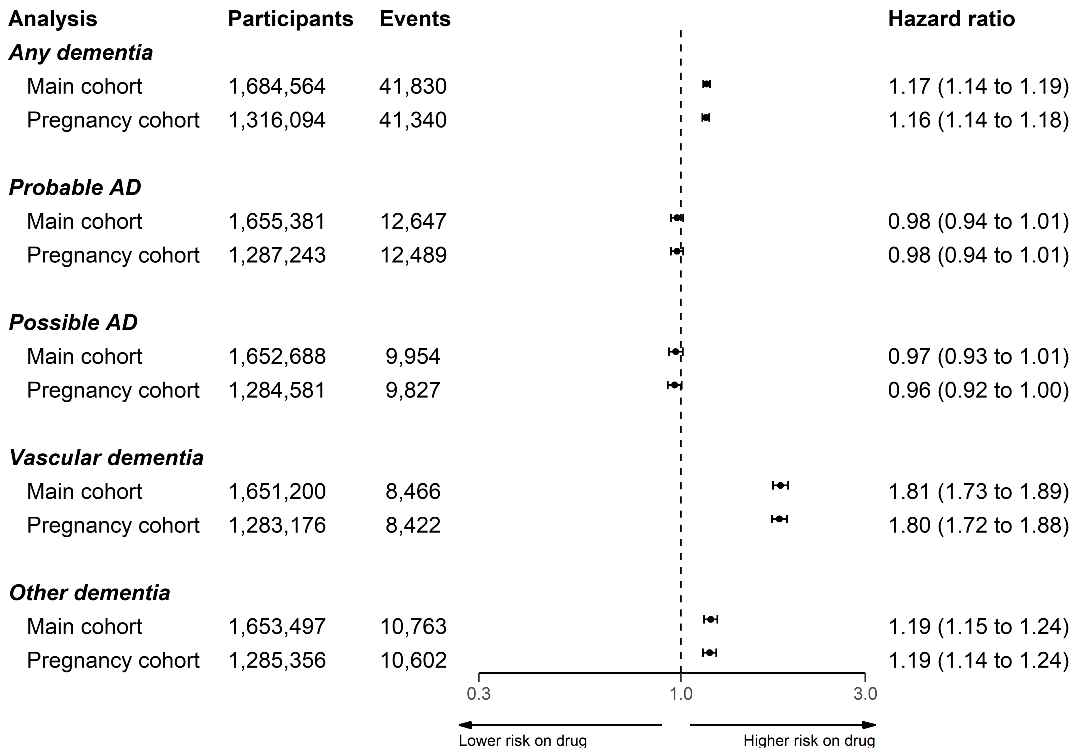

Figure 5.10: Sensitivity analysis: pregnancy cohort - Comparison of analysis using main cohort and a cohort with potentially pregnant participants (coded as any participant under 55 years of age) removed.

Statin properties

In the cohort, statins with lipophilic properties were much more frequently prescribed than hydrophilic statins (Table 5.7). Additionally, there is evidence for an increasing tendency to favour hydrophilic statins in recent years with the proportion of lipophilic statins prescribed falling from 18.2% in 1996-2000 to <1% in 2011-2016.

Table 5.7: Summary of statin properties - Number of patients prescribed lipophilicity vs hydrophilicity statins, by grouped year of prescription.

Prescription Year Group	Hydrophilic	Lipophilic	Total
<=2000	7037 (18.2%)	31531 (81.8%)	38568
2001-2005	21427 (10.3%)	187018 (89.7%)	208445
2006-2010	3566 (1.6%)	217726 (98.4%)	221292
2010<	1115 (0.9%)	119035 (99.1%)	120150

When stratifying by statin properties, hydrophilic statins were less harmful in the any, vascular and other dementias outcomes compared to lipophilic statins (Figure 5.11). Additionally, in the AD outcomes, hydrophilic statins were associated with a small reduction in risk, compared to the weak evidence for an effect for lipophilic statins.

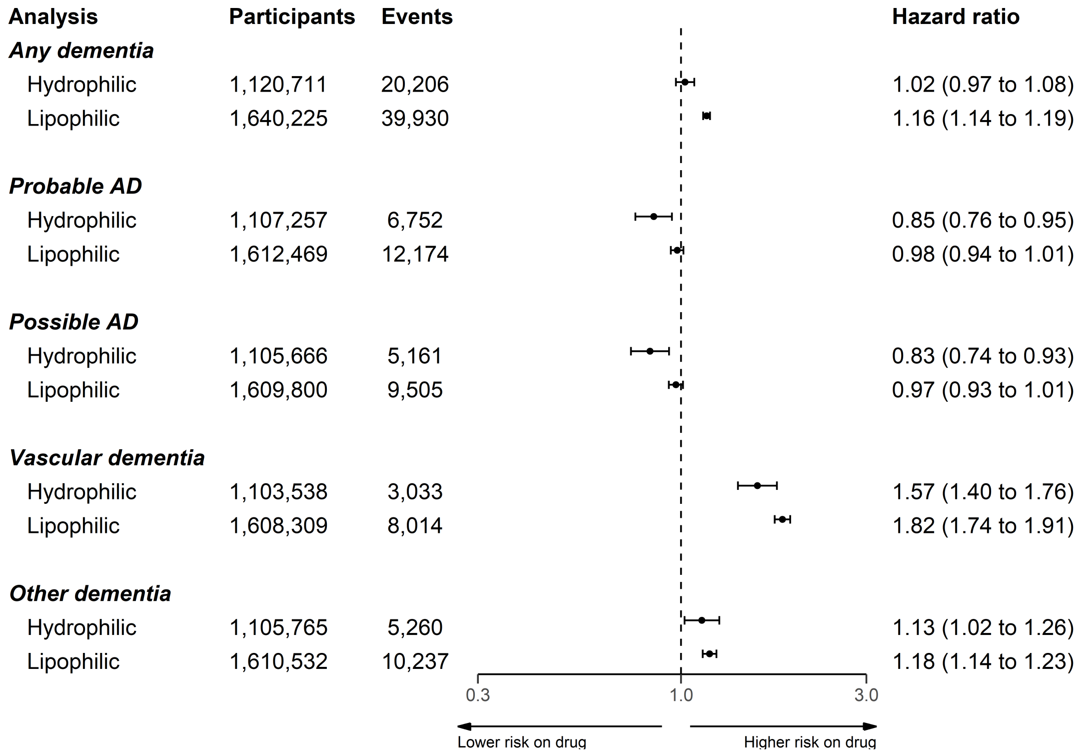

Figure 5.11: Sensitivity analysis: statin properties - Effect estimates obtained from the fully-adjusted time-varying model with participant age as the time scale, stratified by statin properties (hydrophilic vs lipophilic).

Impact of dementia code lists

When using the Smeeth *et al.* code lists to define dementia outcomes, hazard ratios of 1.19 (95%CI: 1.07-1.32) and 1.33 (95%CI: 1.26-1.42) were obtained for the Alzheimer's disease and non-Alzheimer's ("other") dementia outcomes, respectively. While direct mapping to the outcomes used in this analysis was not possible, the most comparable outcomes are "probable Alzheimer's disease" (HR:0.98, 95%CI:0.94-1.01) and "other dementia" (HR:1.19, 95%CI:1.15-1.24).

5.4 Discussion

5.4.1 Summary of findings

Lipid-regulating agents showed little evidence of an association with probable and possible Alzheimer's disease when compared to no treatment but were associated with increased risk of the all-cause dementia, vascular dementia and other dementias diagnoses. The estimate observed in each case was driven by the effects observed in the statin subgroup because a substantial majority of participants prescribed an LRA were prescribed a statin. For the other drug classes, no association was found with any outcome, with two exceptions. Ezetimibe was associated with increased risk of vascular and other dementias, while fibrates were associated with increased risk of all-cause dementia and probable Alzheimer's disease.

The effect estimates were robust to the exclusion of potentially pregnant participants, and for all outcomes except probable AD, no variation across grouped year of entry was observed. When looking at the statin subgroup alone, statin properties appeared to have a modifying effect, with hydrophilic statins being less harmful in the any, vascular and other dementias outcomes compared to lipophilic statins.

5.4.2 Interpretation of results

This section will expand on a potential explanation for the observed results detailed above. However, as the comparison of evidence across different sources is the aim of the triangulation exercise presented in later chapters, a detailed comparison with other published literature will not be provided here, except where needed to illustrate a methodological point. For a detailed comparison of the results presented above with the existing evidence base identified by the systematic review, see Chapter 7.

Confounding by indication

A likely explanation for the observed increased risk of vascular and other dementias with lipid-regulating agent use is residual "confounding by indication", which represents an important limitation of this analysis. While the term has been used to describe different sources of bias in epidemiological analyses,[309] it is used here to described the role of risk factors that both prompt treatment and increase the risk of the outcome, thus causing a distorted positive association between the treatment and outcome (see Figure 5.12). In causal inference nomenclature, statins and dementia are said to be *d*-connected, as there is an open "backdoor" path between them via the uncontrolled confounders.[310] In the context of this analysis, this means a confounding variable (or, more likely, variables) both prompts prescription of statins and also represents a risk factor for the development of the vascular dementia. A similar confounding structure likely exists for ezetimibe, another hypercholesterolemia treatment, providing an explanation for the association of vascular/other dementia but not Alzheimer's disease with this drug.

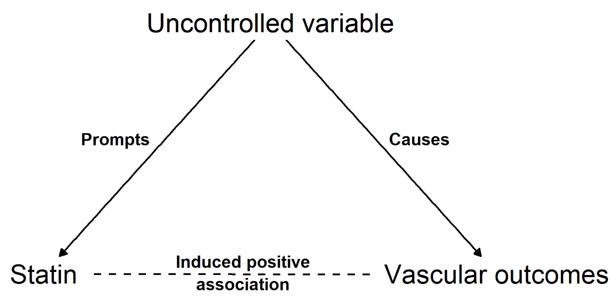

Figure 5.12: Confounding by indication causal diagram - Directed acyclic graph illustrating how confounding by indication could induce a positive association between statins and vascular dementia.

Conditioning entry into the study on being either "at-risk" or already diagnosed with hypercholesterolemia was employed in a pre-emptive attempt to mitigate confounding by indication, but evidence from the control outcomes suggests this was unsuccessful. The slight harmful effect observed for the backpain outcome is substantially smaller than that observed for the ischemic heart disease outcome, indicating that the majority of the uncontrolled confounding is likely related to vascular factors. The slight effect observed for the negative control of backpain could be due to incomplete control for socioeconomic status, as deprivation data was provided in twentiles to preserve patient privacy.[311,312]

In line with this, an increasingly harmful effect is observed when moving from the probable and possible Alzheimer's disease outcomes to the other dementia outcome, and finally to the vascular dementia outcomes. This pattern suggests that the strength of the residual confounding by indication increases as the proportion of cases with a vascular component in an outcome definition increases. Given confounding related to vascular factors, this pattern is also expected based on the decision tree for assigning outcomes in the presence of greater than one dementia code. Under this system, the Alzheimer's disease outcomes require a "pure" condition and the presence of any vascular or other dementias codes excludes participants from this group (Figure 5.1).

A review of other available literature suggests that this observation (a harmful effect of lipid-regulating agents on vascular-related outcomes) is not unusual. Using a conventional epidemiological technique, a previous analysis also found an increased risk of coronary heart disease (analogous to the ischemic heart disease outcome used in this analysis) in those taking statins (HR: 1.31, 95%CI: 1.04-1.66).[313] In that study, controlling for confounding by indication through the use of a trial emulation analysis gave an estimate of 0.89 (95%CI: 0.73-1.09), a more comparable though less conclusive estimate to that observed in RCTs of statin use (0.73, 95%CI: 0.67-0.80).[314]

Given the absence of vascular dementia in the published literature, as highlighted in the previous chapter, the unexpected increase in vascular dementia risk with statin use is particularly interesting. If previous research encountered similar methodological issues to this analysis, it is possible their results did not make it into the evidence base via a publication bias mechanism where unexpected or assumedly incorrect results are less likely to be submitted or accepted for publication.

Statin properties

This analysis found that hydrophilic statins were less harmful in the any, vascular and other dementia outcomes compared to lipophilic statins, and were associated with a small reduction in the risk of the probable and possible AD outcomes. The increased precision of the estimates for lipophilic versus hydrophilic statins is expected, as the two most commonly prescribed statins are lipophilic (simvastatin and atorvastatin).[315]

A widely discussed concept in the literature surrounding statin use and cognitive outcomes is the fact that lipophilic statins are more likely to be able to cross the blood brain barrier, and so have a more potent protective effect by directly lowering brain cholesterol.[316] My findings that hydrophilic statins appear to be more protective/less harmful than their lipophilic counterparts runs counter to this assertion.

An initial interpretation of the different associations observed in the two groups was that the lipophilic statins may be more potent, and so are prescribed to patients with a higher underlying vascular load, leading to increased confounding by indication in this group. However, the statin with the strongest lipid lowering effect that is available via the NHS, rosuvastatin, is hydrophilic.

Impact of code lists

As part of a sensitivity analysis exploring the impact of outcome code-lists, I used definitions for Alzheimer's disease and other dementias obtained from a previously published paper (Smeeth *et al.*).[214] Using these lists in my analytical set-up, I found a harmful association of statin use with both outcomes.

This finding disagrees with the results of the original analysis, which found evidence for a protective effect of statin use on all-cause dementia (HR: 0.81, 95%CI: 0.69-0.96) and non-AD dementia (HR: 0.82, 95%CI: 0.69-0.97), but little evidence of an effect on AD (HR: 0.81, 95%CI: 0.49-1.35).

However, comparison of the results obtained using the two sets of code lists was deemed less useful following a detailed comparison of the codes used. While all of the codes used to define Alzheimer's in the Smeeth *et al.* paper are included in the probable Alzheimer's code-list (see Figure 5.13), I included several additional codes used to define this outcome (including, for example, "Eu00013: [X]AD disease type 2"). Additionally, several of the codes used to define "Possible Alzheimer's" in this analysis are included in the "Other dementia" code list used by Smeeth.

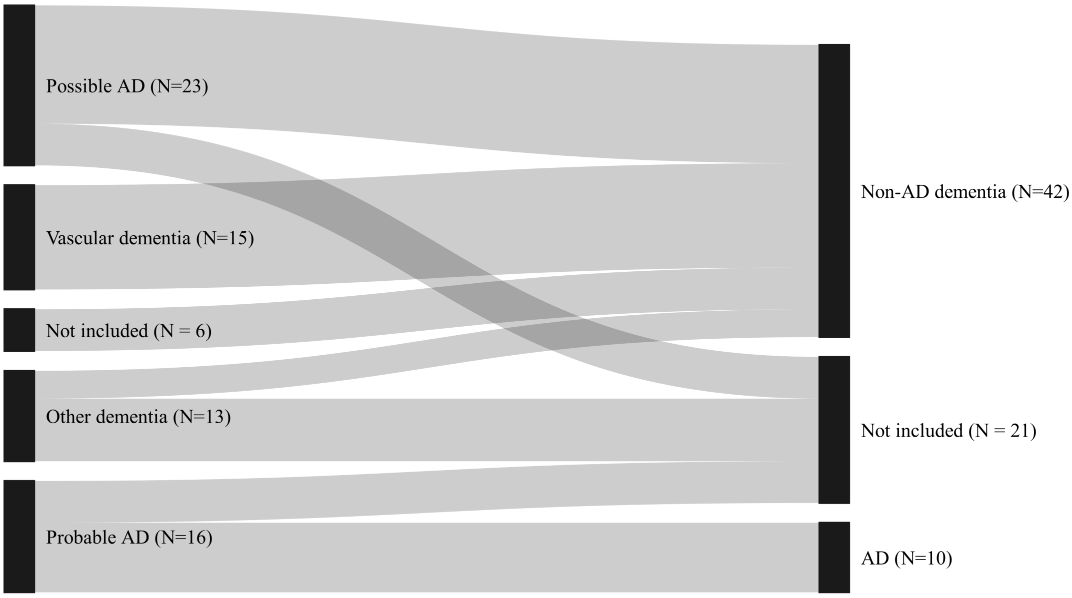

Figure 5.13: Comparison of code lists - Sankey diagram comparing the codes used in this analysis with those used in the Smeeth *et al* paper.[214] The outcomes and number of codes contributing to each are presented (the Smeeth *et al* outcomes are on the right-hand side of the figure). The joining lines showing the overlap between the categories in the two analyses.

This analysis serves to illustrative the importance of the code lists chosen to define the outcomes of interest in EHR, particularly if they are used to define competing outcomes (e.g., AD vs non-AD dementia). The different codes used by Smeeth *et al.*, in addition to an analytical approach that adjusted for covariates defined after the index date, may go some way to explaining why my analysis obtained different results despite the substantial overlap in the data sources used.

5.4.3 Strengths and limitations

The primary strength of this analysis is the relative size of the CPRD. Having reviewed the existing literature, as identified by the systematic review element of this thesis, this analysis of 1,684,564 participants is one of the largest available studies of this research question. Additionally, this analysis followed LRA users and non-users from a common index date, using a time-updating treatment indicator to correctly assign time-at-risk to the exposed and unexposed groups. This approach has been less commonly used in the literature and allows for the mitigation of potential immortal time bias. It is also one of few studies that provide evidence on the association of LRA use and vascular and other dementias. Finally, it used negative and positive controls to assess the potential for residual confounding.

However, the findings of this analysis are subject to several limitations in addition to the confounding by indication discussed above. There is a strong possibility of differential misclassification of dementia-related conditions based on the exposure.[317] As an illustrative example, those with memory complaints may be more likely to be classified as vascular dementia than Alzheimer's disease if their medical records contain prescriptions for lipid-regulating agents. Further, there is potential for general non-differential misclassification of the outcome due to the varying positive predictive value of electronic health record code lists to identify dementia cases.[318,319]

Misclassification of outcomes is not the only issue introduced by the use of EHR codes to define outcomes. Comparing and contrasting between different studies is particularly difficult because of the impact that the use of different code lists can have on the analysis. This problem is illustrated by the discrepancy between the results when using the code lists defined for this study and those used by Smeeth *et al.* This presents a particular challenge in comparing research across different time-periods and coding systems.

A further limitation stems from the possibility of uncontrolled confounding due to genetic factors. The number of $Apo\mathcal{E}4$ alleles represents the strongest genetic risk factor for Alzheimer's disease, but also substantially increases LDL cholesterol levels,[320] potentially prompting treatment with a statin or other lipid regulating agent. I was unable to control for $Apo\mathcal{E}$ genotype in this analysis because I did not have access to genetic data on participants. As a result, any protective association between LRA use and the Alzheimer's disease outcomes may be masked by residual negative confounding by $Apo\mathcal{E}$.

Finally, as with many studies of dementia, there is a risk of reverse causation in my analysis. Dementia and associated conditions have a long prodromal period, during which preclinical disease could cause indications for the prescription of a lipid-regulating agent. Enforcing a minimum period of follow-up would address this limitation, but the use of a time-varying treatment indicator in this analysis prevents the use of this approach (see Appendix A.5.2 for a fuller discussion of this topic).

5.4.4 Enabling easy synthesis of this analysis

The raw data supporting this analysis is not publicly available because access to the CPRD data is controlled by a data monitoring committee. However, when data are not readily available, sharing the analysis code and summary statistics represents a way for readers to validate the findings.[136]

In light of this and my own experiences in attempting to extract information for papers assessing preventative treatments, as documented in Section 4.5.5, the outputs from this analysis have been made readily available. All code, Read code lists and summary statistics (namely the tables presented in this chapter plus summary tables of effect estimates) can be downloaded in a machine readable format from the archived repository for this project (`https://github.com/mcguinlu/CPRD-LRA`). This open approach should enable easy inclusion of this analysis in future evidence synthesis exercises, allowing new work to build on that presented here.

5.5 Summary

- In this chapter, I produced new evidence on the association of lipid-regulating agents with incidence of all-cause dementia, Alzheimer's disease, vascular dementia, and other dementia.

- I found little evidence for an effect of lipid-regulating agents on probable or possible Alzheimer's disease. However, lipid-regulating agent use was associated with an increased risk of all-cause, vascular and other dementias. In all cases, the estimated associations for the "any LRA" analyses were driven by those observed in the large statin subgroup.

- I attempted to account for important sources of bias through use of a time-varying treatment indicator. However, the control outcomes included in the analysis provided evidence for only partially controlled confounding by indication, likely related to vascular factors. Additionally, there was the potential for differential misclassification of dementia subtype on the basis of the exposure. Combined, these biases reduce the confidence in my findings, in particular the unexpected increase in risk of vascular dementia associated with statin use.

- Findings from this analysis are used as an additional source of evidence in the triangulation exercise presented in Chapter 7.

These particular systematic reviews [individual participant data reviews] remain yardsticks against which the quality of other reviews continues to be judged.

— Ian Chalmers, 1993[321]

6

Individual participant data meta-analysis of blood lipid levels and dementia outcomes

Contents

Lay Summary

This chapter examines the raw data pertaining to participants in previously published, relevant studies, a method of analysis called Individual Participant Data (IPD) meta-analysis. It uses this data to investigate the relationship between lipid levels and dementia risk, which is unique from the previous chapter because that chapter used published results rather than individual-level data.

I applied for access to 37 unique data sources for this analysis, however, only a small proportion of these data sources (n = 3, 8.1%) provided the requested data.

The resulting analysis of these data sources did not suggest a relationship between any blood lipid and any dementia outcome. The sole exception was an increased risk of vascular dementia in those with higher triglyceride levels. In addition, the participants age and sex did not appear to influence the relationship of lipid fractions and dementia outcomes.

The reasons for the low response rate to requests for data are explored in this chapter. Finally, I suggest future studies to investigate how data access rates could be improved.

6.1 Introduction

Individual participant data (IPD) meta-analyses are considered to be the gold standard form of evidence synthesis, allowing for the application of a common selection model and analytical approach across all identified cohorts.[92] They are particularly useful when investigating the impact of participant-level characteristics, something that is not possible with aggregate data unless the results are stratified by the characteristic of interest.[92,322] Knowledge of which groups a treatment will benefit most (or harm least) is a core aim of the move towards personalised medicine.[98,323] IPD analyses also offer a mechanism by which previously unanalysed datasets can be incorporated into an analysis, thus expanding the evidence base for a particular research question.

Previous work has suggested a difference in the effect of lipids on dementia risk based on participant age and sex.[59,221] The systematic review presented in Chapters 3 & 4 could not investigate this effect because the number of included studies in the lipid fraction meta-analyses was small, due to both the relatively small number of studies reporting on lipids and the poor reporting of summary statistics of participant characteristics in those that did. Additionally, best practice guidance recommends against basing the decision to perform an IPD meta-analysis on between-study heterogeneity in a summary data meta-analysis, because similar distributions of participant covariates across studies may mask a true effect.[98]

As such, the aims of this analysis are two-fold. Firstly, I plan to perform an IPD meta-analysis across identified cohorts to examine the impact of participant age-at-measurement and sex on the relationship between lipids and dementia risk. Secondly, I aim to expand the evidence base for the effect of lipids on dementia outcomes by obtaining estimates from previously unanalysed cohorts available via the Dementia Platform UK, a large consortium of dementia cohorts.

6.2 Methods

6.2.1 Eligibility criteria

Study design

Eligible data sources for this analysis were prospective cohort studies (see Section 6.2.2 for details on how these studies were identified). Data sources which were cross-sectional, either by design or due to the available data (e.g., a study recorded data on participants at multiple time-points or "waves", but only data from a single wave could be accessed) were excluded. Similarly, due to the time and cost restraints within the scope of my thesis project, studies making use of population-level electronic health records were ineligible. These studies are problematic in that they often require extensive project proposals in order to gain access to the data.

No restrictions were put on the number of participants or the length of follow-up, though it was a requirement that participants were dementia free (or assumed to be dementia free, based on age at entry) at baseline.

Exposures/outcome definition

I considered four blood lipid fractions as part of this analysis, namely: total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and triglycerides (TG). Cohorts were eligible for inclusion if they contained data on at least one of these lipid fractions, recorded as a continuous variable (i.e., studies with binary "hypercholesterolemia" exposure would be excluded).

In line with the analyses presented in other chapters, eligible cohorts were those containing data on at least one outcome of interest, namely: all-cause dementia, Alzheimer's disease, or vascular dementia.

6.2.2 Applying for data access

Potentially eligible data sources were identified via two approaches, each with a distinct focus. The approaches are described in detail in the following sections. For both approaches, the number of cohorts responding to the request for data access and, where applicable, the reasons given for a refusal were recorded.

Cohorts identified by the systematic review

The first approach focused on previously analysed observational prospective cohort studies examining the effect of blood lipid levels on dementia outcomes, as identified by the systematic review presented in Chapters 3 & 4. The data sources used in each of these cohort analyses were screened against the criteria listed in the previous section, and eligible cohorts were approached for data access. In the first instance, the first/corresponding author of the publication was emailed in Autumn 2020. If this approach did not elicit a response within two months, the last author was contacted, on the basis that the first/corresponding author may have been a more junior member of the research group who had moved to a different institution.

Cohorts contained in Dementia Platform UK

The second approach focused on incorporating relevant, previously unanalysed data into the analysis, thus providing additional evidence on the relationship between blood lipids and dementia risk. This was achieved through the Dementia Platform UK (DPUK), a collaborative grouping of existing dementia cohorts established by the Medical Research Council which works with data owners to make their data readily accessible for secondary analysis.[108] It provides access to 42 cohorts with over 3 million participants, and makes use of a central streamlined application process for all cohorts, with the intent of making it easier to access data from existing data sources.

Cohorts included in the DPUK were assessed against the eligibility criteria, and in Autumn 2020, an application for access to a subset of 17 cohorts was made via the common-access procedure.

6.2.3 Primary analysis

Data cleaning and harmonisation

Where data on one of the exposures (TC, LDL-c, HDL-c, TG) was missing, it was inferred from the other three fractions (where available) using the Friedwald formula (Equation (1.1)). Lipid levels were retained as continuous variables rather than dichotomising into a binary hypercholesterolemia exposure, given the additional statistical power this adds to the meta-analysis.[98,324] Where lipid measurements were reported in *mg/dL*, these were converted to *mmol/L*.

Across all cohorts, data cleaning was performed in a similar manner, standardizing to commonly named variables so that a single model could be applied using functional programming.[325] The advantage of this approach is that it reduces the likelihood of errors in model mis-specification if changes are required in variables names from cohort to cohort. Following data cleaning, summary statistics for each data source were calculated and compared with publicly available statistics to ensure no errors were introduced in the data cleaning process, in line with best practice.[326]

Covariate definition

A range of additional variables were included in the analysis, intended to address the potential for confounding. With an awareness that discrepancies are common in the set of available covariates across cohorts included in an IPD analysis, I defined an idealised set of covariate domains to be age, sex, education, BMI, $Apo\mathcal{E}4$ status, smoking/alcohol status, ethnicity, and prevalent diabetes or cardiovascular disease. This set covers key risk factors for dementia/Alzheimer's disease in addition to general cardiovascular risk factors. Details on how these variables were coded, given the available data, are presented in Section 6.3.3.

Missing data

Missing data in this analysis was classified as either relating to missing values (a data on a variable of interest was available in a cohort, but some values were missing) or missing variables (a cohort did not collect data on a variable of interest). Variables with missing values were identified, and 20 imputed datasets were created.[293] Imputation was performed using MICE (Multiple Imputation by Chained Equations) and was implemented in R using the `mice` package in R.[327]

Missing variables were originally intended to be addressed using a previously published method.[328] Here, the correlation between the fully-adjusted and partially-adjusted estimate in cohorts with the full set of covariates is used to estimate the fully-adjusted effect in those cohorts missing covariates. However, this method requires several large cohorts to contain the full set of covariates, a condition this analysis failed to meet given the very low response rate. As such, two other common approaches were employed.[328] In the primary analysis, all cohorts were adjusted for the set of common covariates across cohorts (Model 1: age, sex, smoking, alcohol, education, diabetes). As a sensitivity analysis, cohorts with the full complement of covariates (Whitehall II and EPIC) were analysed using a maximally-adjusted model (Model 2: Model 1, further adjusted for ethnicity, prevalent ischemic heart disease and BMI). Results between the common-set-adjusted (Model 1) and maximally-adjusted (Model 2) models were then compared.

IPD analysis

In terms of the analytic approach taken, a two-stage IPD analysis was used. Under a two-stage approach, estimates for the effect of each lipid fraction on incident dementia were first calculated for each data source. More specifically, a logistic regression model adjusted for relevant covariates (as detailed in the above section) was used to quantify the effect of a 1 *mmol/L* increase in each lipid fraction on each dementia outcome.

Results were expressed as odds ratios (OR). Examination of the data available via the DPUK indicated that the common time-to-event approach used in studies of dementia outcomes would be precluded by the absence of detailed time-to-event data. An overall effect estimate was then produced by combining data-source-specific estimates in a random-effects meta-analysis (see Section 3.2.9 for a broader discussion of meta-analysis methods).

A two-stage IPD approach was employed for a number of reasons. Firstly, and most importantly, a two-stage approach allows for siloed data, enabling researchers who are unwilling/unable to provide their data to obtain the effect estimates themselves, following a specified analysis plan, and share these with the IPD team.[92] Secondly, it allows for the production of forest plots of within-cohort estimates, something which is useful for the triangulation exercise in Chapter 7. Finally, a two-stage approach is simpler to model because it uses standard well-documented summary effect estimate meta-analysis techniques, and automatically accounts for methodological issues such as clustering within cohorts[329] and the potential for ecological bias.[330]

Investigating the effect of participant-level covariates

In order to investigate the interaction of participant-level characteristics (age and sex) with lipid levels, lipid-covariate interaction terms were extracted and synthesised using a fixed effects meta-analysis.[331] All interaction analyses were performed using the common-set-adjusted model (Model 1). To avoid ecological bias, where the between-study association does not reflect the within-study associations, cohorts where there was no within-study variation in the covariate of interest were excluded from the interaction analysis for that covariate.[330] As an example, it is impossible to estimate the impact of sex on the lipid/dementia relationship in a study which contains only female participants.

6.3 Results

6.3.1 Data access

Of the 37 studies to which I applied for data access, only three (8.1%) were included in the final analysis. Figure 6.1 details whether the cohorts eventually included in the review were identified by the systematic review or via the DPUK portal. In addition, the reasons for cohorts being from the analysis are presented, stratified by application approach.

In summary, the requests for data from cohorts identified by the systematic review were characterised by a very low response rate (N = 5, 25%). For the five cohorts that did respond, common reasons given by authors for not sharing the data included that they: no longer worked with the same group and did not know if the data was available or how to obtain it; no longer had access to the data; or were currently performing, or intended to perform, a similar analysis as the one proposed.

With respect to the application to DPUK cohorts, where a dedicated project manager liaises with data owners on the applicants' behalf, the overall response rate was higher. However, even using this streamlined approach, a positive response was obtained for approximately half (N =9, 53%) of the approached cohorts.

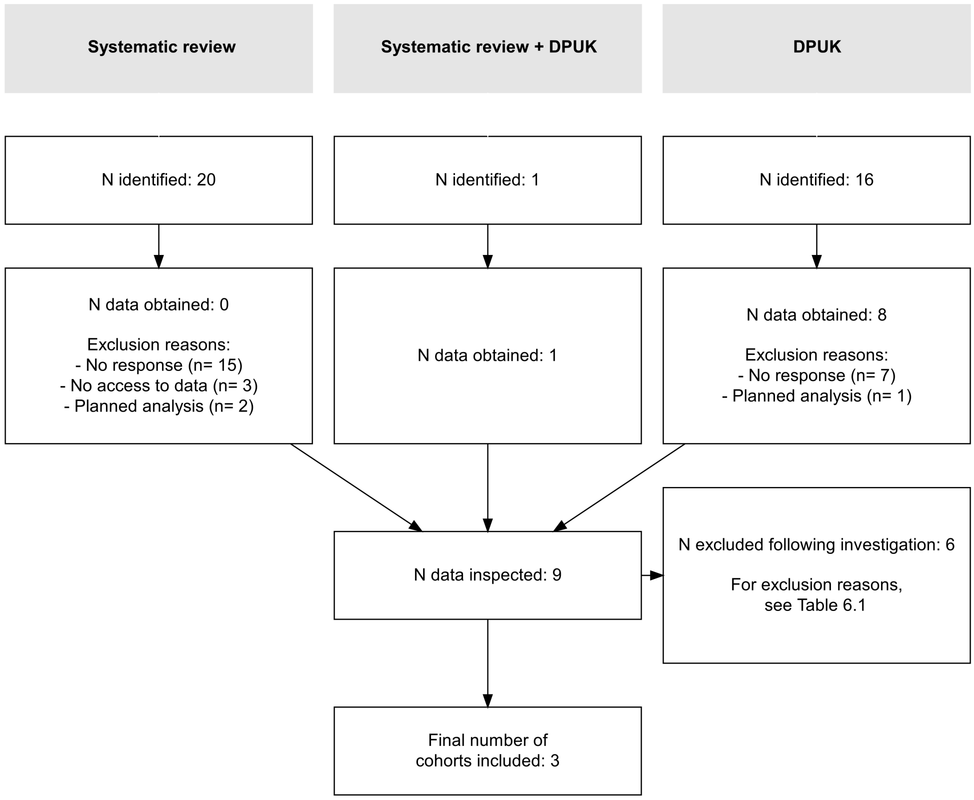

Figure 6.1: Flowchart detailing sources of data for the IPD analysis - The number of cohorts approached and the reasons for exclusion are stratified by identification method (systematic review vs DPUK).

As highlighted in Figure 6.1, there was little overlap between cohorts identified by the systematic review and those contained in the DPUK (1), indicating that the DPUK is a useful source of unanalysed data with respect to this question. A single cohort (Whitehall II) was identified by the systematic review and was also present in the DPUK.

Nine cohorts (8 DPUK only, 1 Systematic review + DPUK) responded positively to requests for data access. However, on inspection of data provided, six of these cohorts were excluded and the reason for exclusion in each case is shown in Table 6.1. In summary, two cohorts contained were memory-complaint cohorts, containing participants unlikely to be free of dementia at baseline (BRACE, MEMENTO). Two cohorts, despite being designed as multi-wave studies, only shared data related to a single wave and so represented cross-sectional data (Generation Scotland, NICOLA). Finally TRACK HD is a genetic cohort where cohort owners advised me that dementia will inevitably develop in mid-life driven by the Huntington's (HTT gene) mutation and that this effect would likely far outweigh the effect of lipids. Finally, the ELSA study was excluded based on the dichotomous definition of the exposure variable.

Table 6.1: Exclusion reasons for cohorts providing data - Number of cohorts approach and the reasons for a lack of data access, stratified by whether the cohort was identified by the systematic review or via the DPUK.

Cohort	**Reason**
BRACE	Memory complaint cohort - unlikely to be dementia free at baseline
ELSA	Lipid exposure reported as a binary variable
Generation Scotland	Cross-sectional - only one wave of data available
MEMENTO	Memory complaint cohort - unlikely to be dementia free at baseline
NICOLA	Cross-sectional - only one wave of data available
TRACK HD	HTT gene carriers (i.e. premanifest Huntington's Disease)

6.3.2 Included data sources

The three data sources used in this analysis are described in detail in the following sections. Of note, all included data sources were based in the United Kingdom. This is due to the majority of included datasets being identified via the Dementia Platform UK route (Figure 6.1), which as implied by the name, has a narrow geographical focus.[108]

Caerphilly Prospective Study

The Caerphilly Prospective Study (CaPS) is a longitudinal study of men in South Wales, UK.[332,333] Blood lipids (TC, LDL-c, HDL-c and TG) were measured at baseline in 1979-1983, and from Phase III (1989-1993) onwards, a battery of cognitive tests was introduced. Dementia outcomes were determined using data obtained during Phase V (2002-2004), giving between 19-25 years of follow-up. The cohort contains data on dementia outcomes sub-classified as vascular and non-vascular dementia. Data was available for all covariates of interest except for ethnicity, BMI, prevalent IHD and $Apo\mathcal{E}4$ status. While the CaPS study collected data on height/weight (from which BMI can be calculated as $\frac{weight}{height^2}$) and prevalent heart disease, these were not available from the DPUK version of the CaPS data.

Epic Norfolk

The European Prospective Investigation of Cancer (EPIC) - Norfolk is a population-based cohort, containing men and women recruited from 35 general practices in Norfolk between 1993 and 1998.[334,335] Dementia was ascertained at the 5th Health Check-up (2016-2018), providing between 18-25 years of follow-up. The added evidential value of the EPIC cohort is small, given the fact that the data obtained contains only 8 dementia events. The cohort contains no information on dementia subtype, while all covariates of interest bar $Apo\mathcal{E}4$ were available.

Whitehall II

The Whitehall II study is a prospective cohort study of men and women recruited between 1985 and 1989 from the civil service in London.[336] Lipid measurements were available from the third wave of the study, conducted between 1991-1993. The cohort is linked with the Hospital Episode Statistics (HES) database, a database containing details of participant events at NHS hospitals in England. which was used to capture dementia outcomes.[337] HES data was available up to March 2015, providing between 22-24 years of follow-up. Information was available on dementia type, which was classified as all-cause dementia, Alzheimer's disease or vascular dementia. This data source contained details on all covariates of interest except for $Apo\mathcal{E}4$ status.

Of note, the Whitehall II cohort was analysed in one of the included studies identified by the systematic review presented in Chapters 3 & 4,[246] meaning that a comparison between the published result and the analysis reported here was possible.

6.3.3 Covariate definition & missing data

Based on available data across cohorts, smoking was classified as never/ever/current, while alcohol consumption was classified as never/ever. Ever use in this case refers to participants who do not currently smoke/drink alcohol but did so in the past. Education was categorised into 4 levels (None, O-levels, A-levels, Degree). BMI was treated as a continuous variable while presence of vascular co-morbidities was treated as dichotomous.

A key consideration in the definition of covariates across cohorts was the classification of age. The Whitehall II study, the largest cohort to which I had access, only shared age data in five-year age bands (e.g., 40-44, 45-49, etc.). To ensure comparability across the cohorts, I created identical categories in the CaPS and EPIC data. This grouped age variable was then used in all subsequent analyses.

Missing values in collected variables was common across the cohorts. A matrix of covariates for each included cohort, describing both missing variables and the proportion of missing values within collected variables, can be seen in Appendix A.6.1. The Whitehall II and EPIC cohorts contained data on all but one covariates of interest, while three missing covariates were identified in the CaPS cohort, namely education, prevalent ischemic heart disease, BMI and ethnicity. No included cohort provided information on the *Apo$\mathcal{E}$4* status of participants, and so this variable could not be adjusted for in the analysis.

6.3.4 Analytical results

Descriptive statistics

Across the three cohorts, 11,835 participants were included in this analysis (Whitehall II = 8208, EPIC = 1115, CaPS = 2512). All cohorts contained data on the four lipid fractions of interest (or sufficient data from which to calculate them) and on all-cause dementia outcomes. The only other dementia outcome examined across cohorts was vascular dementia, which was reported in the CaPS and Whitehall II studies. The definitions of dementia outcomes used across cohorts can be seen in Appendix A.6.2. Cumulatively, there were 542 cases of all-cause dementia, with 114 further classified as vascular dementia. Summary statistics for each cohort are provided in Table 6.2.

Table 6.2: Characteristics of IPD cohorts - Summary of characteristics for cohorts included in the IPD analysis. Variables not available from a cohort are denoted by "-". See Appendix A.6.1 for details on the proportion of missing data within collected variables.

	Whitehall II	**Epic**	**CaPS**
N	8208	1115	2512
Age group, Median	45-49	50-54	50-54
Male, N (%)	5679 (69.2)	495 (44)%	2512 (100)
BMI, Mean (SD)	25.3 (3.75)	25.8 (3.58)	-
Education >18 yrs, N (%)	2576 (31.4)	252 (22.6)	20 (0.8)
Smoke ever, N (%)	2678 (32)	490 (43)	2110 (83.9)
Alcohol ever, N (%)	6612 (80.6)	37 (3.3)	2235 (89)
Ethnicity (white), N (%)	7387 (90)	1107 (99.3)	-
IHD, N (%)	7 (0.1)	63 (5.7)	-
TC, Mean (SD)	6.49 (1.16)	5.93 (1.08)	5.93 (1.15)
LDL-c, Mean (SD)	4.40 (1.04)	3.77 (0.96)	3.74 (1.12)
HDL-c, Mean (SD)	1.43 (0.414)	1.43 (0.41)	1.37 (0.41)
TG, Mean (SD)	1.49 (1.14)	1.67 (1.04)	1.83 (1.21)
Dementia, N (%)	287 (3.5)	8 (0.7)	247 (9.8)
Alzheimer's, N (%)	92 (1.1)	-	-
Vascular dementia, N (%)	37 (0.5)	-	77 (3.1)
Non-vascular dementia, N (%)	-	-	170 (6.8)

Abbreviations: BMI - Body mass index; IHD - Ischemic heart disease; HDL - Low-density lipoprotein cholesterol; LDL - Low-density lipoprotein cholesterol; TG - Triglycerides.

Main effects

The results from the main effect analysis across the varying lipid fractions on each dementia outcome considered can be seen in Figures 6.2 & 6.3, respectively. There was weak evidence for an association of any lipid level with either all-cause or vascular dementia, with the exception of a harmful association between raised triglycerides and vascular dementia (OR: 1.25, 95%CI: 1.01-1.54, 6.3). For the sole cohort containing data on the Alzheimer's disease outcome (Whitehall II), there was weak evidence for an association of this outcome with any lipid fraction (results shown in comparison with previous analysis of this cohort in Figure 6.9)

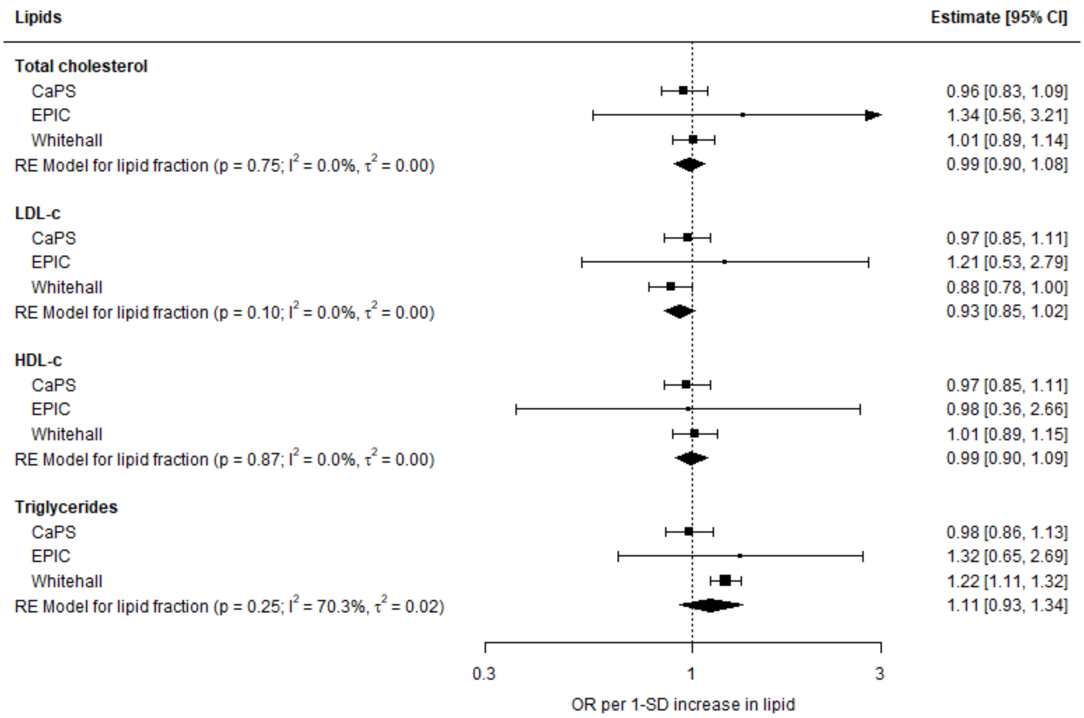

Figure 6.2: IPD meta-analysis of all-cause dementia - Using Model 1 (adjusted for age, sex, smoking, alcohol, education and diabetes), an IPD random-effects meta-analysis was applied to investigate the association of a 1-SD increase in each lipid fraction with all-cause dementia outcomes.

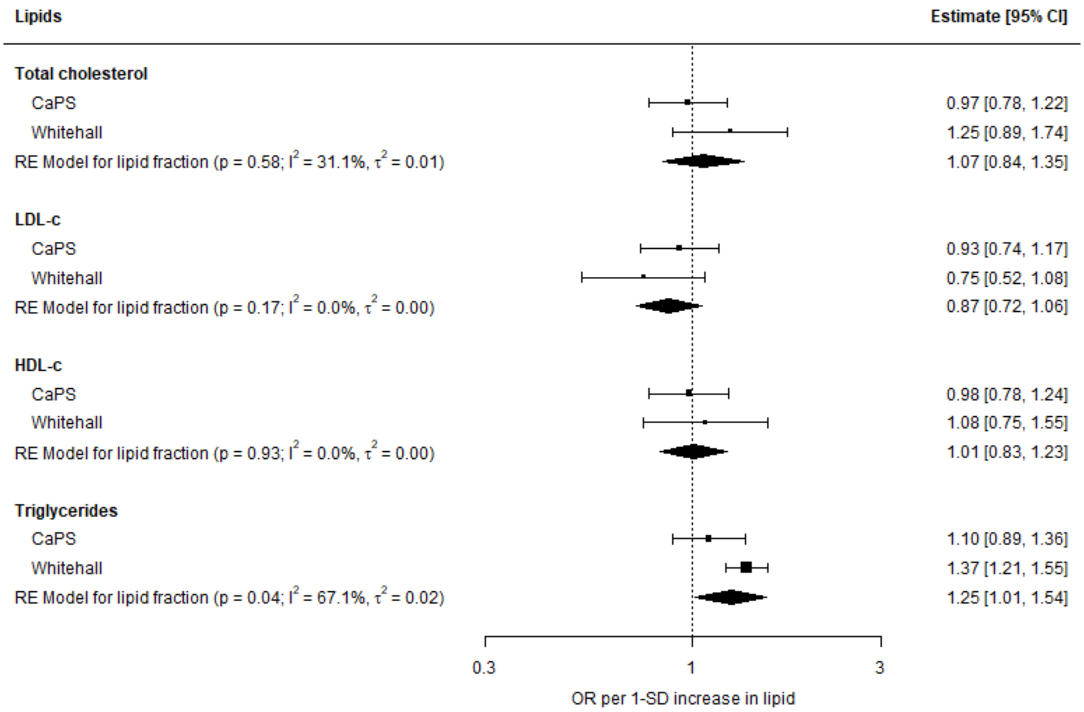

Figure 6.3: IPD meta-analysis of vascular dementia - Using Model 1 (adjusted for age, sex, smoking, alcohol, education and diabetes), an IPD random-effects meta-analysis was applied to investigate the association of a 1-SD increase in each lipid fraction with vascular dementia outcomes. Note that the vascular dementia outcome was only available in the CaPS and Whitehall II cohorts (see Table 6.2).

Estimates from the common-set-adjusted model (Model 1: adjusted for age, sex, smoking, alcohol, education and diabetes) were comparable to the fully-adjusted model (Model 2: Model 1 further adjusted for ethnicity, prevalent ischemic heart disease, and BMI) for the effect of lipids on all-cause dementia in cohorts reporting all covariates of interest (Figure 6.4).

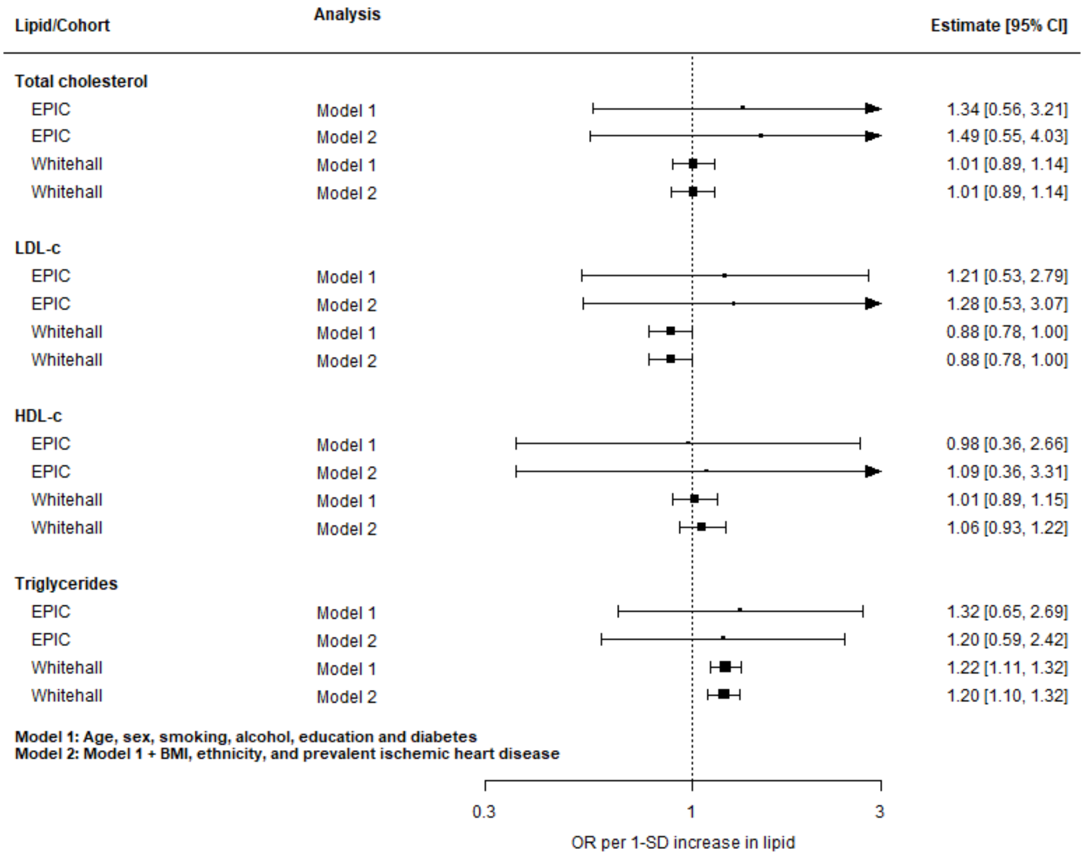

Figure 6.4: Comparison of partially- and maximally-adjusted model - Results from the common-set-adjusted (Model 1) and fully-adjusted (Model 2) analyses for the all-cause dementia outcome were compared for the two cohorts containing a full set of covariates (EPIC, Whitehall II).

Interaction effects

Given the minimal effect of further adjustment in the maximally-adjusted model, the common-set-adjusted model (Model 1) was used to perform the interaction analyses.

The maximally-adjusted model (Model 2) could have been employed in the analysis of the effect of sex, as both EPIC and Whitehall II had a full complement of covariates (CaPS contains only men and so was excluded from this analysis). However, I decided to employ the same underlying model across the interaction analyses to aid comparability between the age and sex interaction estimates.

For all-cause dementia, there was no evidence of an interaction of lipid levels with either age group or sex (Figures 6.5 & 6.6).

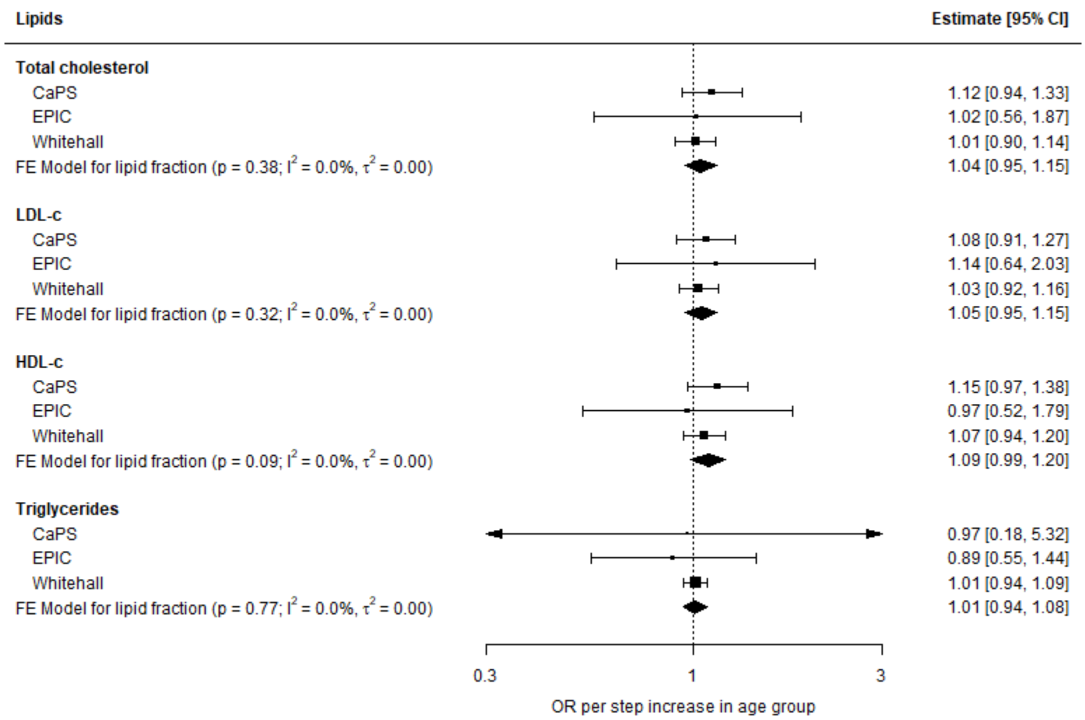

Figure 6.5: Meta-analysis of age-lipid interaction terms for all-cause dementia - Age was grouped into 5-year age bands, and the effect estimates presented represent the OR per 1-step increase in age group. Estimates were obtained using the common-set-adjusted model (Model 1: age, sex, smoking, alcohol, education, diabetes).

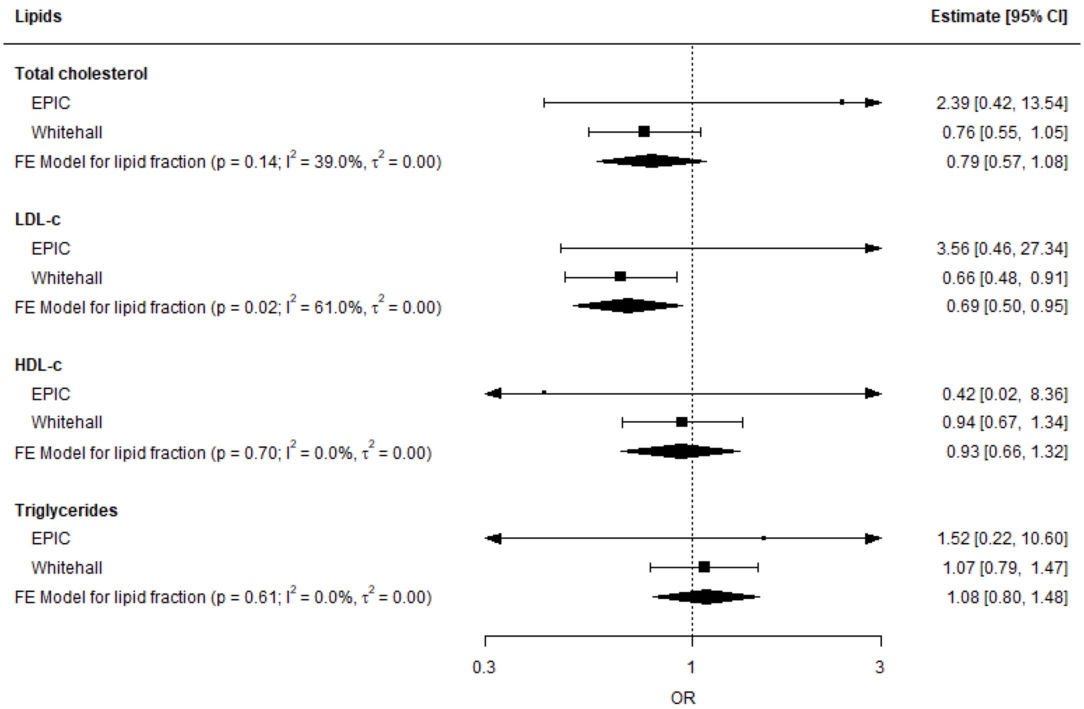

Figure 6.6: Meta-analysis of sex-lipid interaction terms for all-cause dementia - Estimates were obtained using the common-set-adjusted model (Model 1: age, sex, smoking, alcohol, education, diabetes) and refer to the effect of male gender on the lipid/all-cause dementia association. The CaPS cohort was excluded from this analysis because it contains only a single sex and therefore provides no information on the lipid-sex interaction.

For the consideration of vascular dementia, I was only able to explore the effect of age, as only the CaPS and Whitehall cohorts contained details on vascular dementia as an outcome. As discussed above, the CaPS data contained a single sex which meant it was excluded from the exposure-sex analysis, leaving Whitehall II as the sole eligible study.

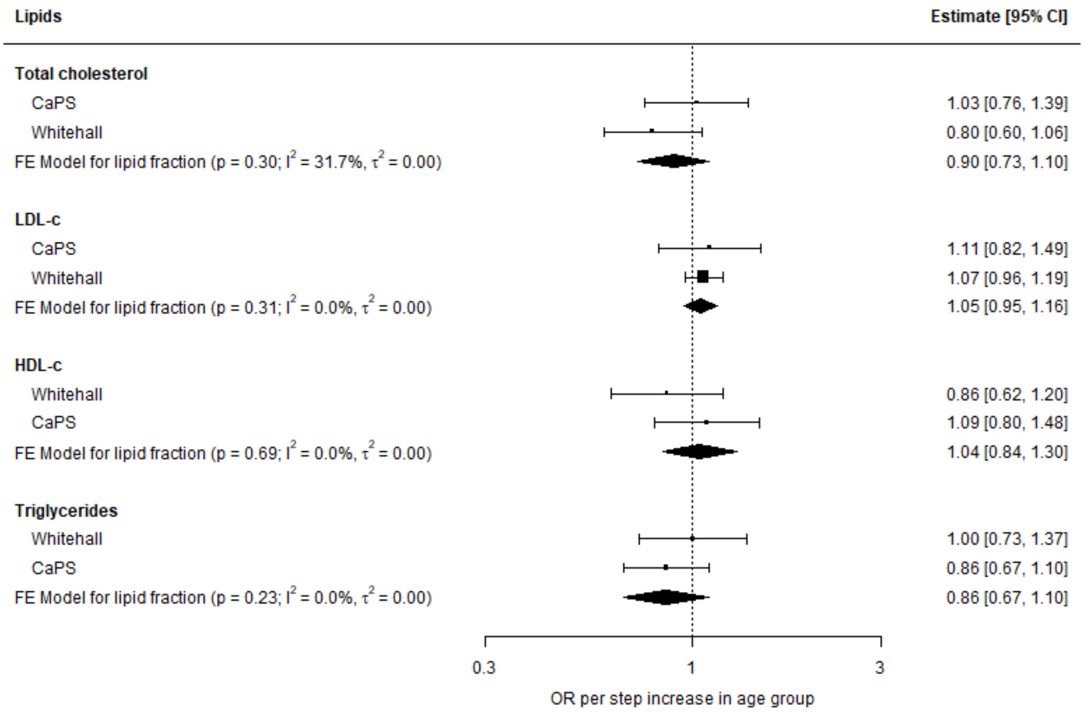

Figure 6.7: Meta-analysis of age-lipid interaction terms for vascular dementia - Age was grouped into 5-year age bands, and the effect estimates presented represent the OR per 1-step increase in age group. Estimates were obtained using the common-set-adjusted model (Model 1: age, sex, smoking, alcohol, education, diabetes).

6.4 Discussion

6.4.1 Summary of findings

This analysis requested data from 37 data sources, but only obtained data from three, all of which were based in the United Kingdom. No evidence for an effect of lipids on the risk of dementia or related outcomes was identified, except for a harmful association of raised triglycerides with risk of vascular dementia. Similarly, there was weak evidence for an interaction of the effect of lipid levels on dementia outcomes with participants' age (grouped into 5-year bands) or sex.

A detailed comparison of the findings presented above with the existing evidence base identified by the systematic review (Chapters 3 & 4), is presented as part of the triangulation exercise in Chapter 7. As such, this discussion will not provide a detailed comparison of the results of this analysis with other published literature, except to compare between this analysis and previously published results using the same data source.

6.4.2 Limitations

Low response rate to request for data

The obvious key limitation of this analysis is the very low response rate to requests for data access, which may bias the results if there are systematic differences in the association of lipids with dementia outcomes between cohorts that share data and those that do not.[338] Whether or not to press ahead with an IPD analysis in the absence of all (or even most) data is a personal decision, and some previous analyses have highlighted where they decided not to pursue an IPD analysis.[339] For the purposes of this thesis, the decision was made to conduct the IPD analysis because it provided training in application of IPD methods in addition to providing new evidence that will be incorporated into the triangulation exercise detailed in Chapter 7.

A low response rate is not unexpected, given that a review of IPD studies published between 1987 and 2015 found that fewer than half managed to obtain data from greater than 80% of studies, and that in many cases, the exact percentage of studies for which data was obtained was not accurately reported.[101] However, it is assumed that the ~10% response rate encountered in this analysis is at the lower end of the scale.

There are many likely reasons for this low response rate to requests for data access. In general terms, there are several well-documented barriers that prevent data from being made readily available, including concerns regarding participant privacy, fear of "scooping" or "parasitic" behaviour, and a lack of trust between primary and secondary researchers.[106] More specific to this analysis, IPD meta-analysis including studies other than randomised controlled trials have less success in obtaining IPD from previous published studies.[101] Additionally, while no evidence is available on whether the characteristics of the researcher who is requesting data access influences the response rate and eventual decision, there is the possibility that my position as a PhD student meant I was less likely to elicit a positive response than a well-known senior academic might. The timing of the requests for data access, coinciding with a global pandemic, may also have affected the response rate as researchers prioritised COVID-related work.

Finally, in investigating the potential reasons for the low response rate, I discovered that the method of contact used (email) has been shown to be less successful in eliciting responses from authors when compared with telephoning (which was not used in this analysis).[340] One of the reasons for this may be that the email addresses reported on publications are more likely to be out of date for older publications. Anecdotally, post-hoc investigation of a subset of cohorts revealed that several corresponding/first authors were no longer at the same institution as when the study was reported, and as a result, were unlikely to have access to the institutional email address listed on the study publication. Despite attempts to track authors as they move between institutions, out-of-date contact details may have contributed to the low response rate.

The obstacles to data access described above are in theory what the DPUK was built to address. However, even with the help of the streamlined application process afforded by the DPUK, accessing sufficient data was a challenge. The response rate among DPUK cohorts a year after application was just 50%. In addition, some cohorts responded saying that the proposed study question was already under investigation by another group, and that they would not share the data on this basis. In light of this, a centralised database of ongoing analyses being performed using DPUK data would be of enormous help, reducing research waste and providing opportunities for collaboration. Finally, the DPUK process would be aided by a clearer distinction between those cohorts that are "DPUK native" (i.e., where a copy of the data is already held on DPUK servers) versus externally hosted, seeing as the response time for externally hosted cohorts is likely to be much longer.

Uncontrolled confounding

A key limitation of this analysis is the potential for uncontrolled confounding. Across all cohorts, adjustment for *Apo$\mathcal{E}$4* was not possible as I did not have access to genetic data on participants. *Apo$\mathcal{E}$4* is a strong risk factor for both increased LDL-c levels and Alzheimer's disease,[320,341] and failing to adjust for this factor means residual confounding in the LDL-c fraction results is likely.

More generally, systematically missing variables required a trade-off between inclusion of cohort data and appropriate control for confounding. The final choice of the common-set-adjusted model for use in the interaction analyses means there is the potential for residual confounding. However, sensitivity analysis comparing the common-set-adjusted (Model 1) and fully-adjusted (Model 2) models in cohorts with a full complement of covariates indicated that further adjustment for BMI, ethnicity, education and prevalent IHD had minimal impact on the effect estimates. Of note, this is comparable with the analysis of the CPRD data presented in the previous chapter, where adjustment for variables beyond age and sex had a limited impact on the observed effect estimates (see Section 5.3.4).

Comparison with a previous analysis

For the single cohort (Whitehall II), a previously published analysis was available. Tynkkynen *et al.*[246] analysed the association of blood lipids and risk of all-cause dementia and Alzheimer's disease across several cohorts, including the Whitehall II cohort. In an attempt to validate my approach, I compared the results from the maximally-adjusted model (Model 2) in this analysis with those reported by Tynkkynen *et al.* for both all-cause dementia and Alzheimer's disease.

The results for the Alzheimer's disease outcome were comparable (Figures 6.9)). However, for the vascular dementia outcome (Figure 6.8), I identified a discrepancy in the association of triglycerides with all-cause dementia estimated by the two analyses. Tynkkynen *et al.*[246] found a protective effect of triglycerides on this outcome (HR: 0.69, 95%CI: 0.56-0.85) while this analysis found evidence for a harmful effect (OR: 1.26, 95%CI: 1.12-1.41).

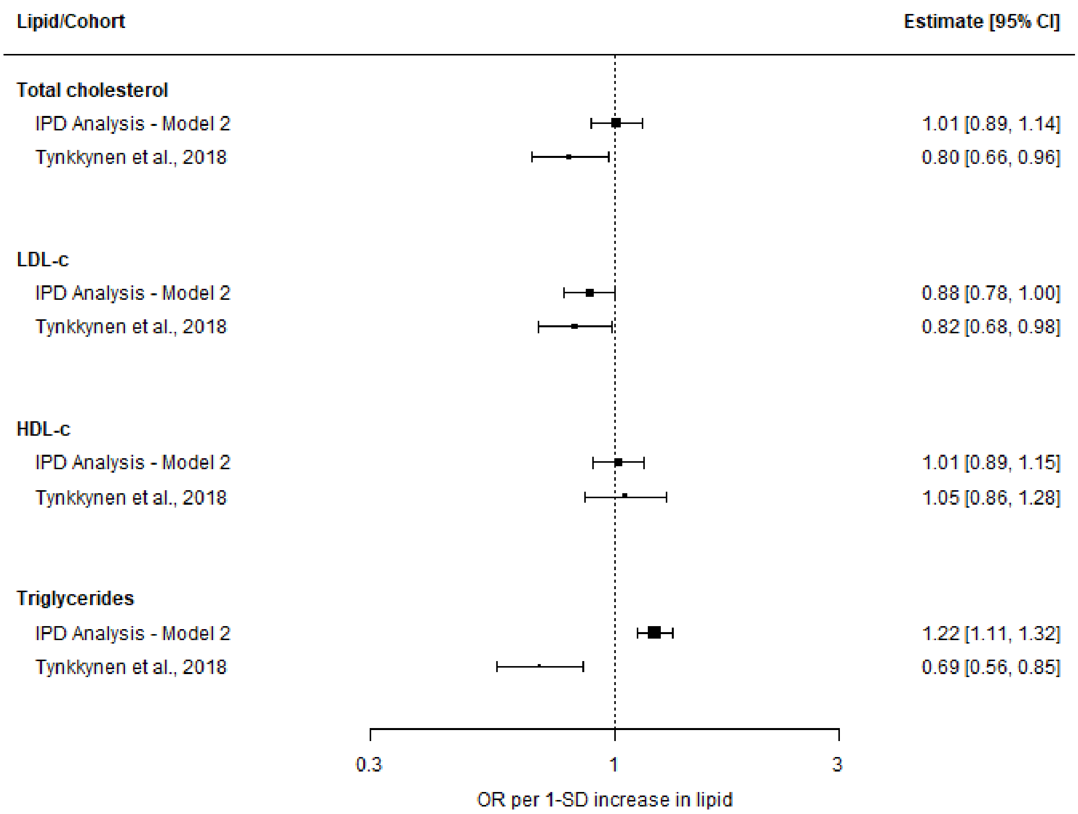

Figure 6.8: Comparison of two analyses of the Whitehall II cohort (all-cause dementia) - A published analysis by Tynkkynen *et al.*[246] had previously examined the association of lipid fractions and all-cause dementia in the Whitehall II cohort. The results of the two analyses are shown above and were broadly comparable, except for the triglyceride fraction. Potential reasons for this discrepancy are discussed in the main text.

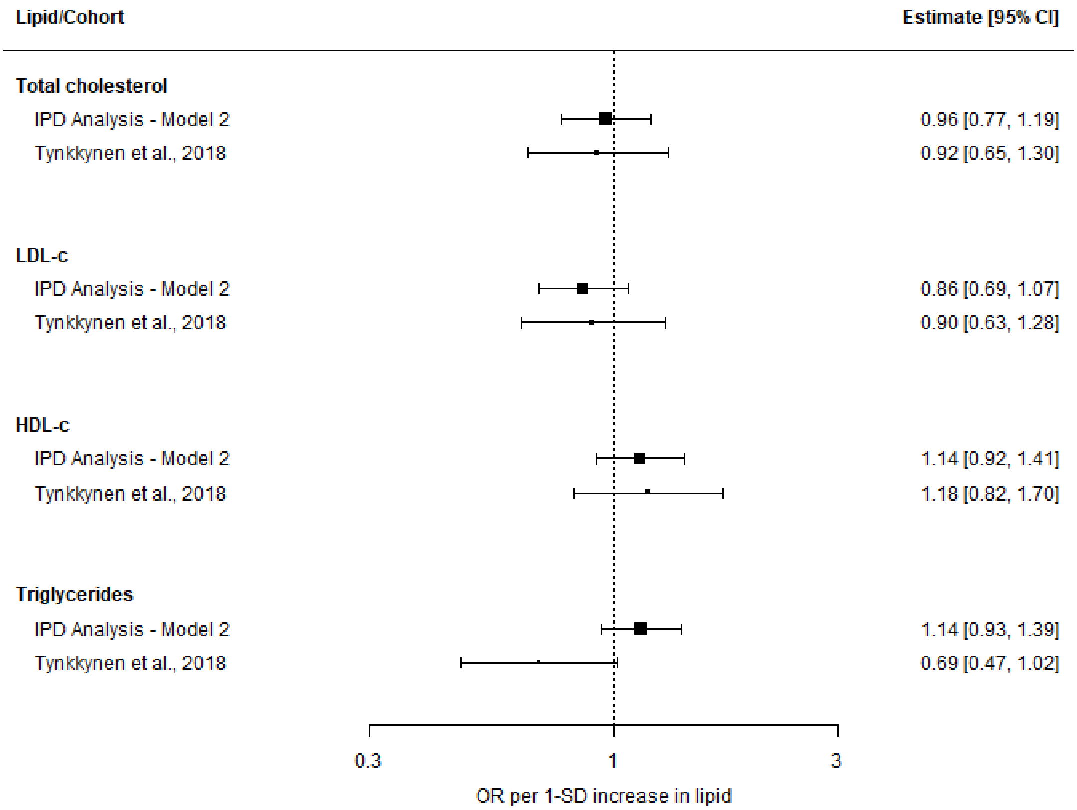

Figure 6.9: Comparison of two analyses of the Whitehall II cohort (Alzheimer's disease) - A published analysis by Tynkkynen *et al.*[246] had previously examined the association of lipid fractions and Alzheimer's disease in the Whitehall II cohort. The results of the two analyses are shown above and were broadly comparable.

Investigation revealed several possible reasons for this discrepancy. The first is that while this analysis uses multiple imputation to address missing data, the Tynkkynen *et al.* analysis does not describe how missing data was handled. However, the reduced precision in the reported estimates suggest a complete case analysis. This interpretation is supported by a comparison of summary statistics, which illustrated that my analysis had substantially more dementia events (N =287 in this analysis vs. n=114 in Tynkkynen *et al.*), suggesting that incomplete records were discarded in the previous analysis. Finally, the covariates adjusted for in each analysis were similar, though the previous analysis had access to genetic data allowing it to adjust for *ApoE4* status. However, given that *ApoE4* is a risk factor for increased LDL-c rather than triglycerides,[320] it seems unlikely that additional adjustment for this variable is responsible for the discrepancy in the findings observed.

6.4.3 Strengths

While this analysis did not manage to obtain and analyse a large proportion of identified data, a central strength of this analysis is the use of a systematic approach to identify and attempt to contact relevant cohorts. Furthermore, it also enabled incorporation of two previously unanalysed datasets - the CaPS and EPIC Norfolk cohorts - thus providing additional evidence that is used in the triangulation exercise reported in Chapter 7.

A further strength is the ability of this analysis to investigate the effect of participant characteristics (namely age and sex) on the association of blood lipids and dementia outcomes. To the best of my knowledge, no previous review has examined the interaction of these factors with the observed associations.

Finally, this analysis provides new evidence on a previously unexplored outcome (vascular dementia), adding to the extremely small evidence base for this outcome identified by the systematic review presented in Chapters 3 & 4. This is relevant even in the previously analysed Whitehall II cohort because the previous analysis by Tynkkynen *et al.* did not report on this outcome.

6.4.4 Reflections on the process

In hindsight, attempting to undertake a large-scale IPD meta-analysis as part of a larger PhD project may have been overly ambitious. Data harmonization between cohorts in an IPD analysis is an often under-appreciated challenge,[326] and in line with this, data cleaning for this analysis took substantially longer than expected. While the cohort response rate was substantially lower than expected, given the time and resources required for the cleaning and harmonisation of data from just three cohorts, a situation in which all 37 cohorts responded positively would have been logistically challenging within the scope of a PhD.

6.4.5 Future work

While it is tempting to suggest that an IPD analysis of lipid levels be reattempted, without empirically guided approaches to increase the response rate, this may just result in a similarly small set of studies as described here. In line with the limitations considered earlier in this chapter, future methodological work could formally consider the effect of requester characteristics (sex, location, career stage) on response rates in IPD analyses.

Additionally, the production of detailed guidance for handling cases where covariates are systematically missing would represent a useful contribution to the topic. Much of the literature around IPD analysis is focused on the synthesis of RCTs, where additional covariate information is needed primarily for the assessment of treatment-covariate interactions rather than the adjustment of the effect estimate for confounding. Given the wide availability of non-randomised cohorts, improved guidance on this challenge would support future work.

Finally, movement towards increased use of unique and persistent researcher identifiers, such as those offered by the ORCID programme,[342] would help with contact issues. Researchers move institutions regularly as their contracts come to an end, and so the institutional contact details provided on publications are frequently out of date.

6.5 Summary

- In this chapter, I performed an IPD meta-analysis to investigate the effect of blood lipid levels on the risk of incident dementia. There was a very low response rate to requests for data access, resulting in the analysis of three relevant cohorts.

- I found weak evidence for an association of any lipid with either all-cause or vascular dementia, except for an increased risk of vascular dementia associated with raised triglycerides. Similarly, there was weak evidence that the association of blood lipids and dementia outcomes varied by participant age or sex.

- I discussed potential reasons for the low response rate and explored other limitations of this analysis. I highlighted the contribution of this work to the wider topic via the analysis of previously unexplored cohorts (CaPS & EPIC) and outcomes (vascular dementia). Finally, I recommended that future research could formally investigate the impact of the characteristics of the requesting researcher on data access rates.

- The new evidence produced by this analysis will be incorporated, along with evidence identified or produced in the previous chapters, into the triangulation analysis presented in the following chapter.

Next on my list of features to be specially considered I would place the consistency of the observed association. Has it been repeatedly observed by different persons, in different places, circumstances and times?

— Austin Bradford Hill, 1965[343]

7

Aetiological triangulation across new and existing evidence sources: a qualitative and quantitative approach

Contents

Lay summary

Sources of evidence often contain limitations which reduce our confidence in their results. To minimise the impact of these limitations, a method has been developed called triangulation which looks at multiple sources addressing the same question. If the result from each source points towards the same answer, this improves our confidence in the conclusion.

In this chapter, I describe a new approach for triangulation, which combines two existing methods. This approach is used to ensure that the results meet the following criteria:

- robustness - do we believe the result, based on the methods/results of the study?
- relevance - does the source provide useful evidence relevant to the question we are interested in?

This triangulation approach is quantitative in nature, meaning I have tried to combine the results from different sources mathematically to obtain one single overall result. I have applied this method to assess the following relationships of interest:

- the effect of midlife LDL-c on Alsheimer's disease
- the effect of midlife triglycerides on vascular dementia

My method did not support the existence of an effect in either relationship of interest. I close the chapter by suggesting future work to further develop and improve upon the new method presented.

7.1 Introduction

Aetiological triangulation, or simply triangulation, is the process of comparing and contrasting across different sources of evidence. Triangulation is broadly comparable to Bradford-Hill's criteria of "consistency", that is the replication of an observed relationship across several different contexts,[343] where contexts are assumed to have different underlying bias structures. More formally it can be defined as:

> The practice of strengthening causal inferences by integrating results from several different approaches, where each approach has different (and assumed to be largely unrelated) key sources of potential bias.[109]

This approach represents a significant step forward from the current practice of synthesising evidence from only one type of study (e.g., randomised controlled trials (RCTs), non-randomised studies of exposures (NRSE) or interventions (NRSI)). The most common implementation of this method to date has been in the form of *qualitative triangulation* - that is the identification and narrative comparison of diverse evidence sources with respect to their underlying bias structures.[109]

However, qualitative triangulation faces issues at scale. There is a need to include all evidence to avoid potential confirmation bias,[344] yet as the number of evidence sources increases, it is not possible to narratively compare and contrast across multiple results in any meaningful way. This fact is illustrated by previous exemplars of triangulation only considering a small number of individual results.[109,345] To overcome this limitation, some attempts have considered the output of a meta-analysis of similarly designed studies to be a single source of evidence, and have assessed bias in relation to this summary result. While this approach keeps the number of individual sources of evidence manageable, it loses useful information on the specific biases inherent to each result contributing to the summary estimate. For example, while it may be true that all non-randomised studies share some minimal level of bias, competing extents and directions of bias in individual results may be masked by the use of summary estimates. In addition, previous attempts at qualitative triangulation have not systematically assessed the indirectness of the results, namely the differences between the question of interest and the question addressed by a study.

Taken together, these limitations to qualitative triangulation detail a need for a more systematic way to integrate across multiple evidence sources as the number of individual results contributing to the exercise increases. One such approach is *quantitative triangulation*, where results from different evidence sources are combined numerically while accounting for the key sources of bias and indirectness in each. This chapter, in addition to providing a narrative comparison of the existing and new evidence identified by this thesis, builds on recent developments in risk-of-bias assessment and methods for bias-/indirectness-adjusted meta-analysis to propose a generalised framework for quantitative triangulation. The framework, along with the methodological challenges to its implementation, is illustrated via two case studies examining the causal effect of lipids on dementia outcomes.

7.2 Data sources

The triangulation exercises presented in this chapter draw on the research produced in each of the preceding chapters. More specifically, this chapter builds on the comprehensive systematic review of existing evidence presented in Chapters 3 & 4. This evidence base is then supplemented by new evidence on the association of statin use with dementia outcomes in the CPRD (Chapter 5) and the association of lipids (namely, total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides (TG)) with dementia outcomes in previously unanalysed datasets accessed via the DPUK (Chapter 6).

Table 7.1 summarises the research question each data source has attempted to address, the exposures and outcomes considered in each case, and the contribution of each chapter to the triangulation exercise presented here.

Table 7.1: Summary of research designs included in this thesis -The research projects performed as part of this thesis and used as evidence sources in this triangulation exercise are summarised. Note that Chapter 2 is intentionally not included in this table, as it describes a research tool rather than a research study.

Chapter	Research Question	Exposure/ Intervention	Outcome	Contribution to evidence synthesis framework
Chapter 3/4	Based on the available evidence; (i) are lipid fractions associated with subsequent dementia risk, stratified by subtype? (ii) Are lipid regulating agents associated with subsequent dementia risk, stratified by subtype?	Lipids (HDL-c, LDL-c, TC, TG), Lipid regulating agents (statins, ezetimibe, fibrates, etc.)	Dementia, stratified by subtype	Provides overview of existing evidence, including detailed risk-of-bias assessments for each result
Chapter 5	Are lipid regulating agents associated with dementia risk in a large scale electronic health record database?	Seven classes of lipid regulating agents	Dementia, stratified by subtype	Provides additional observational data on vascular dementia (under-represented in the literature) Provides a source of observational evidence created using a method with distinct sources of bias to those identified by the systematic review
Chapter 6	Are lipid levels associated with dementia risk in previously unanalysed prospective cohort studies?	Lipids (HDL-c, LDL-c, TC, TG)	All-cause dementia VaD	Provides additional evidence from unanalysed datasets Provides additional observational data on vascular dementia (under-represented in the literature)

Additionally, both the qualitative and quantitative triangulation exercises used the detailed risk-of-bias assessments performed and presented as part of the systematic review (Chapters 3 & 4). Similarly, risk-of-bias assessments were performed for each new source of evidence presented in this thesis. The risk of bias tools used to assess each result are described in detail in Section 3.2.8, but in summary, randomised controlled trials (RCTs) were assessed using the RoB 2 tool;[162] non-randomised studies of interventions (NRSI) using the ROBINS-I tool;[159] non-randomised studies of exposures (NRSE) using an early adapted version of the ROBINS-E tool (see Section 3.2.8);[163,164] and Mendelian randomisation (MR) studies using the Mamluk et al. tool.[166]

7.3 Qualitative (narrative) triangulation

As part of a qualitative triangulation of the new and existing evidence identified by this thesis, all information sources were initially grouped by outcome, and the findings from each source were narratively compared and contrasted. Potential reasons for heterogeneity between study designs were examined with specific reference to the risk-of-bias in each.

All-cause dementia

Analysis of lipid levels across both the systematic review (Chapters 3 & 4) and the individual participant data (IPD) analysis (Chapter 6) found extremely weak evidence for an association of any lipid fraction with all-cause dementia (in the systematic review: TC - HR: 0.97, 95%CI: 0.88-1.07; LDL - HR: 0.97, 95%CI: 0.86-1.08; HDL - HR: 1.05, 95%CI: 0.96-1.14; TG - HR: 0.90, 95%CI: 0.74-1.09). Similarly, meta-analysis of studies identified by the review which examined a binary hypercholesterolemia provided weak evidence for an association of this risk factor with Alzheimer's disease (HR: 1.11, 95%CI: 0.97-1.27). Finally, a meta-analysis of RCTs of statin use (OR: 1.07, 95%CI: 0.70-1.66) and of MR analyses of genetic instruments that mimic statin use (RR: 0.90, 95%CI: 0.29-2.81) found weak evidence of an association, providing indirect evidence on the effect of lipid lowering on this outcome.

In contrast, the meta-analysis of statin use found a slight protective effect for the all-cause dementia outcome (HR: 0.75, 95%CI: 0.67-0.84), although many of the studies in this analysis were found to be at risk of immortal time bias, which would be expected to favour the statin use. Finally, analysis of the association of statin use with all-cause dementia in the CPRD (Chapter 5) found evidence of a harmful association (HR:1.16, 95%CI:1.14-1.19). However, this finding is likely to be driven by the substantial confounding by indication identified in the vascular dementia subgroup.

For fibrates, an alternative lipid-regulating agent, there was some evidence of an increased risk of all-cause dementia in the CPRD (HR:1.28, 95%CI:1.08-1.52), though this was not consistent in the meta-analysis of previous studies examining the association of fibrates and all-cause dementia (HR: 0.89, 95%CI: 0.75-1.07).

Alzheimer's disease

Meta-analysis of lipid levels in the systematic review found extremely weak evidence for an association of any lipid fraction with Alzheimer's disease (in the systematic review: TC - HR: 1.01, 95%CI: 0.94-1.09; LDL - HR: 1.06, 95%CI: 0.98-1.16; HDL - HR: 0.99, 95%CI: 0.91-1.07; TG - HR: 1.00, 95%CI: 0.84-1.18). Similarly, meta-analysis of studies examining a binary hypercholesterolemia provided weak evidence for an association of this risk factor with Alzheimer's disease (HR: 0.89, 95%CI: 0.70-1.12). A meta-analysis of MR analyses of genetic instruments that mimic statin use found weak evidence for an association of lipid lowering with Alzheimer's disease (RR: 0.76, 95%CI: 0.51-1.14).

In contrast, the meta-analysis of statin use found a slight protective effect on this outcome (HR: 0.78, 95%CI: 0.66-0.93), though similar to the all-cause dementia outcome, many of the studies in this analysis were found to be at risk of immortal time bias. However, the CPRD analysis, which attempted to account for this potential bias through the use of time-varying treatment indicator, found weak evidence for an effect (HR:0.98, 95%CI:0.94-1.01). The validity of this finding was limited by the potential for differential misclassification on the basis of the exposure in the CPRD analysis.

Finally, only one of the three cohorts included in the IPD analysis (Whitehall II) contained data on Alzheimer's disease. However, a previously published analysis (Tynkkynen *et al.*[246]) examining the association of lipid levels with Alzheimer's disease in this cohort was identified by the systematic review. The results of this previous analysis are incorporated into the results of the meta-analysis reported above, and so the IPD analysis provided no new information on this outcome.

Vascular dementia

There was a general absence of existing evidence on vascular dementia outcomes. Meta-analysis of published results was only possible for the total cholesterol lipid fraction (HR: 1.05, 95%CI: 0.79-1.41). A meta-analysis of studies examining hypercholesterolemia also found weak evidence for an association with vascular dementia (HR: 1.20, 95%CI: 1.00-1.44). Similarly, a meta-analysis of statin use found weak evidence for an effect on this outcome (HR: 0.99, 95%CI: 0.79-1.25). The CPRD analysis found evidence for a harmful association of statin use (HR:1.81, 95%CI:1.73-1.9), though this finding is likely to be the result of severe confounding by indication related to vascular factors, as identified through the use of control outcomes.

The IPD analysis provided supporting evidence for the absence of an effect of any fraction on vascular dementia, with the sole exception of triglycerides. Raised triglycerides were associated with an increased incidence of vascular dementia across two previously unanalysed cohorts (OR: 1.25, 95%CI: 1.01-1.54), although there is the potential for uncontrolled confounding due to the limited information available on important covariates. With respect to evidence on treatments for hypertriglyceridemia, examination of fibrates in the CPRD provided weak evidence of an association with vascular dementia (HR:1.29, 95%CI:0.83-2.02).

7.4 Quantitative triangulation

The qualitative comparison presented above identified no consistent effect of any lipid fraction on any dementia outcome across the evidence sources presented in this thesis. However, it is clear that this qualitative approach faces difficulties in interpretation when the number of individual results available is large, as discussed in the introduction to this chapter. This is true even when using summary estimates from meta-analyses of primary studies, which sacrifice valuable information on the biases inherent to each individual result.

In the following section, I propose and apply a novel quantitative triangulation framework to address these limitations. This approach incorporates recent advancements in the way that bias in results is assessed (namely the move to domain-based assessment tools)[162] and existing methods for bias-/indirectness-adjusted meta-analysis[346] to integrate the numerical results of the multiple approaches. Despite the absence of any clear signals across the evidence base, as detailed in the previous section, I have used the evidence identified and produced by this thesis to illustrate the novel methodological approach.

7.4.1 Methods

The proposed framework involves the following steps:

1. Define the causal question of interest
2. Identify relevant evidence sources and standardise effect directions
3. Specify an idealised version of each study
4. Assess the extent and direction of bias/indirectness in each result
5. Define modifying terms for bias and indirectness in each result
6. Calculate bias-/indirectness-adjusted results and perform meta-analysis

Each step is described in comprehensive detail in the sections below. To better illustrate the bias-/indirectness adjustment process detailed in the subsequent sections, the process for calculating the adjusted estimate is described in detail for a single result. Following this, the framework is then applied to two case studies.

Definition of the causal questions of interest (case-studies)

Using the ROBINS-E framework,[163] I defined the parameters of my causal questions of interest:

Case study #1: Effect of mid-life LDL-c on Alzheimer's disease

- *Population of interest*: General population
- *Exposure of interest*: Low density lipoprotein cholesterol
- *Exposure window of interest*: Mid-life (45-60)
- *Summary measure of exposure over time*: Average exposure
- *Outcome of interest:* Alzheimer's disease

Case study #2: Effect of mid-life triglycerides on vascular dementia

- *Population of interest*: General population
- *Exposure of interest*: Triglycerides
- *Exposure window of interest*: Mid-life (45-60)
- *Summary measure of exposure over time*: Average exposure

- *Outcome of interest:* Vascular dementia

These causal questions were chosen for several reasons. Firstly, the work presented in the previous chapters had identified some evidence for an association in these exposure/outcome pairs. Secondly, given the long prodromal period between the onset of physiological changes in the brain and presentation of dementia symptoms, it seems likely that conditions during the mid-life period are particularly important. Finally, examining the causal impact of a lipid fraction on a specific outcome (e.g., Alzheimer's disease), rather than a composite outcome (e.g., all-cause dementia), focuses on a single causal pathway rather than including several conditions in the outcome definition that likely have very different mechanisms of disease. In addition, previous work presented in this thesis illustrated that the component conditions (in this case Alzheimer's disease and vascular dementia) are likely to be subject to very different confounding structures (see Section 5.4.2), and the use of a composite all-cause outcome in the triangulation framework may mask this.

Identify relevant results

Once the causal question of interest had been defined, relevant individual results were obtained from the data sources described in Section 7.2. In a broad sense, this meant extracting results that examined the relationship between the exposure/outcome pair, either directly (e.g., non-randomised studies of LDL-c levels) or indirectly (e.g., non-randomised studies of statins, or MR studies using genetic instruments for LDL-c levels).

Effects were standardised to refer to the risk resulting from a "reduction" in the lipid fraction. For both non-randomised studies and Mendelian randomisation analysis of lipid levels, the association is usually reported in terms of an increase in the lipid fraction. In this case, the effect estimates were inverted to ensure consistency across study designs.

Specify idealised version of each study

Once the set of relevant results have been identified, an idealised study for each should be described. An idealised study can be viewed as a replicate of the study producing the result of interest but with all sources of bias removed. The risk of bias is then assessed against this idealised study, while the causal question addressed by each idealised study is compared with the target causal question to define the indirectness of each result.

Note that all of the risk-of-bias tools used to assess non-randomised studies required specification of an idealised version of the study, against which bias was assessed. If using a risk-of-bias assessment tool that does not require this step, the idealised version of the study should be defined in advance of risk-of-bias assessment.

Assess risk and direction of bias in each result

The assessment of bias in each result is discussed in Section 7.2 above. For the sake of consistency and ease of computing, I mapped the different acceptable risk-of-bias judgements in each tool to a harmonised set: “Low”, “Moderate”, and “High”. The exact mapping can be seen in Table 7.2. Of note, no mapping was performed for the critical risk-of-bias levels present in the tools for non-randomised studies. This is in accordance with current best practice in evidence synthesis, which is to exclude all studies at critical risk of bias from further quantitative synthesis.[159]

Table 7.2: Mapping of risk-of-bias judgements across assessment tools - The different acceptable levels of bias across the risk-of-bias assessment tools used were mapped to a harmonised set. Note that no mapping for "Critical" risk of bias was performed, as best practice recommends that studies at critical risk of bias are excluded from quantitative syntheses.

Harmonised	RoB2	ROBINS-I / ROBINS-E	MR
Low	Low	Low	Low
Moderate	Some concerns	Moderate	Moderate
High	High	Serious	High
-	-	Critical	-

In addition to assessing the extent of bias, as defined by the three levels detailed above, I recorded the predicted direction and type of bias in each domain. This was achieved via an additional question at the end of each bias domain, which asked assessors to predict the expected direction of bias in that domain. Note that this question is currently only formally included in two existing tools (ROB2/ROBINS-I), but I employed an identical approach during assessment of non-randomised studies of exposure and Mendelian randomisation studies. Acceptable responses to this question included:

- "Favours experimental"/"Favours comparator" (defines an additive bias)
- "Towards null"/"Away from null" (defines a proportional bias)
- "Unpredictable"

As indicated in the options above, the response to this question is also used to determine the predicted type of bias as either additive or proportional. Proportional biases are dependent on the magnitude of the effect, while additive biases are not.[346]

For additive biases, determining the absolute direction of bias was simply a case of whether the bias is expected to shift the effect estimate to the left or right on an imaginary forest plot. For example, the estimate would be shifted to the right if a bias was predicted to favour the comparator (Figure 7.1).

In contrast, for proportional biases, whether the estimate should be increased or decreased proportionally depends on the current position of the point estimate relative to the null. For example, if the effect estimate represents a protective effect (below the null), then bias towards the null would be adjusted for by moving the effect estimate proportionally to the right. In contrast, if the effect of the intervention is harmful (effect estimate above the null), bias towards the null would be adjusted for by moving the effect estimate proportionally to the left. Both scenarios are illustrated using example data in Figure 7.1.

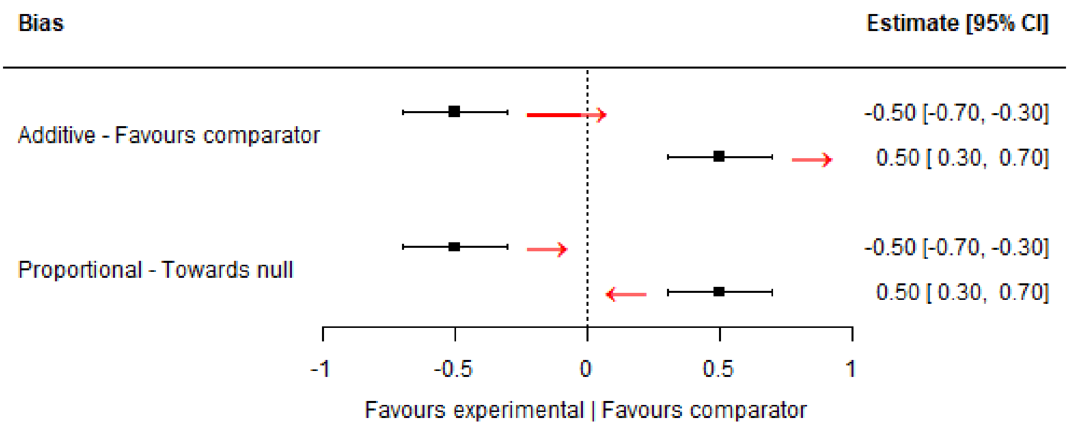

Figure 7.1: Calculating the absolute direction of biases, based on bias type - For additive biases, the direction is consistent regardless of the position of the effect estimate relative to the null - bias "favouring the comparator" will always pull the effect estimate to the right and can induce a change from a protective to harmful effect. In contrast, the position of the effect estimate is accounted for when determining the absolute direction of proportional biases, defined as towards or away from the null.

The predicted direction and type of bias was not recorded for domains at "Low" risk of bias. Finally, for some domains, only one type of bias is allowed. For example, in the confounding domains in the ROBINS-I/ROBINS-E tools, only the "Favours experimental"/"Favours comparator" and "Unpredictable" options are available, meaning that bias in this domain will always be considered additive.

Visualisation of extent and direction of bias

To aid with the quantitative triangulation exercise, I created a new method to visualise the extent, direction and type of bias in each result, enabling detailed comparison across different studies contributing to a synthesis. Similar to the standard paired forest plots introduced in Chapter 3, these "bias direction" plots show the level (or extent) of bias across the domains for each result reported using coloured blocks. However, in contrast to the previous forest plots, symbols are used to illustrate the predicted absolute direction of bias in that domain. Distinct symbol pairs are used to denote additive and proportional biases. Illustrations of these are provided in the Section 7.4.2.

Assign modifying values to risk/direction of bias

Following definition of the extent, type and direction of bias in each domain, I assigned a prior distribution on the log scale to each combination. For example, a "high" additive bias in jth domain of the ith study is defined as $\delta_{i,j}^{\text{High}}$ and uncertainty around this estimate is given by a distribution with mean μ and variance σ^2:

$$\delta_{i,j}^{\text{High}} = f(\mu_{i,j}^{\text{High}}, {\sigma_{i,j}^{\text{High}}}^2) \tag{7.1}$$

The sign of $\mu_{i,j}^{\text{High}}$ is defined by the absolute direction of the bias. If the bias is expected to pull the effect to the left, $\mu_{i,j}^{\text{High}}$ is given a negative sign, and if it is expected to pull the effect to the right, it is given a positive sign.

One key feature of the domain-based risk-of-bias tools is that the domains are considered interchangeable - i.e., a "high" judgement in one domain is equivalent to a "high" judgement in any other. As such, for this analysis, I assumed that the distributions assigned to each extent of bias were identical across all values of j, that is, were identical for all domains in the risk-of-bias assessment tool. To illustrate for additive biases:

$$\delta_{i,1}^{\text{High}} = \delta_{i,2}^{\text{High}} = ... = \delta_{i,j}^{\text{High}}$$

and similarly

$$\delta_{i,1}^{\text{Moderate}} = \delta_{i,2}^{\text{Moderate}} = ... = \delta_{i,j}^{\text{Moderate}}$$

Reasonable values for the position and spread of the prior distributions were informed by a previously reported expert bias elicitation exercise.[346] Using open data from that study, I calculated the average values for the mean and variance of the adjustment distributions across all biases considered by that exercise (see Appendix A.7.1 for more details on how these were calculated). For the purposes of this illustrative analysis and to highlight the generalised nature of the code used to perform the analysis (see Section 7.5.5), I used the calculated values to inform two scenarios of modifying distributions (Table 7.3) for additive biases, and a single set for proportional biases. In the first scenario, the relationship between the position assigned to each additive bias judgement is linear. In the second scenario, the step from "Moderate" to "High" is twice that from "Low" to "Moderate". Across both additive and proportional biases, the variance of the "High" judgement distribution was defined to be greater than that of the "Moderate" judgement.

Table 7.3: Prior distributions mapped to different extents of bias - Prior values assigned to additive and proportional biases, defined as log-normal distributions with mean μ and variance σ^2 using the notation $N(\mu, \sigma^2)$. For additive biases, two scenarios were defined (see main text). Note that proportional biases are defined on the log scale for ease of calculation but are exponentiated prior to their use for adjustment (see Equations (7.2) & (7.3) below).

Bias Level	**Additive bias**		**Proportional bias**
	Scenario 1	**Scenario 2**	
Low	-	-	-
Moderate	N(.09, .05)	N(.09, .05)	N(.03, .016)
High	N(.18, .1)	N(.27, .1)	N(.06, .032)

Where the direction of bias in a domain was unpredictable for a given result, the mean of the prior distribution for that domain was set to 0 but the appropriate variance for the recorded extent of bias was retained (e.g., for an unpredictable "High" additive bias, the distribution would be $N(0, 0.1)$ under Scenario 1). In other words, adjusting for bias in a domain with an unpredictable direction of bias has no impact on the position of the effect estimate but does increase the uncertainty around it.

Under the method reported in Turner *et al.*,[346], total additive bias (denoted using subscript δ) in result i is then described by mean $\mu_{i\delta}$ and variance $\sigma^2_{i\delta}$, which are simply the sum of the mean and variance of all additive biases in the ith result. Similarly, the total proportional bias (denoted using subscript β) in the ith result is described by mean $\mu_{i\beta}$ and variance ${\sigma_{i\beta}}^2$. This are defined as

$$\mu_{i\beta} = exp(\alpha_i + {\psi_i}^2) \tag{7.2}$$

$${\sigma_{i\beta}}^2 = \Big\{exp({\psi_i}^2) - 1\Big\}exp(2\alpha_i + {\psi_i}^2) \tag{7.3}$$

where α_i and ${\psi_i}^2$ are the sum of mean and variance values for all proportional biases in the ith result.

Note that the total additive bias is maintained on the log scale, while the total proportional bias has been exponentiated.

Assessing and assigning prior values to indirectness

The indirectness of a result (also termed external bias, external validity, relevance, generalisability, or applicability) is defined here as the discrepancy between the research question addressed by the "idealised" study and the causal question of interest.

An identical approach was employed to assess, and assign prior distributions to, the indirectness in each result. The target question for each result was compared against the causal question of interest with respect to three domains, defined as important by the GRADE framework for assessing the certainty of evidence:[347] population, intervention/exposure, and outcome. I again used the scale of “Low/”Moderate“/”High" to quantify the extent of indirectness in each domain. All indirectness was defined *a priori* as being proportional in nature (i.e. depending on the magnitude of the effect), in line with previous work on this topic.[346,348] As above, data from the previous elicitation exercise were used to inform reasonable prior distributions for each level of indirectness (Table 7.4).

Table 7.4: Prior distributions mapped to different extents of indirectness - Prior values assigned to proportional indirectness, defined as log-normal distributions with mean μ and variance σ^2 using the notation $N(\mu, \sigma^2)$. Note that all indirectness in this analysis was defined *a priori* to be proportional, and so no distributions for additive indirectness were defined.

Bias Level	Proportional bias
Low	-
Moderate	N(.06, .016)
High	N(.12, .032)

As an illustrative example, consider the first causal question of the interest in this exercise, the effect of LDL-c in mid-life on Alzheimer’s disease. Here, studies of lipid levels in this time period would require minimal adjustment, whereas studies examining statin use (indirect exposure/intervention) in late-life (indirect population) would be adjusted and down-weighted due to reduced relevance to the causal question.

Once the extent and direction of indirectness has been assessed, total proportional indirectness is then calculated in the same manner as total proportional bias (see Equations (7.2) & (7.3)).

Combining in a bias-/indirectness-adjusted meta-analysis

Using the method reported in Turner *et al.*,[346] once total additive and proportional bias and indirectness are calculated, they are used to define an adjusted estimate for each result included in the synthesis.

The adjusted estimate for result i, $\hat{\theta}_i$, is defined as:

$$\hat{\theta}_i = \frac{y_i - \mu^{\mathrm{In}}_{i\beta}\mu^{\mathrm{In}}_{i\delta} - \mu^{\mathrm{B}}_{i\delta}}{\mu^{\mathrm{B}}_{i\beta}\mu^{\mathrm{In}}_{i\beta}} \tag{7.4}$$

where $\mu^{\mathrm{B}}_{i\delta}$ and $\mu^{\mathrm{B}}_{i\beta}$ refer to the total additive and proportional bias, and $\mu^{\mathrm{In}}_{i\delta}$ and $\mu^{\mathrm{In}}_{i\beta}$ refer to the total additive and proportional indirectness, respectively. Note that in this exercise, the total additive indirectness $\mu^{\mathrm{In}}_{i\beta} = 1$ because all indirectness was defined *a priori* as being proportional.

The standard error of this estimate ($\mathrm{SE}(\hat{\theta})$) is then calculated as:

$$\mathrm{SE}(\hat{\theta}) = \left(\frac{1}{\mu^{\mathrm{B}}_{i\beta}\mu^{\mathrm{In}}_{i\beta}}\right)^2 \left(s_i^2 + \left(\mu^{\mathrm{B}}_{i\beta}2 + \sigma^{\mathrm{B}}_{i\beta}\right)\left(\hat{\theta}^2\sigma^{\mathrm{In}2}_{i\beta} + \sigma^{\mathrm{In}2}_{i\delta}\right) + \sigma^{\mathrm{B}}_{i\beta}\left(\hat{\theta}\mu^{\mathrm{In}}_{i\beta} + \mu^{\mathrm{In}}_{i\delta}\right)^2 + \sigma^{\mathrm{B}2}_{i\delta}\right) \tag{7.5}$$

Once each individual result had been adjusted using this approach, I performed a random effects meta-analysis using the unadjusted and adjusted results. I also compared the adjusted results under the two scenarios of additive bias. I extracted the overall effect estimates, along with measures of heterogeneity in each case (τ^2, I^2).[259,349]

7.4.2 Results

Single study

As an illustrative example of the process using a single result, the bias and indirectness inherent to the estimate of the effect of statin use on Alzheimer's disease in the CPRD (as analysed in Chapter 5) are considered here. For this result, there were three domains at greater than low risk of bias: bias due to confounding, bias due to definition of the outcome, and bias in the selection of the reported result (Figure 7.2). In Domain 1 (bias due to confounding), the study did not adjust for *Apo$\mathcal{E}$* status, which is predicted to mask any true association between statins and Alzheimer's disease (see Section 5.4.3 for a fuller discussion). As such, the bias is predicted to *favour the comparator* and so the absolute direction of bias is to the right. In Domain 6 (bias in measurement of the outcome), there was a high risk of differential misclassification on the basis of the exposure. Here, a history of statin use may make a diagnosis of vascular dementia more likely than Alzheimer's disease, and so for this outcome, this bias is predicted to *favour the experimental* (in this case, an intervention). As such, the absolute direction of bias is to the left. In Domain 7 (bias in selection of the reported result), for consistency with the other NRSI, in the absence of a protocol the bias is assumed to be *away from the null*. Given the position of the effect estimate below the null, the absolute direction of bias in this domain is to the left.

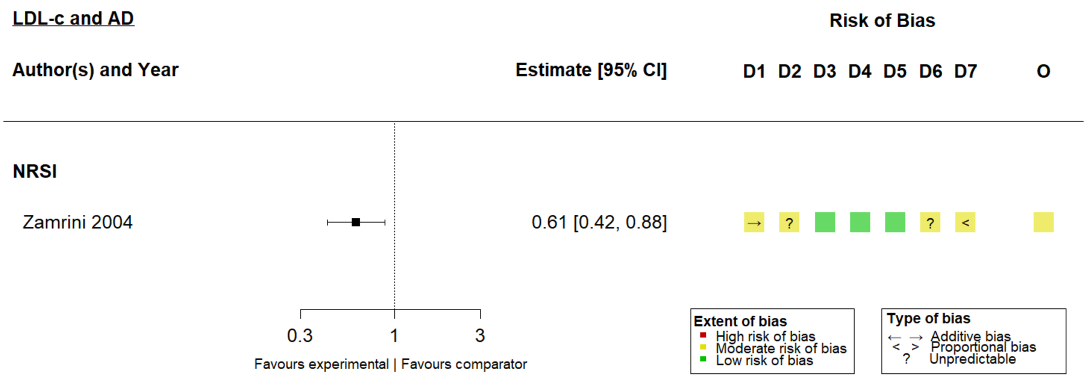

Figure 7.2: Bias direction plot for a single study - Summary of result and the predicted direction of bias in each domain of bias for the effect of statin use on Alzheimer's dementia, as estimated in Chapter 5. Additive biases are characterised using arrows, while the proportional biases are denoted using $<$ and $>$. A question mark indicates that the direction of bias was unpredictable.

Indirectness was intentionally not displayed in the plot above because these figures are created using `robvis` which is focused on creating visualisations of risk-of-bias data. In addition, I found it more useful to articulate the indirectness of a result in tabular format. With respect to this example result, I judged it to be at low risk in the population and outcome domains (Table 7.5). However, the result refers to the effect of statins on Alzheimer's disease risk, rather than LDL-c levels directly, putting it at high risk of indirectness in the intervention/exposure domain.

Overall, assessing the predicted direction of indirectness was more challenging than assessing the predicted direction of bias. In this case, treatment with statins may result in temporary lowering of lipid levels which could thus underestimate the true effect of LDL-c lowering (indirectness towards the null). In contrast, statins may have an effect on Alzheimer's disease through a mechanism other than their LDL-c lowering effect and so the effect may be overestimated (indirectness away from null). As such, I judged the direction of indirectness in this domain to be unpredictable.

Table 7.5: Assessment of indirectness for a single example study - The target setting for the causal question of interest (effect of midlife LDL-c on Alzheimer's disease) and the idealised version of a single example study are compared. The risk and predicted direction of indirectness resulting from discrepancies between the target setting and idealised study are shown.

Domain	**Target setting**	**Idealised version of single study**	**Level**	**Direction**
Population	General population, dementia free at baseline	UK general population, >45 years of age, dementia free at baseline	Low	-
Intervention/ exposure	Average low density lipoprotein cholesterol levels at midlife (45-60)	Initiation of statin use	High	Unpredictable
Outcome	Alzhiemer's disease, assessed using recognised clinical criteria	Alzheimer's disease cases extracted from EHR	Low	-

The unadjusted estimate of the effect of LDL-c on Alzheimer's disease was 0.61 (95%CI: 0.42-0.88). After accounting for the biases and indirectness described, the adjusted result was 0.57 (95%CI: 0.25-1.31), representing a minimal shift in the position of the effect estimate but a substantial decrease in precision.

Case study #1: effect of LDL-c at midlife on Alzheimer's disease

From the data sources identified in Section 7.2, I identified 21 results relevant to my first causal question of interest. Most (N = 20) were identified via the systematic review,[54,72,74,190–192,197,201,202,205,206,211,213,214,219,220,246,249,254] while Chapter 5 provided an additional estimate via the CPRD analysis. The extent, type and direction of predicted bias for each result can be seen in the bias-direction plot presented in Figure 7.3, stratified by study design.

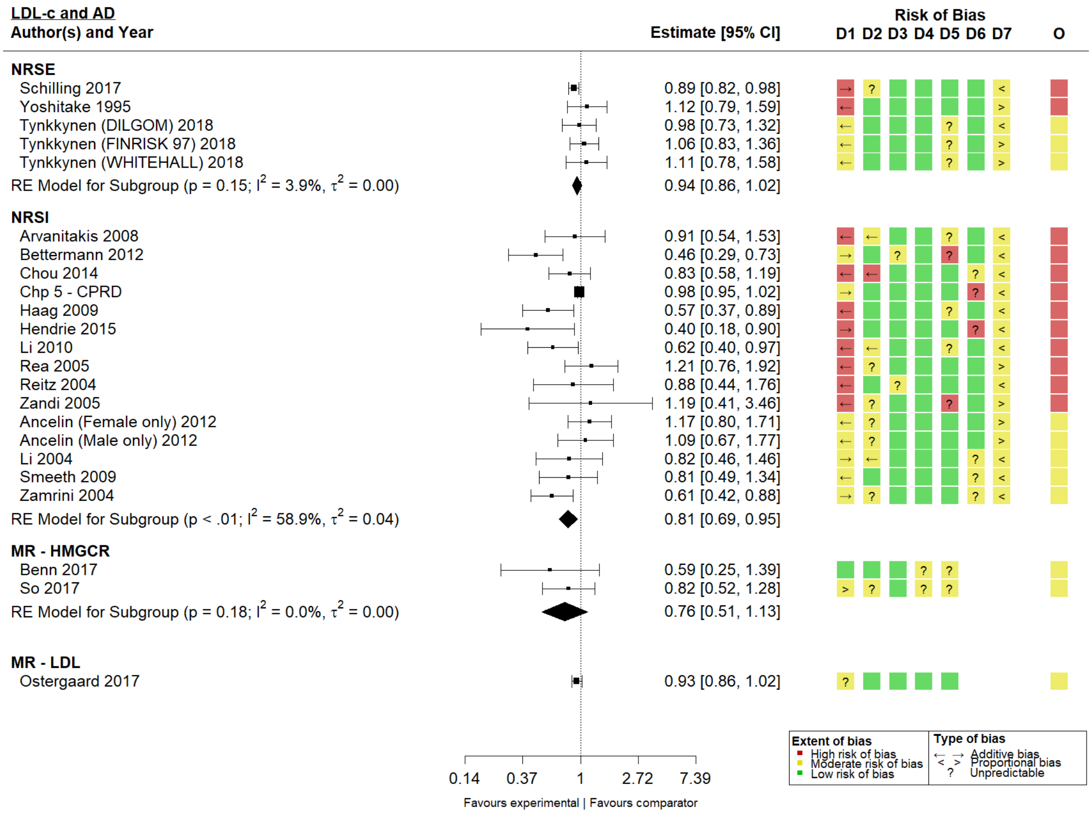

Figure 7.3: Bias direction plot for LDL-c/Alzheimer's disease - Summary of the unadjusted results and internal biases related to effect of LDL-c on Alzheimer's disease, stratified by study design.

The results of the unadjusted and the bias-/indirectness-adjusted (under Scenario 1) are shown in Figure 7.4. Following adjustment for bias and indirectness, the observed effect attenuates to the null (unadjusted 0.90, 95%CI: 0.83-0.97; adjusted 0.94, 95%CI: 0.86-1.02). Additionally, adjustment for bias and indirectness substantially reduced the heterogeneity between studies (unadjusted $\tau^2 = 0.0099$, $I^2 = 50\%$; adjusted $\tau^2 = 0$, $I^2 = 0\%$). However, as can been seen from the right panel in

Figure 7.4, this reduction in heterogeneity between studies is largely achieved via a reduction in the precision of each individual result.

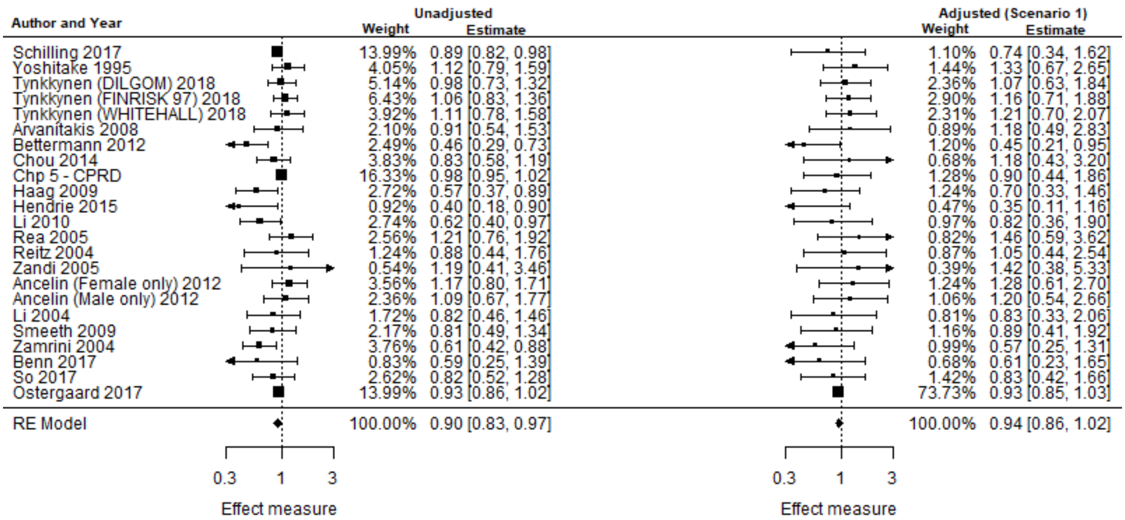

Figure 7.4: Bias-/indirectness-adjusted meta-analysis of midlife LDL-c on Alzheimer's disease - Random-effects meta-analysis of the association of midlife LDL-c with Alzheimer's disease, using unadjusted and bias-/indirectness-adjusted results. Note the substantial decrease in the weight assigned to the result of the CPRD analysis between the two plots, which is due to the high levels of bias/indirectness in this result as described in the above sections.

No substantial differences were observed between the summary estimates obtained under the two scenarios of additive bias (Appendix A.7).

Case study #2: effect of triglycerides at midlife on vascular dementia

From the data sources identified in Section 7.2, I identified 7 results relevant to the causal effect of triglycerides at midlife on vascular dementia. Four were identified via the systematic review,[226,238,249] while Chapter 5 provided two additional estimates from unanalysed datasets (CaPS and Whitehall II), and Chapter 6 provides an estimate for the effect of fibrates, a treatment for hypertriglyceridemia. The extent, type and direction of predicted bias for each result can be seen in the bias-direction plot presented in Figure 7.5, stratified by study design.

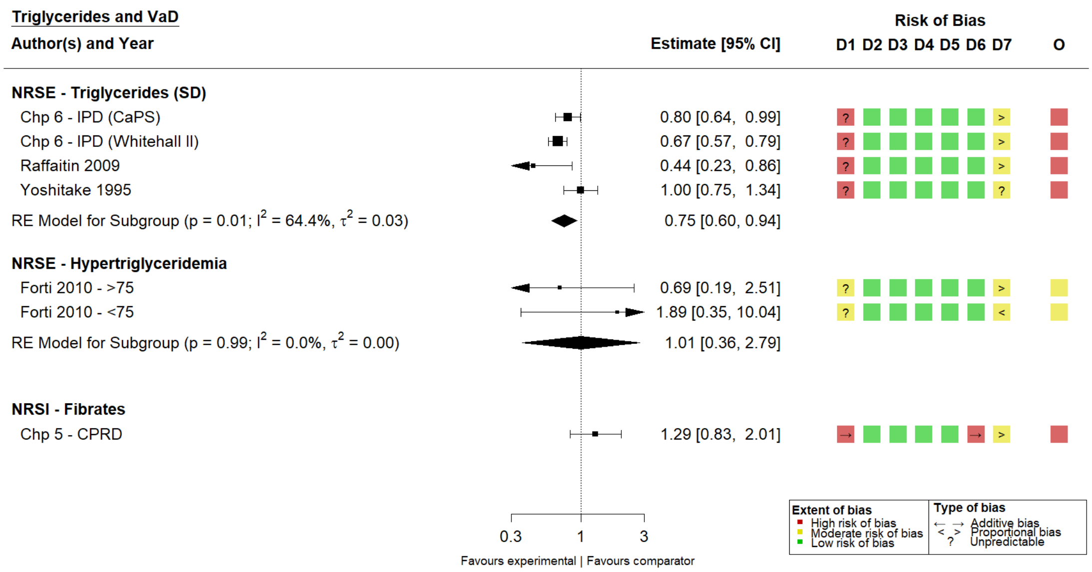

Figure 7.5: Bias direction plot for triglycerides/vascular dementia - Summary of the unadjusted results and internal biases related to effect of triglycerides on vascular dementia, stratified by study design.

Comparison of the unadjusted and bias-/indirectness-adjusted results for the effect of triglycerides on vascular dementia did not demonstrate a substantial difference (unadjusted 0.82, 95%CI: 0.64-1.05; adjusted 0.79, 95%CI: 0.58-1.07; Figure 7.6), though again, heterogeneity between the adjusted results was greatly reduced (unadjusted $\tau^2 = 0.054$, $I^2 = 65\%$; adjusted $\tau^2 = 0$, $I^2 = 0\%$). Similarly there was minimal difference between the results under the two scenarios of bias (Figure A.6 in Appendix A.7).

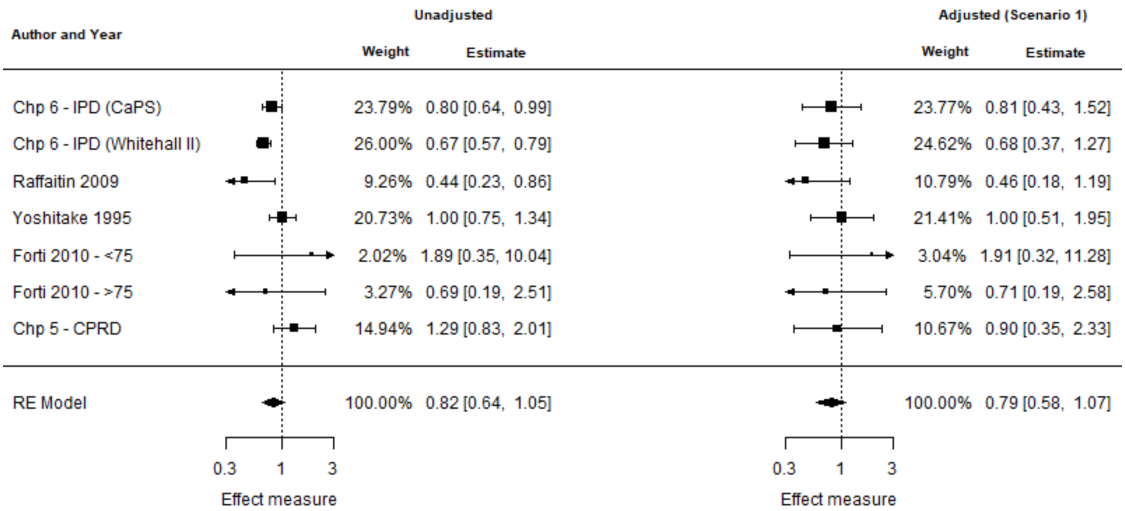

Figure 7.6: Bias-/indirectness-adjusted meta-analysis of midlife triglycerides on vascular dementia - Random effects meta-analysis of the association of midlife triglycerides and vascular dementia, using unadjusted and bias-/indirectness-adjusted (Scenario 1) results.

7.5 Discussion

7.5.1 Summary of findings

This chapter has narratively synthesised the evidence identified and produced by the previous chapters, highlighting the absence of any consistent association between various blood lipid fractions and any dementia outcome.

In addition, it has developed a generalised framework for quantitative triangulation, building on existing methods for systematic domain-based risk of bias assessment and bias-/indirectness-adjusted meta-analysis. To illustrate the method, I considered two causal questions: the effect of LDL-c at mid-life with Alzheimer's disease and the effect of triglycerides on vascular dementia. In the quantitative triangulation framework, there was weak evidence for an effect in relation to either of the causal questions considered. The heterogeneity between results produced by different study designs contributing to the analysis was substantially reduced using this method, though this was largely due to a reduction in the precision of each individual result.

7.5.2 Limitations

The quantitative analysis presented in this chapter is subject to some strong methodological limitations, which are discussed in detail below.

Defining reasonable prior distributions for bias and indirectness

The key limitation of the quantitative synthesis presented in this chapter is the lack of empirical evidence available for the prior distributions of bias and indirectness. While I attempted to address this by informing the prior distributions using data from a previous expert elicitation exercise, the extent of bias/indirectness in that analysis may not generalise to the one presented here.

Ideally, these prior distributions would be based on empirical data on the effect of different domains of bias/indirectness on a result. Most meta-epidemiological studies examining the effect of different methodological issues studied only randomised controlled trials,[350,351] and the estimates of bias they produce may not hold for non-randomised study designs. However, the prior distributions defined here are broadly comparable to previously reported estimates of the impact of bias in non-randomised trials. For example, a previous simulation study estimated that, in the absence of a true effect of LDL-c, *Apo$\mathcal{E}$4* would induce a risk ratio of 1.09 with risk of dementia per 1-SD increase in LDL-c.[352] This is comparable to the mean assigned to the prior log-normal distribution mapped to "Moderate" additive bias ($N(0.09, 0.05)$, Table 7.3).

A further limitation is the assumption that the distributions of bias are identical across domains of bias. Previous evidence from meta-epidemiological studies of randomised controlled trials that investigated the effects of different biases indicates that this is unlikely to be the case.[353] The generalised framework for quantitative triangulation, presented here and available via the `triangulate` package (see Section 7.5.5), allows for domain-specific distributions of bias/indirectness. As more information on the effect of specific sources of bias becomes available, such domain-specific distributions should be used.

Finally, for the "bias due to confounding" domain, it may in fact be more reasonable to adjust on a per-confounder basis rather than mapping to a "Moderate" or "High" extent of bias. In this approach, prior distributions are assigned to each of the confounders pre-specified as part of the ROBINS-I/ROBINS-E tools.[159] Then, rather than assigning a domain level distribution based on an arbitrary judgement of how many important confounders are missing, the result is adjusted for each confounder not accounted for in the original analysis.

Accuracy of bias-/indirectness-assessment

A key issue in this analysis is the accuracy of the assessment of bias and indirectness in each result. It has been widely demonstrated that the inter-rater agreement when using risk-of-bias tools is low with regards to the extent of bias assigned to each domain[354–356] Though not previously studied, given the difficulty in assessing the predicted direction of bias, agreement on this aspect of the tools is likely to be lower still.

A further issue in this regard is that the rigour of the tools may not be equivalent. This issue can be illustrated by the Ostergaard *et al.* study[72] having low risk of bias across all domains and thus receiving a substantial proportion of the weight in the first case study (Figure 7.4). While the RoB suite of tools (RoB 2.0, ROBINS-I, ROBINS-E) were developed by an expert working group and have been widely used, the Mamluk *et al.* tool[166] used to assess risk of bias in Mendelian randomisation studies was designed by the authors for use in their own review. If the Mamluk tool is failing to adequately assess bias in Mendelian randomisation studies, then any analysis based on its assessments is likely to be subject to bias. This observation is particularly problematic given the default position of the ROBINS-I and ROBINS-E tool to require a “Moderate” judgement in the confounding domain. Under these conditions, it is possible that a well-performed cohort study (low risk of bias across everything other that bias due to confounding) will be downweighted versus a potentially poor MR study.

Low and critical risk of bias

As illustrated in Table 7.2, studies at critical risk of bias were not included in the analysis. While this is in line with best practice, there is theoretically no reason why studies with this extent of bias could not be included in the proposed framework. However, the estimation of an appropriate prior distribution for the effect of “Critical” bias would be substantially more challenging, and so was avoided here.

A related issue is the “Low” risk of bias judgement. In this analysis, I assumed that domains at “Low” risk of bias did not require any adjustment. However, “Low” risk of bias is not equivalent to the absence of bias, and potentially should still be adjusted for, if only minimally. In this case, defining the predicted direction of bias would be particularly challenging in the absence of obvious sources of bias.

Combination of different effect measures

A final limitation of this analysis is the synthesis of different effect estimates. As discussed in Section 3.2.9, hazard ratios are not directly comparable to odds ratios because they inherently account for person time-at-risk.[169] Non-randomised studies (NRSI/NRSI) of dementia outcomes reported hazard ratios and Mendelian randomisation studies reported odds ratios, and as such the resulting synthesis may be biased by the integration of these two different effect measures. This is primarily a concern for common outcomes because the odds, risk and hazard ratios approximate each other when the outcome is rare.

In the case of common outcomes, an extra step may be needed in the framework to assesses whether it is reasonable to synthesis across different effect estimates.

7.5.3 Strengths

The core strength of this analysis is that it is based on a comprehensive systematic review, supplemented by two additional primary studies to fill in the identified evidence gaps. In general, triangulation of any sort should be considered a natural extension of evidence synthesis, and therefore should follow best practice in relation to finding and critically assessing all relevant information. Additionally, the approach presented here also builds on recent developments in bias assessment to “explode out” the component results of a meta-analysis and consider the effects of bias/indirectness in each separately.

A further advantage of this method comes from the ability to specify the prior distributions for each level of bias/indirectness in advance of performing the assessments. Expert elicitation of the extent of bias/indirectness using a panel of methodologists and topic experts is a powerful technique but the point at which it is deployed in the framework is important. In previous attempts at bias-/indirectness-adjusted meta-analysis, the extent of bias in each study was assessed via an elicitation process,[346,348,357] during which experts were aware of the results of each analysis. This approach is potentially subject to differential misclassification of the impact of bias/indirectness on the basis of the results because there is no way to ensure that results at a similar level of bias for confounding (for example) are being adjusted by the same amount across studies. As an illustrative example, if experts are influenced by the knowledge of the effect estimate in a study, then a result at “Moderate” risk of confounding and demonstrating a stronger protective effect may receive greater adjustment than a study at the same risk of confounding but with a more modest effect. This is likely to be particularly problematic where experts have preconceived ideas about the true effectiveness of the intervention.

Separating the assessment of bias/indirectness from the assignment of modifying values to each judgement will limit the potential for this misclassification. Using the framework proposed, reasonable modifying distributions for each level of bias can be defined *a priori* by the study team using the elicitation procedure detailed previously.[346] This approach would be similar to how important confounders and co-interventions are defined in advance when performing ROBINS-I/ROBINS-E assessments.[159] As an example, expert elicitation could be used to *a priori* define an additive bias distribution of N(0.1,0.7) for "Moderate" risk of bias in Domain 1 of the ROBINS-I tool (bias due to confounding). Risk-of-bias assessments would then be performed, and each result at "Moderate" risk of bias in Domain 1 is adjusted using this pre-specified distribution.

Finally, accounting for bias using an incorrect prior distribution is no less problematic than synthesising and drawing conclusions from effect estimates that are treated as unbiased, a common occurrence in systematic reviews.[185] While this analysis may be limited by the absence of empirically-derived adjustment distributions, it at the very least acknowledges the uncertainty of evidence due to bias/indirectness via a reduction in precision.

7.5.4 Future research

An obvious avenue for future work in relation to quantitative triangulation is the identification of empirical prior distributions for the effect of bias/indirectness in non-randomised studies using meta-epidemiological approaches. This will be substantially more challenging than examining the effect of bias in RCTs,[353] given the absence of an underlying database of meta-analysis of non-randomised studies.

Future development of this framework should also account for bias at the analysis level in terms of missing evidence.[168] For example, there is at least one known study relevant to the triglycerides/vascular dementia case study that reported a non-significant result but provided insufficient details to be included in the analysis.[224] Ideally, a quantitative triangulation framework would further account for this proportional meta-bias (seeing as bias due to missing evidence is most likely to bias away from the null due to publication bias mechanisms), in addition to result-specific biases.

Appreciation that both the risk-of-bias and indirectness of a result should be examined is growing. Indeed, some existing tools for the assessment of diagnostic test accuracy[358] and prediction models[359] consider indirectness (termed applicability in these tools) alongside the assessment of bias. Future iterations of the core risk-of-bias tools (RoB 2, ROBINS-I, ROBINS-E) could take this into account, though there is a competing argument that indirectness is already handled via tools such as the GRADE framework.[347] In addition, simple steps like harmonising the risk-of-bias judgements across tools and making the direction of bias question mandatory (even if users default to "Unpredictable") would represent an improvement in the tools and encourage users to think about how the biases assessed affect the corresponding result. Similarly, software that implements a risk-of-bias tool should allow for direction/extent of bias question and carefully consider how this data will be exported.

7.5.5 Outputs

There are two key outputs from this chapter. The first is an R package, `triangulate`, available at `https://github.com/mcguinlu/triangulate`. Personal communication with the authors of the bias-/indirectness-adjusted meta-analysis approach resulted in the STATA code to implement the adjusted model.[346] This has since been generalised as part of the `triangulate` R package to enable other users to apply the approach detailed here. The package allows for preprocessing of domain-based risk-of-bias data to correctly identify the direction of bias relative to the effect estimate, use of domain-specific prior distributions, production of bias direction plots (via the tool described in Appendix B.2), calculation of bias/indirectness-adjusted estimates for each result and synthesis of these adjusted results in a standard random-effects meta-analysis.

The second key output is an example dataset for the LDL-c/Alzheimer's disease causal question addressed in this chapter. Available via the `triangulate` package, this data will provide developers of new triangulation methods with an example dataset on which to test new tools, something which seriously hindered development of this work.

7.6 Summary

- In this chapter, I narratively described the evidence identified or produced in previous chapters and highlighted the issues with a qualitative approach to triangulation when there are several sources of evidence.

- I then illustrated a proposed generalised framework for quantitative triangulation, exploiting existing methods in evidence synthesis and recent developments in the assessment of different risks of bias. I illustrated this method using two case studies: the effect of mid-life LDL-c on Alzheimer's disease, and the effect of mid-life triglycerides on vascular dementia.

- I discussed the limitations of this proposed method, given the absence of empirically based priors for the impact of bias/indirectness, and proposed future research (i.e. meta-epidemiological studies) that would address them.

- In summary, quantitative triangulation is a promising field that should be considered a natural extension of evidence synthesis. The implications of the synthesised evidence presented here to clinical practice, public health and future research is considered in the following chapter.

Science knows it doesn't know everything.

Otherwise, it'd stop.

— Dara Ó Briain, 2008[360]

8
Discussion

Contents

Lay summary

In this final chapter, I describe the results of each previous chapter and compare my results with those of two recent large studies. I describe how doctors and those working in public health should use the results of my work, and highlight issues that may limit the usefulness of my findings. Finally, I describe future research that would build on my findings to move the field forward.

8.1 Introduction

The central aim of this thesis was to infer the causal effect of blood lipid levels on dementia outcomes via evidence synthesis methods. In this discussion, I will review the contribution of each chapter to this aim, summarise the principal findings and methodological innovations of the thesis, and discuss the implications of my findings for both clinical and public health practice. I consider the overall strengths and limitations of this thesis as a coherent body of work and suggest avenues for impactful future research that would build on the research presented.

8.1.1 Chapter summary

This thesis is comprised of a mix of methodological and applied research chapters.

In **Chapter 1**, I introduced the core concepts considered in this thesis and framed the research presented in relation to a theoretical framework of evidence synthesis.

In **Chapter 2**, I presented a new tool for the systematic searching of health-related preprints and detailed two use cases for preprint metadata beyond the systematic searching of this evidence source.

In **Chapter 3**, I described the methods of a comprehensive systematic review of all available evidence on the association of both lipid levels and lipid-regulating agents with dementia outcomes. The results of this analysis are then presented in **Chapter 4**.

In **Chapter 5**, I described an analysis of the association of lipid-regulating agent use and dementia outcomes in the CPRD, a large electronic health record database. I made use of positive and negative control outcomes to illustrate insufficiently controlled confounding.

In **Chapter 6**, I presented an individual participant data meta-analysis of the association of lipid levels and dementia outcomes, using previously unanalysed data accessed via the Dementia Platform UK.

Finally, in **Chapter 7**, I proposed a new method for the systematic integration of multiple evidence sources as part of quantitative triangulation framework. I illustrated the method using two case studies (the effect of LDL-c on Alzheimer's disease and the effect of triglycerides on vascular dementia), drawing on the evidence identified or produced by previous chapters.

8.2 Summary of clinical findings

8.2.1 Effect of blood lipids on dementia outcomes

Given that the results of the different components of this thesis are discussed in detail as part of the triangulation analysis (see Section 7.3), here I briefly summarise the key findings.

Overall, I did not identify a consistent effect of any blood lipid fraction (total cholesterol, LDL cholesterol, HDL cholesterol or triglycerides) on any dementia outcome (all-cause dementia, Alzheimer's disease or vascular dementia). While published non-randomised studies provided evidence for a protective effect of lipid-lowering via statin use on Alzheimer's disease and the IPD analysis suggested a harmful effect of raised triglycerides on vascular dementia, these effects were not maintained when incorporated along with other sources of evidence in a quantitative triangulation framework. Similarly, the IPD analysis did not provide evidence for an interaction of patient characteristics (age/sex) with the association of blood lipids and dementia outcomes, other than a slight protective effect of male gender on the LDL-c/all-cause dementia relationship. However, this analysis was limited by the low number of cohorts analysed.

In the published literature, statins were by far the most studied lipid-regulating agent in relation to dementia outcomes. Given the large proportion of patients taking statins as indicated by my analysis of the CPRD data, this finding is unsurprising. Finally, there was a substantial absence of evidence for vascular dementia.

8.2.2 Comparison with new evidence

Since the searches underpinning the systematic review described in this thesis were performed (July 2019), further studies on this topic have been published. Two of these, notable for the analysis of large UK cohorts, are discussed here.

The first is a large-scale analysis of 953,635 patients in the CPRD, followed from their first LDL-c measurement.[352] The study found evidence for a slightly increased risk of dementia with higher LDL-c levels at mid-life, driven by the finding for the Alzheimer's disease subgroup. These results are consistent with the findings presented in this thesis, particularly as this study did not have access to $Apo\mathcal{E}4$ status and so could not adjust for confounding by this variable. $Apo\mathcal{E}4$ is a key risk factor for both Alzheimer's disease and raised LDL-c levels,[320] and so could explain the harmful association observed. This is supported by a simulation analysis reported within this study, which used published information to predict that $Apo\mathcal{E}4$ would induce a risk ratio of 1.09 per 1-SD increase in LDL-c in the absence of a true causal effect.

The second analysis examined 502,226 participants in the UK Biobank, a large population-based prospective cohort study.[361,362] The analysis found no association between lipids measured at mid-life and dementia outcomes. This finding is again comparable to the results of this thesis. However, similar to the study discussed above, this analysis did not have access to genetic data and so may be subject to residual confounding by *Apo$\mathcal{E}$*4 genotype.

8.2.3 Implications for clinical practice

Given the absence of any consistent signals across the evidence sources analysed, there are no clear indications for clinical practice arising from this thesis. While my research did not provide any strong evidence for an effect of lipid-lowering on dementia outcomes, the cumulative strength of evidence is also insufficient to rule out an effect.

Given this ambiguity, the use of statins should be restricted to their primary and well-understood purpose of lipid-lowering to reduce the risk of cardiovascular events. However, it is important to recognise that even under a scenario where a strong harmful effect of lipid-lowering on dementia outcomes was identified, whether or not to prescribe a statin at mid-life will always be guided by factors other than dementia prevention. Patients must live to a certain age in order to be at risk of dementia (with the exception of familial early-onset dementias), which is substantially less likely if hypercholesterolemia at mid-life is left unchecked.

In summary, clinicians should be aware of the uncertainty of evidence surrounding the effect of lipid-lowering on dementia outcomes and should be prepared to convey the same to patients.

8.2.4 Implications for public health

Similarly, given the ambiguity of evidence, there are no clear implications for public health practice. However, the role of public health, and particularly continuous population surveillance, may be important in providing a further source of evidence in relation to the effect of lipid lowering on dementia. As an illustrative example, the Cognitive Function and Ageing Study (CFAS) II (2008-2011) showed a reduction in the age-specific prevalence rates of dementia when compared to CFAS I (1989-1994).[363] The authors interpreted this reduction as the result of improved education and better control of vascular risk factors, in line with broader thinking on the impact of population-level changes in risk factors.[364] In a similar manner, public health practitioners could examine summary-level statistics of GP prescription data to attempt to relate lipid-lowering treatment to temporal or geographical trends in dementia incidence.

It may well prove difficult to assess if any observed trends are due to a true effect or to confounding or ecological biases. However, because dementia outcomes will be monitored anyway for incidence/prevalence estimation and planning of services/care, this approach could provide a ready source of further evidence with a distinct bias structure to the approaches already considered in this thesis.

8.3 Summary of methodological contributions

In addition to addressing the causal impact of lipids on dementia outcomes, the research described in this thesis represents a number of novel contributions to the field of evidence synthesis methodology.

8.3.1 Inclusion of preprinted evidence

Preprints are an important source of evidence, and future information specialists may wish to search health-related preprints as part of a wider systematic review. To support this, I developed a new tool, `medrxivr`, as discussed more fully in Chapter 2. The tool has been well received by the community, and its use in systematic reviews[365–367] and scoping searches[128] has been reported. In addition, the preprint metadata provided by the tool has been used in several meta-research studies.[126,127,129]

8.3.2 Bias

One of the central methodological contributions of this thesis has been on the conduct, visualisation, and incorporation of bias assessments as part of an evidence synthesis exercise.

In terms of assessment, I applied domain-based tools to evidence relevant to the effect of lipids on dementia outcomes and highlighted the limitation of the available tools for Mendelian randomisation studies. I also piloted and provided feedback on a forthcoming tool for assessing the risk of bias due to missing evidence. In the primary analysis of data from the CPRD, I used negative control outcomes to assess the potential for bias due to insufficiently controlled confounding by indication.

In terms of visualisation of bias, I have made a number of methodological contributions. I built a well-received R package to create paired forest plots (see Appendix B.2), and developed this further to enable users to produce the bias direction plots illustrated in Chapter 7.

Finally, I made several novel contributions around the incorporation of bias into analyses. These were intended to encourage authors of reviews to actively consider the impact of bias in their syntheses, something that empirical evidence suggests happens infrequently at present.[185] The new methods introduced by this thesis range from the forest plots stratified by overall risk of bias level presented in Chapter 4 to the more advanced triangulation framework presented in Chapter 7.

8.3.3 Triangulation framework

The proposed quantitative triangulation framework represents the final novel contribution of this thesis to evidence synthesis methodology. Using pre-specified adjustment distributions mapped to the results of the domain-based risk-of-bias and indirectness assessments, this approach provides a systematic way to account for biases/indirectness across studies. In addition, it explicitly seeks to include both direct and indirect evidence and separates the assessment of bias/indirectness in each result from the definition of distributions representing the impact of bias/indirectness.

Ideally, this framework should be based on the results of a comprehensive systematic review, which identifies all evidence (both direct and indirect) related to a causal question of interest. This would represent a break from the current practice of limiting review to a single type of evidence, and would result in fewer, more comprehensive reviews. In the current context of concern over research waste, a concentration of effort in fewer reviews may be advantageous. Section 4.5.2 illustrates the duplication of reviews in relation to the topic of this thesis, while an assessment of the COVID-19 literature found that, for a specific clinical question, there were substantially more reviews (25) than available primary studies (17).[368]

Finally, the framework proposed here could (fairly) be criticised over the validity of the prior distributions of bias/indirectness chosen. However, the assumptions made about the impact of bias in this thesis are no stronger than those made when synthesising effect estimates as though they were unbiased. The proposed framework at the very least recognises the uncertainty introduced by bias/indirectness and decreases the precision of the overall effect estimate on this basis.

In summary, the proposed triangulation framework could enable better use of all available evidence to address causal questions.

8.4 Overall strengths and limitations

The strengths and limitations of each aspect of this thesis have been discussed in the respective chapter. Here, I highlight the strengths and weaknesses of this thesis as a body of work.

8.4.1 Strengths

There are four key strengths to this thesis as a whole. Firstly, the identification and triangulation of evidence across study designs and publication status sets this thesis apart from previous syntheses of the evidence on this topic.

Additionally, this thesis has also produced new evidence on the association of blood lipids with dementia outcomes in previously unanalysed cohorts and provided additional information on a previously under-studied relationship (lipids/LRA and vascular dementia).

A further strength of this thesis is the production of software to support the novel evidence synthesis techniques used. Extensive documentation has been written to guide users through usage of the tools and example data are provided, enabling future researchers to readily apply the methods described.

Finally, substantial effort has been invested to make the research documented in this thesis as reproducible as possible - this is documented more fully in Appendix A.8.1.

8.4.2 Weaknesses

However, there are also four key limitations to this thesis. As with many studies of dementia outcomes, a limiting factor in the interpretation of the results is the absence of a detailed pathological mechanism. It is possible that statins have a true effect on dementia risk via some pathway other than lipid-regulation, but without knowledge of the mechanism, the plausibility of this relationship cannot be assessed.

Secondly, each analysis presented here makes use of secondary data sources, be it published literature, electronic health records, or existing cohorts. Secondary data can limit the type of analyses performed (for example, in the IPD analysis presented in Chapter 6, absence of time-to-event data prevented the use of hazard ratios to quantify dementia risk) and the validity of the data if collected for purposes other than research. For example, the accuracy of dementia diagnoses in electronic health records is known to be variable.[318]

Thirdly, missing evidence was a common limitation across this thesis. In Chapters 3 & 4, several studies stated that they did not report the results of an analysis because the results were not significant. This was particularly common among non-randomised studies of exposure examining blood lipids directly. Similarly, an absence of evidence on vascular dementia, potentially due to a publication bias mechanism, limited the analysis of this outcome. Missing evidence was also an issue in the IPD meta-analysis reported in Chapter 6, in the form of a poor response to data access requests. In addition, the absence of empirically based distributions of bias/indirectness for use with the triangulation framework limited the credibility of the results produced.

A final weakness stems from the geographical focus of the data analysed in this thesis. All primary analysis presented drew on data from the UK (CPRD, CaPS, EPIC Norfolk, Whitehall II), while the majority of studies identified by the review were based in westernised countries (Figure 4.2). This, combined with the limited evidence for different ethnicities available even within high income settings, may limit the generalisability of the results presented to different populations.

8.5 Lessons learned

As part of a reflective learning process throughout my PhD, I maintained a catalogue of failures (available in Appendix A.8.2) describing analytical mistakes, failed experiments, and unsuccessful grant applications. However, I found there was one central learning point from this thesis, namely, to be slightly less ambitious when planning future research projects.

The proposal for the program of research underpinning this thesis was created in advance of starting my PhD because a detailed plan was required in order to secure the funding that supported me through my studies. In hindsight, the decision to take a broad approach to the inclusion of dementia outcomes resulted in a larger workload than anticipated, particularly when also considering evidence from multiple different study designs. Additionally, as dementia subtypes likely have very different aetiological pathways, it may have been better to focus on a single subtype (e.g., Alzheimer's disease) when considering the causal effects of lipids. Similarly, attempting to undertake a full individual participant data meta-analysis as a single part of a larger program of research was overly ambitious, given that data cleaning and harmonisation for just three cohorts turned out to be a substantial undertaking.

In the future, armed with the experience gained through conducting the research presented here, I will be better placed to scope and design research projects.

8.6 Future work

Several avenues of future research are proposed, building on the novel work presented here. These are grouped by topic in the following sections.

8.6.1 Generation of new evidence from RCTs

It is customary at this point in the discussion of results based (primarily) on observational data to recommend that a large-scale randomised controlled trial (RCT) be performed to assess the effect of the proposed intervention. Given the costs and logistical challenges associated with trials examining outcomes with long prodromal periods such as dementia, a more efficient approach is offered by the opportunistic post-trial follow-up of existing RCTs of lipid-regulating agents.

This approach has already been used to assess long-term (11-20 years) safety outcomes of statin use, using participant recontact[369] and linkage with electronic health records to identify events.[370] A similar approach could be used to assess the impact of randomisation to statins at midlife on subsequent risk of dementia outcomes. Use of data linkage would represent the most cost-efficient approach,[371] though as noted in Chapter 5, there is the potential for non-differential misclassification when defining dementia outcomes using electronic health records.

8.6.2 Evidence on vascular dementia

As highlighted by the results of the systematic review presented in Chapter 4, there is an absence of evidence on vascular dementia across the existing evidence base. While the primary studies presented here go some way towards supplementing this evidence base, future work is needed both to investigate the reasons for this evidence gap (e.g., due to an absence of primary data, challenges in the analysis of this outcome as documented in Chapter 5, or a publication bias mechanism) and to address it.

However, it seems unlikely that further analysis of observational data alone will be sufficient to investigate this outcome, given the evidence of strong confounding by indication presented by the analysis of statins and vascular dementia (Chapter 5). Even using cutting-edge methods, such as a target trial emulation approach, previous analyses have not replicated the known protective effect of statins on coronary heart disease identified by RCTs (see Section 5.4.2).[313] Similarly, available Mendelian randomisation studies are limited to a single one-sample analysis of HMGCR variants as a proxy for statin treatment. This study suggested a protective effect of lipid-lowering on vascular dementia, although there was a moderate risk of bias in this analysis and the effect was attenuated to the null when including a wider range of lipid-lowering variants.

Taken together, these points reinforce the need for a large-scale genome-wide association study (GWAS) of vascular dementia, similar to those currently available for Alzheimer's disease, to identify genetic variants associated with this outcome that future two-sample Mendelian randomisation studies could exploit. While GWAS of this outcome are likely to be methodologically challenging, given the difficulty in diagnosing "pure" vascular dementia, it would be a worthwhile endeavour and allow for the assessment of genetically driven risk factors beyond those considered in this thesis.

8.6.3 Preprinted evidence

In terms of evidence synthesis methodology, future work on preprinted evidence could address how to handle discrepancies between the preprinted and published versions of a paper when identifying results for inclusion in a synthesis. This will be particularly important in cases where the results are substantially different between the two versions or if a result available in the preprint manuscript is not presented in the published version.

The `medrxivr` tool enables programmatic searching of health-related preprints, and future work could incorporate the tool, along with software to search other literature sources, into an automated searching pipeline as part of a living systematic review.[372] In addition, the ready access to preprint data afforded by the tool will enable future meta-epidemiological studies to examine factors which may influence eventual publication (for example, significant results, geographical location/gender/career stage of first author, or some other factor). Finally, the tool will allow future research to assess the impact of peer review and editorial guidelines on manuscripts through comparison of the same paper at two stages (preprinted versus published). This approach was used to explore the impact of editorial polices on open data sharing, as discussed in Chapter 2, but could be applied to other aspects of the publication process.

8.6.4 Reviewing Mendelian randomisation studies

As noted in Chapter 4, methods for the inclusion of Mendelian randomisation studies in evidence synthesis exercises are not yet sufficiently developed, particularly in comparison to other study designs. Future work could aim to validate search strategies for this study design, paying particular attention to the range of terms used to define the analytical approach (e.g., genetic instrumental variable analysis). In addition, as discussed in Section 7.5.2, the lack of an established risk-of-bias tool for Mendelian randomisation studies limits subsequent analyses that require systematic assessment of bias, such as the quantitative triangulation framework proposed here. Creation of a domain-based tool for this study design, which accounts for the differences in potential biases between one- and two-sample approaches, should be considered a priority.

Finally, the inclusion of multiple two-sample Mendelian randomisation studies using identical summary statistics can falsely increase the precision of the summary effect estimate if treated as independent results. It would be interesting to examine how this issue has been addressed in existing reviews of Mendelian randomisation studies, and based on this research, develop best practice guidance for future evidence syntheses.

8.6.5 Systematic reviews and quantitative triangulation

Quantitative triangulation is an area ripe for future work. The approach presented here will benefit from future meta-epidemiological studies to better define the impact of bias/indirectness, as discussed in detail in Section 7.5.2. Similarly, future work could expand the framework proposed here to account for meta-biases, such as those introduced by missing evidence. Tools such as ROB-ME will enable this, but the optimum method to adjust for this synthesis-level - as opposed to study-level - bias will need to be determined. Finally, the application of the framework to other causal questions will help to identify sticking points and may lead to refinement of the process.

8.7 Overall conclusions

To conclude, this thesis has provided new evidence concerning the role of blood lipids as a modifiable risk factor for dementia and highlighted the considerable uncertainty that still remains in relation to this causal question. In addition, it has developed new methods and tools, specifically around the inclusion of preprints in systematic reviews and the quantitative triangulation of evidence sources, which will enable future evidence synthesists to better address important causal questions.

9
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Appendices

A

Appendices by Chapter

Contents

A.1 Chapter 1

A.1.1 Publications beyond the scope of this thesis

In addition to publications arising directly from this thesis (described in Section 1.7.1 and included in Appendix B.3), I have been involved in a number of external research projects. Taken together, these additional projects provided extensive experience in evidence synthesis methods and in collaborating across large teams.

During 2020, I was involved in the updating of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. My contributions were focused on the data sharing aspects of the guidelines and on building the PRISMA2020 interactive web application. Publications arising from this work are listed below:

- *Page, M.J., Moher, D., Bossuyt, P., Boutron, I., Hoffmann, T., Mulrow, C., Shamseer, L., Tetzlaff, J., Akl, E., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E., Mayo-Wilson, E., McDonald, S.,* ***McGuinness, L.A.****, Stewart, L., Thomas, J., Tricco, A., Welch, V.A., Whiting, P., McKenzie, J. (2021). PRISMA 2020 statement: updated guidelines for reporting systematic reviews and meta-analyses. BMJ 372:n71. DOI: 10.1136/bmj.n71*

- *Page, M.J., Moher, D., Bossuyt, P., Boutron, I., Hoffmann, T., Mulrow, C., Shamseer, L., Tetzlaff, J., Akl, E., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E., Mayo-Wilson, E., McDonald, S.,* ***McGuinness, L.A.****, Stewart, L., Thomas, J., Tricco, A., Welch, V.A., Whiting, P., McKenzie, J. (2021). PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 372:n160. DOI: 10.1136/bmj.n160*

- *Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2021). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. MedRxiv, DOI: 10.1101/2021.07.14.21260492*

In response to the COVID-19 pandemic, I worked with a team of evidence synthesists to develop a literature searching/screening pipeline. This work underpinned a living systematic review on impact of the COVID-19 pandemic on self-harm and suicidal behaviour. Subsequently, the pipeline enabled rapid reviews of related questions, such as the impact on specific study populations.

- *John, A., Okolie, C., Eyles, E., Webb, R.T., Schmidt, L.,* ***McGuinness, L.A.****, Olorisade, B.K., Arensman, E., Hawton, K., Kapur, N. and Moran, P., 2020. The impact of the COVID-19 pandemic on self-harm and suicidal behaviour: a living systematic review. F1000Research, 9(1097). DOI: 10.12688/f1000research.25522.2*

- *John, A., Eyles, E.,* ***McGuinness, L.A.****, Okolie, C., Olorisade, B.K., Schmidt, L., Webb, R.T., Arensman, E., Hawton, K., Kapur, N. and Moran, P., 2020. The impact of the COVID-19 pandemic on self-harm and suicidal behaviour: protocol for a living systematic review. F1000Research, 9(644), p.644. DOI: 10.12688/f1000research.24274.1*

- *Eyles, E., Moran, P., Okolie, C., Dekel, D., Macleod-Hall, C., Webb, R. T., Schmidt, L., Knipe, D., Sinyor, M.,* ***McGuinness, L. A.****, Arensman, E., Hawton, K., O'Connor, R. C., Kapur, N., O'Neill, S., Olorisade, B., Cheng, H.-Y., Higgins, J. P. T., John, A., & Gunnell, D. (2021). Systematic review of the impact of the COVID-19 pandemic on suicidal behaviour amongst health and social care workers across the world. Journal of Affective Disorders Reports, 6, 100271. DOI: 10.1016/j.jadr.2021.100271*

Finally, I have acted as part of a large review team for a number of other evidence synthesis exercises:

- *Grant, M. C., Geoghegan, L., Arbyn, M., Mohammed, Z.,* ***McGuinness, L.A.****, Clarke, E. L., & Wade, R. (2020). The Prevalence of Symptoms in 24,410 Adults Infected by the Novel Coronavirus (SARS-CoV-2; COVID-19): A Systematic Review and Meta-Analysis of 148 Studies from 9 Countries. PLOS ONE. DOI: 10.1371/journal.pone.0234765*
- *Cheng, H.Y.,* ***McGuinness, L.A.****, Elbers, R.G., MacArthur, G.J., Taylor, A., McAleenan, A., Dawson, S., López-López, J.A., Higgins, J.P., Cowlishaw, S. and Lingford-Hughes, A. (2020). Treatment interventions to maintain abstinence from alcohol in primary care: systematic review and network meta-analysis. BMJ, 371. DOI: 10.1136/bmj.m3934*
- *Schmidt, L., Olorisade, B.K.,* ***McGuinness, L.A.****, Thomas, J. and Higgins, J.P. (2020). Data extraction methods for systematic review (semi) automation. F1000Research, 10:401. DOI: 10.12688/f1000research.51117.1*

A.2 Chapter 2

A.2.1 Code for publication rate analysis

medRxiv automatically links preprints to their published counterparts and provides the DOI of the published article as part of the metadata on a given preprint. Using `medrxivr` to access this data, I could assess the two-year publication rate of preprints originally posted to medRxiv in July 2019. The code used for this analysis is presented below:

```r
# Load relevant packages
library(medrxivr)
library(dplyr)

# Use snapshot of published status from July 2021
  mx_search(
    mx_snapshot("ccedfb8a44304b9fba4e3ba518a8ce4ed2294770"),
    query = "*",
    # Limit to those 129 records published in July 2019
    from_date = "2019-07-01",
    to_date = "2019-08-01"
  ) %>%

# Create indicator to show which records have been published
  mutate(Status = ifelse(published == "NA",
                         "Not published",
                         "Published")) %>%

# Group by indicator variable ("Published"/"Not published")
  group_by(Status) %>%

# Get total number per group, and percentage of total (N=129)
  summarise(N = n(),
            Percent = comma(n() / 129 * 100))
```

As shown in Table A.1, two-thirds of preprints were published within two years of their submission to medRxiv.

Table A.1: Publication status of medRxiv preprints - The publication status of medRxiv preprints deposited in July 2019 was assessed in July 2021 (allowing for a two-year lag) and found that a substantial proportion remained unpublished.

Status	N	Percent
Not published	42	33%
Published	87	67%

A.3 Chapter 3

A.3.1 Deviations from protocol

There were a number of deviations from the pre-registered protocol for the systematic review reported in Chapters 3 & 4:[141]

- I had originally intended to examine both dementia and mild cognitive impairment (MCI) as outcomes of interest. However, given the large number of relevant records for the dementia outcomes, I did not include MCI as an outcome.
- For Mendelian randomisation analyses, I had originally intended to use a panel of experts to assess the risk of bias in this study design. However, through private correspondence with the authors of a review of risk-of-bias assessment tools for Mendelian randomisation studies (since published[167]), I became aware of the Mamluk *et al* tool. Given this tool was considered to be the best available for assessing Mendelian randomisation studies and that it followed a domain-based approach, enabling comparison with tools for other study designs, I decided to use it in the review.
- I performed an additional assessment of the risk of bias due to missing evidence using the ROB-ME tool. This analysis was not planned because the tool did not exist when the protocol was written.

- I had originally intended to assess sources of funding alongside bias. However, on further reading,[373] I learned that any bias introduced by sources of funding would operate through one of the existing domains of the risk-of-bias tools. As such, I did not consider funding sources separately.

- Finally, I performed a dose response meta-analysis to assess the evidence for a non-linear relationship between lipids and dementia outcomes. This marked a departure from the published protocol, as I had not expected the number of studies reporting dementia risk across lipid sub-categories to be sufficient for a dose response analysis.

A.3.2 Web of Science databases searched

Table A.2: Summary of Web of Science databases searched - The contents of the Web of Science core collection can vary depending on an institution's subscription, and so detailing the exact databases and ranges searched is important.

Database	**Abbreviation**	**Years**
Science Citation Index Expanded	SCI-EXPANDED	1900-present
Social Sciences Citation Index	SSCI	1956-present
Arts & Humanities Citation Index	A&HCI	1975-present
Conference Proceedings Citation Index - Science	CPCI-S	1990-present
Conference Proceedings Citation Index - Social Science & Humanities	CPCI-SSH	1990-present
Emerging Sources Citation Index	ESCI	2015-present

A.3.3 Search strategy

An overview of the number of hits per database, in addition to the full line-by-line search results for each database, are presented below.

Table A.3: Summary of number of records identified in each database searched - The full line-by-line search results for each database, are presented in subsequent tables. Note there was substantial duplication across databases, resulting in several thousand duplicates being removed prior to title and abstract screening.

Step	Hits
Medline	6045
EMBASE	10255
PyscINFO	800
CENTRAL	1473
Web of Science	4874
Total (pre-deduplication)	**23447**
Duplicates	-7338
Total (post-deduplication)	**16109**

Table A.4: MEDLINE search strategy - Full list of search terms used to identify relevant records in the MEDLINE bibliographic database. The number of records returned per search term is also displayed.

#	Search term	Hits
1	dement*.ti,ab.	103404
2	alzheimer*.ti,ab.	132832
3	exp Dementia/	154234
4	exp Alzheimer Disease/	87346
5	Pick* disease.ti,ab	2794
6	globular glial tauopathy.ti,ab	24
7	primary progressive aphasia.ti,ab	1051
8	logopaenic aphasia.ti,ab	0
9	posterior cortical atrophy.ti,ab	381
10	(age-associated) adj2 (memory decline).ti,ab	11
11	((mild or slight) adj2 (cognitive or cognition) adj2 (disorder* or defect* or deficit* or disabilit* or dysfunction or impair*)).ti,ab.	14883
12	((cognit$ or memory or cerebr$ or mental$) adj3 (declin$ or impair$ or los$ or deteriorat$ or degenerat$ or complain$ or disturb$ or disorder$)).ti,ab.	182141
13	(MCI or aMCI or CIND or non-aMCI).ti,ab	16893
14	(cognitive impair*).ti,ab	56411
15	Cognition Disorders/	62602
16	Cognitive Dysfunction/	11999
17	Mild Cognitive Impairment/	11999
18	or/1-17	407352
19	lipid*.ti,ab.	462968
20	lipoprotein*.ti,ab.	140438
21	cholesterol.ti,ab.	227679
22	hypercholesterol*.ti,ab.	33093
23	hypocholesterol*.ti,ab.	3347
24	triacylglycerol.ti,ab.	11077
25	lipemia*.ti,ab.	1836
26	dyslipid?emia.ti,ab.	29128
27	hyperlipid?emia*.ti,ab.	25134

Table A.4: MEDLINE search strategy - Full list of search terms used to identify relevant records in the MEDLINE bibliographic database. The number of records returned per search term is also displayed. *(continued)*

#	Search term	Hits
28	hypolipid?emia.ti,ab.	271
29	HDL.ti,ab.	61231
30	LDL.ti,ab.	71176
31	VLDL.ti,ab.	12485
32	triglyceride*.ti,ab.	104904
33	exp Dyslipidemias/	76480
34	exp Cholesterol/	155339
35	exp Lipoproteins/	141558
36	or/19-35	777210
37	statin*.ti,ab.	39998
38	atorvastatin.ti,ab.	7994
39	cerivastatin.ti,ab	646
40	fluvastatin.ti,ab.	1795
41	pravastatin.ti,ab.	3940
42	rosuvastatin.ti,ab.	3175
43	simvastatin.ti,ab.	8933
44	pitavastatin.ti,ab	816
45	lovastatin.ti,ab.	3667
46	fibrat*.ti,ab.	3135
47	("fibric acid" adj3 derivat*).ti,ab.	341
48	bezafibrate.ti,ab	1523
49	fenofibrate.ti,ab	3109
50	gemfibrozil.ti,ab	1802
51	clofenapate.ti,ab	39
52	clofibrate.ti,ab	3035
53	ciprofibrate.ti,ab	481
54	(bile adj3 sequest*).ti,ab.	816
55	colestyramine.ti,ab	60
56	colestipol hydrochloride.ti,ab	52
57	colesevelam hydrochloride.ti,ab	71
58	nicotinic acid*.ti,ab.	5854
59	inositol nicotinate.ti,ab	30
60	niacin.ti,ab	4631
61	ezetimibe.ti,ab.	2766
62	acipimox.ti,ab	292
63	evolocumab.ti,ab	394
64	alirocumab.ti,ab	350
65	lomitapide.ti,ab	150
66	(omega-3-acid adj2 ethyl ester*).ti,ab	85
67	meglutol.ti,ab	2
68	Meglutol/	134
69	exp Anticholesteremic Agents/	71609
70	exp Fibric Acids/	9523
71	exp Ezetimibe/	1954
72	exp Nicotinic Acids/	36409
73	or/37-72	138108
74	18 and 36	19659
75	18 and 73	2287
76	74 or 75	21029
77	Animals/ not (Animals/ and Humans/)	4552498
78	76 not 77	18226
79	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	2299133

Table A.4: MEDLINE search strategy - Full list of search terms used to identify relevant records in the MEDLINE bibliographic database. The number of records returned per search term is also displayed. *(continued)*

#	Search term	Hits
80	((epidemiologic or prospective or retrospective or cross-sectional or case control* or cohort or longitudinal or followup or follow-up) adj3 (study or studies)).ti,ab,kf.	1043484
81	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	656500
82	(cohort? adj2 (analys* or compar* or data or study or studies)).ab.	184866
83	(population adj2 (based or data* or study or studies or register? or survey? or surveillance)).ab.	200506
84	or/79-83	2933516
85	controlled clinical trial.pt.	93095
86	randomized controlled trial.pt.	483099
87	clinical trials as topic/	187183
88	(randomi#ed or randomi#ation or randomi#ing).ti,ab,kf.	585795
89	(RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or crossover or cross-over or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or subsitut* or treat*))).ti,ab,kf.	512675
90	placebo.ab,ti,kf.	203773
91	trial.ti.	199586
92	(control* adj3 group*).ab.	498141
93	(control* and (trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kf.	19035
94	((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,kf.	165010
95	double-blind method/ or random allocation/ or single-blind method/	266392
96	or/85-95	1616814
97	84 or 96	4175140
98	MENDELIAN RANDOMIZATION ANALYSIS/	736
99	Mendelian randomi*.ti,ab,kf.	1647
100	98 or 99	1738
101	RANDOMIZED CONTROLLED TRIALS AS TOPIC/	124147
102	(RCT? or (randomi#ed adj2 (control* or intervention* or experiment* or trial* or study or studies))).ti,ab,kf.	405207
103	((random* or comparative or intervention? or treatment?) adj3 (efficacy or effect*)).ti,ab,kf.	435773
104	(clinical adj (intervention? or trial?)).ti,ab,kf.	346211
105	CLINICAL TRIALS AS TOPIC/ or CONTROLLED CLINICAL TRIALS AS TOPIC/	192430
106	TREATMENT EFFECT/	904484
107	or/101-106	1894420
108	100 AND 107	313
109	instrument* variab*.ti,ab,kf.	2380
110	((causal* or causative) adj3 (associat* or infer* or implicat* or effect* or predict* or factor? or risk? or relat*)).ti,ab,kf.	54710
111	((gene* adj2 (associat* or risk? or varia* or determinant?)) or risk variant?).ti,ab,kf.	234808
112	(disease* adj3 (expos* or associat* or etiolog* or pathogenesis or risk?)).ti,ab,kf.	304605
113	risk factor?.mp.	1045594
114	exp CAUSALITY/	782487
115	"confounding factors (epidemiology)"/	9873
116	(confound* or nonconfound* or non-confound*).ti,ab,kf.	113902
117	(statistics or epidemiolog* or ((genetic* or molecular) and medicine)).jw.	205082
118	or/109 -117	1768577
119	108 and 118	273
120	98 and 101	27
121	119 or 120	277

Table A.4: MEDLINE search strategy - Full list of search terms used to identify relevant records in the MEDLINE bibliographic database. The number of records returned per search term is also displayed. *(continued)*

#	Search term	Hits
122	97 or 121	4175143
123	78 and 122	6045

Table A.5: Embase search strategy - Full list of search terms used to identify relevant records in the Embase bibliographic database. The number of records returned per search term is also displayed.

#	Search term	Hits
1	dement*.ti,ab.	150297
2	alzheimer*.ti,ab.	182305
3	exp Dementia/	332818
4	exp Alzheimer Disease/	184019
5	Pick* disease.ti,ab	3399
6	globular glial tauopathy.ti,ab	52
7	primary progressive aphasia.ti,ab	1877
8	logopaenic aphasia.ti,ab	0
9	posterior cortical atrophy.ti,ab	714
10	(age-associated) adj2 (memory decline).ti,ab	17
11	((mild or slight) adj2 (cognitive or cognition) adj2 (disorder* or defect* or deficit* or disabilit* or dysfunction or impair*)).ti,ab.	24705
12	((cognit$ or memory or cerebr$ or mental$) adj3 (declin$ or impair$ or los$ or deteriorat$ or degenerat$ or complain$ or disturb$ or disorder$)).ti,ab.	259650
13	(MCI or aMCI or CIND or non-aMCI).ti,ab	31158
14	(cognitive impair*).ti,ab	88915
15	Cognition Disorders/	35208
16	Cognitive Dysfunction/	80947
17	Mild Cognitive Impairment/	23295
18	or/1-17	613530
19	lipid*.ti,ab.	568453
20	lipoprotein*.ti,ab.	168172
21	cholesterol.ti,ab.	295493
22	hypercholesterol*.ti,ab.	45908
23	hypocholesterol*.ti,ab.	3985
24	triacylglycerol.ti,ab.	12534
25	lipemia*.ti,ab.	2013
26	dyslipid?emia.ti,ab.	51477
27	hyperlipid?emia*.ti,ab.	40531
28	hypolipid?emia.ti,ab.	318
29	HDL.ti,ab.	95530
30	LDL.ti,ab.	108193
31	VLDL.ti,ab.	16654
32	triglyceride*.ti,ab.	147716
33	exp Dyslipidemias/	64190
34	exp Cholesterol/	286092
35	exp Lipoproteins/	242167
36	or/19-35	1045396
37	statin*.ti,ab.	65212
38	atorvastatin.ti,ab.	13401
39	cerivastatin.ti,ab	848

Table A.5: Embase search strategy - Full list of search terms used to identify relevant records in the Embase bibliographic database. The number of records returned per search term is also displayed. *(continued)*

#	Search term	Hits
40	fluvastatin.ti,ab.	2551
41	pravastatin.ti,ab.	5573
42	rosuvastatin.ti,ab.	5706
43	simvastatin.ti,ab.	13858
44	pitavastatin.ti,ab	1417
45	lovastatin.ti,ab.	4742
46	fibrat*.ti,ab.	4434
47	("fibric acid" adj3 derivat*).ti,ab.	407
48	bezafibrate.ti,ab	1996
49	fenofibrate.ti,ab	4540
50	gemfibrozil.ti,ab	2309
51	clofenapate.ti,ab	32
52	clofibrate.ti,ab	3346
53	ciprofibrate.ti,ab	545
54	(bile adj3 sequest*).ti,ab.	1092
55	colestyramine.ti,ab	133
56	colestipol hydrochloride.ti,ab	59
57	colesevelam hydrochloride.ti,ab	80
58	nicotinic acid*.ti,ab.	5159
59	inositol nicotinate.ti,ab	46
60	niacin.ti,ab	5622
61	ezetimibe.ti,ab.	4636
62	acipimox.ti,ab	394
63	evolocumab.ti,ab	707
64	alirocumab.ti,ab	648
65	lomitapide.ti,ab	239
66	(omega-3-acid adj2 ethyl ester*).ti,ab	141
67	meglutol.ti,ab	3
68	Meglutol/	219
69	exp Anticholesteremic Agents/	178271
70	exp Fibric Acids/	33072
71	exp Ezetimibe/	9146
72	exp Nicotinic Acids/	1946
73	or/37-72	204136
74	18 and 36	36463
75	18 and 73	6013
76	74 or 75	40002
77	Animals/ not (Animals/ and Humans/)	952788
78	76 not 77	39778
79	Clinical study/ OR Case control study/ OR Longitudinal study/ OR Retrospective study/ OR Prospective study/ OR Cohort analysis/ OR cross-sectional studies/	2034044
80	((epidemiologic or prospective or retrospective or cross-sectional or case control* or cohort or longitudinal or followup or follow-up) adj3 (study or studies)).ti,ab,kw.	1493506
81	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	860479
82	(cohort? adj2 (analys* or compar* or data or study or studies)).ab.	280187
83	(population adj2 (based or data* or study or studies or register? or survey? or surveillance)).ab.	286930
84	or/79-83	3106288
85	randomized controlled trial/	551164
86	randomization.de.	82502
87	controlled clinical trial/	462715

Table A.5: Embase search strategy - Full list of search terms used to identify relevant records in the Embase bibliographic database. The number of records returned per search term is also displayed. *(continued)*

#	Search term	Hits
88	*clinical trial/	17542
89	placebo.de.	334642
90	placebo.ti,ab.	287949
91	trial.ti.	270940
92	(randomi#ed or randomi#ation or randomi#ing).ti,ab,kw.	836677
93	(RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or recruit* or split or subsitut* or treat*))).ti,ab,kw.	667211
94	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dummy)).mp.	290312
95	(control* and (trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kw.	25934
96	or/85-95	1682845
97	84 or 96	4464235
98	MENDELIAN RANDOMIZATION ANALYSIS/	1856
99	Mendelian randomi*.ti,ab.	2066
100	98 or 99	2447
101	RANDOMIZED CONTROLLED TRIALS AS TOPIC/	95688
102	(RCT? or (randomi#ed adj2 (control* or intervention* or experiment* or trial* or study or studies))).ti,ab.	557079
103	((random* or comparative or intervention? or treatment?) adj3 (efficacy or effect*)).ti,ab.	611431
104	(clinical adj (intervention? or trial?)).ti,ab.	479774
105	CLINICAL TRIALS AS TOPIC/ or CONTROLLED CLINICAL TRIALS AS TOPIC/	79666
106	TREATMENT EFFECT/	1167457
107	or/101-106	2561978
108	100 AND 107	499
109	instrument* variab*.ti,ab.	2809
110	((causal* or causative) adj3 (associat* or infer* or implicat* or effect* or predict* or factor? or risk? or relat*)).ti,ab.	69566
111	((gene* adj2 (associat* or risk? or varia* or determinant?)) or risk variant?).ti,ab.	302507
112	(disease* adj3 (expos* or associat* or etiolog* or pathogenesis or risk?)).ti,ab.	420445
113	risk factor?.mp.	1243497
114	exp CAUSALITY/	2038
115	"confounding factors (epidemiology)"/	203764
116	(confound* or nonconfound* or non-confound*).ti,ab.	157400
117	(statistics or epidemiolog* or ((genetic* or molecular) and medicine)).jx.	210731
118	or/108-117	2325782
119	108 and 118	499
120	98 and 101	147
121	119 or 120	499
122	97 or 121	4464264
123	78 and 122	10255

Table A.6: PyscINFO search strategy - Full list of search terms used to identify relevant records in the PyscINFO bibliographic database. The number of records returned per search term is also displayed.

#	Search term	Hits
1	dement*.ti,ab.	62001
2	alzheimer*.ti,ab.	56133
3	exp Dementia/	72554
4	exp Alzheimer Disease/	44097
5	Pick* disease.ti,ab	595
6	globular glial tauopathy.ti,ab	13
7	primary progressive aphasia.ti,ab	791
8	logopaenic aphasia.ti,ab	0
9	posterior cortical atrophy.ti,ab	270
10	(age-associated) adj2 (memory decline).ti,ab	8
11	((mild or slight) adj2 (cognitive or cognition) adj2 (disorder* or defect* or deficit* or disabilit* or dysfunction or impair*)).ti,ab.	9577
12	((cognit$ or memory or cerebr$ or mental$) adj3 (declin$ or impair$ or los$ or deteriorat$ or degenerat$ or complain$ or disturb$ or disorder$)).ti,ab.	139004
13	(MCI or aMCI or CIND or non-aMCI).ti,ab	7092
14	(cognitive impair*).ti,ab	33109
15	Cognitive Dysfunction/	34042
16	or/1-15	215471
17	lipid*.ti,ab.	9083
18	lipoprotein*.ti,ab.	3102
19	cholesterol.ti,ab.	7650
20	hypercholesterol*.ti,ab.	826
21	hypocholesterol*.ti,ab.	30
22	triacylglycerol.ti,ab.	70
23	lipemia*.ti,ab.	9
24	dyslipid?emia.ti,ab.	1224
25	hyperlipid?emia*.ti,ab.	1027
26	hypolipid?emia.ti,ab.	2
27	HDL.ti,ab.	1628
28	LDL.ti,ab.	1364
29	VLDL.ti,ab.	100
30	triglyceride*.ti,ab.	2874
31	exp Cholesterol/	2081
32	exp Lipoproteins/	971
33	or/17-32	18467
34	statin*.ti,ab.	5057
35	atorvastatin.ti,ab.	222
36	cerivastatin.ti,ab	11
37	fluvastatin.ti,ab.	17
38	pravastatin.ti,ab.	90
39	rosuvastatin.ti,ab.	55
40	simvastatin.ti,ab.	280
41	lovastatin.ti,ab.	85
42	pitavastatin.ti,ab	20
43	fibrat*.ti,ab.	45
44	("fibric acid" adj3 derivat*).ti,ab.	1
45	bezafibrate.ti,ab	22
46	fenofibrate.ti,ab	40
47	gemfibrozil.ti,ab	22
48	clofenapate.ti,ab	0
49	clofibrate.ti,ab	12
50	ciprofibrate.ti,ab	0
51	(bile adj3 sequest*).ti,ab.	2

Table A.6: PyscINFO search strategy - Full list of search terms used to identify relevant records in the PyscINFO bibliographic database. The number of records returned per search term is also displayed. *(continued)*

#	Search term	Hits
52	colestyramine.ti,ab	0
53	colestipol hydrochloride.ti,ab	0
54	colesevelam hydrochloride.ti,ab	0
55	nicotinic acid*.ti,ab.	154
56	inositol nicotinate.ti,ab	1
57	niacin.ti,ab	173
58	ezetimibe.ti,ab.	19
59	acipimox.ti,ab	1
60	evolocumab.ti,ab	3
61	alirocumab.ti,ab	1
62	lomitapide.ti,ab	1
63	(omega-3-acid adj2 ethyl ester*).ti,ab	1
64	meglutol.ti,ab	0
65	or/34-64	5782
66	16 and 33	3318
67	16 and 65	585
68	66 or 67	3682
69	Animals/ not (Animals/ and Humans/)	7175
70	68 not 69	3680
71	Clinical study/ OR Case control study/ OR Longitudinal study/ OR Retrospective study/ OR Prospective study/ OR Cohort analysis/ OR cross-sectional studies/	1317
72	((epidemiologic or prospective or retrospective or cross-sectional or case control* or cohort or longitudinal or followup or follow-up) adj3 (study or studies)).ti,ab,hw.	173681
73	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	104744
74	(cohort? adj2 (analys* or compar* or data or study or studies)).ti,ab.	23369
75	(population adj2 (based or data* or study or studies or register? or survey? or surveillance)).ab.	48659
76	or/71-75	261952
77	randomization.de.	0
78	*clinical trial/	7000
79	placebo.de.	5253
80	placebo.ti,ab.	38285
81	trial.ti.	27967
82	(randomi#ed or randomi#ation or randomi#ing).ti,ab,hw.	78840
83	(RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or recruit* or split or subsitut* or treat*))).ti,ab,hw.	93430
84	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dummy)).mp.	25258
85	(control* and (trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,hw.	9382
86	or/77-85	159116
87	76 or 86	408627
88	Mendelian randomi*.ti,ab.	106
89	(RCT? or (randomi#ed adj2 (control* or intervention* or experiment* or trial* or study or studies))).ti,ab.	57324
90	((random* or comparative or intervention? or treatment?) adj3 (efficacy or effect*)).ti,ab.	104711
91	(clinical adj (intervention? or trial?)).ti,ab.	34390
92	TREATMENT EFFECT/	22971
93	or/89-92	181514
94	88 AND 93	12

Table A.6: PyscINFO search strategy - Full list of search terms used to identify relevant records in the PyscINFO bibliographic database. The number of records returned per search term is also displayed. *(continued)*

#	Search term	Hits
95	instrument* variab*.ti,ab.	1088
96	((causal* or causative) adj3 (associat* or infer* or implicat* or effect* or predict* or factor? or risk? or relat*)).ti,ab.	20424
97	((gene* adj2 (associat* or risk? or varia* or determinant?)) or risk variant?).ti,ab.	28699
98	(disease* adj3 (expos* or associat* or etiolog* or pathogenesis or risk?)).ti,ab.	23709
99	risk factor?.mp.	118075
100	exp CAUSALITY/	4201
101	"confounding factors (epidemiology)"/	0
102	(confound* or nonconfound* or non-confound*).ti,ab.	28253
103	(statistics or epidemiolog* or ((genetic* or molecular) and medicine)).jw.	9677
104	or/95-103	211022
105	94 and 104	11
106	87 or 105	408627
107	70 and 106	800

Table A.7: CENTRAL search strategy - Full list of search terms used to identify relevant records in the CENTRAL bibliographic database. The number of records returned per search term is also displayed. Note that at the last step, I applied a manual filter via the CENTRAL web interface to limit the search to primary studies.

#	Search term	Hits
1	dement*	21445
2	alzheimer*	11448
3	[mh Dementia]	5224
4	[mh "Alzheimer Disease"]	3015
5	Pick* disease	1059
6	globular glial tauopathy	0
7	primary progressive aphasia	115
8	logopaenic aphasia	0
9	posterior cortical atrophy	68
10	(age-associated) NEAR2 (memory decline)	2696
11	((mild or slight) NEAR2 (cognitive or cognition) NEAR2 (disorder* or defect* or deficit* or disabilit* or dysfunction or impair*))	136
12	((cognit$ or memory or cerebr$ or mental$) NEAR3 (declin$ or impair$ or los$ or deteriorat$ or degenerat$ or complain$ or disturb$ or disorder$))	45
13	(MCI or aMCI or CIND or non-aMCI)	2288
14	cognitive impair*	14935
15	[mh "Mild Cognitive Impairment"]	922
16	[mh "cognition disorders"]	4475
17	[mh "cognitive dysfunction"]	922
18	#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 OR #16 OR #17	38448
19	lipid*	41298
20	lipoprotein*	22336
21	cholesterol	34213
22	hypercholesterol*	7724
23	hypocholesterol*	445
24	triacylglycerol	8029
25	lipemia*	375

Table A.7: CENTRAL search strategy - Full list of search terms used to identify relevant records in the CENTRAL bibliographic database. The number of records returned per search term is also displayed. Note that at the last step, I applied a manual filter via the CENTRAL web interface to limit the search to primary studies. *(continued)*

#	Search term	Hits
26	dyslipid?emia	4929
27	hyperlipid?emia*	4667
28	hypolipid?emia	10
29	HDL	15420
30	LDL	18892
31	VLDL	1944
32	triglyceride*	20436
33	[mh Dyslipidemias]	6753
34	[mh Cholesterol]	9862
35	[mh Lipoproteins]	9416
36	#19 OR #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 OR #34 OR #35	69284
37	statin*	9615
38	atorvastatin	4999
39	cerivastatin	196
40	fluvastatin	725
41	pravastatin	1954
42	rosuvastatin	2260
43	simvastatin	3698
44	lovastatin	950
45	pitavastatin	470
46	fibrat*	503
47	("fibric acid" NEAR/3 derivat*)	161
48	bezafibrate	458
49	fenofibrate	993
50	gemfibrozil	552
51	clofenapate	5
52	clofibrate	370
53	ciprofibrate	48
54	(bile NEAR/3 sequest*)	172
55	colestyramine	88
56	colestipol hydrochloride	29
57	colesevelam hydrochloride	104
58	nicotinic acid*	1183
59	inositol nicotinate	22
60	niacin	1084
61	ezetimibe	1541
62	acipimox	176
63	evolocumab	227
64	alirocumab	254
65	lomitapide	23
66	("omega-3-acid" NEAR/2 "ethyl ester*")	95
67	meglutol	21
68	[mh meglutol]	2
69	[mh "Anticholesteremic Agents"]	5124
70	[mh "Fibric Acids"]	1251
71	[mh Ezetimibe]	635
72	[mh "Nicotinic Acids"]	1951
73	#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72	21694

Table A.7: CENTRAL search strategy - Full list of search terms used to identify relevant records in the CENTRAL bibliographic database. The number of records returned per search term is also displayed. Note that at the last step, I applied a manual filter via the CENTRAL web interface to limit the search to primary studies. *(continued)*

#	Search term	Hits
74	#18 and #36	1605
75	#18 and #73	727
76	#74 and #75	2025
	Limiting to trials rather than reviews/protcols	1473

Table A.8: Web of Science search strategy - Full list of search terms used to identify relevant records in the Web of Science bibliographic database. The number of records returned per search term is also displayed.

#	Search term	Hits
1	TS=dement*	154301
2	TS=alzheimer*	230302
3	TS=Pick* disease	8119
4	TS=globular glial tauopathy	39
5	TS=primary progressive aphasia	1992
6	TS=logopaenic aphasia	4
7	TS=posterior cortical atrophy	1271
8	TS=(age-associated NEAR/2 memory decline)	16
9	TS = ((mild or slight) NEAR/2 (cognitive or cognition) NEAR/2 (disorder* or defect* or deficit* or disabilit* or dysfunction or impair*))	
10	TS = ((cognit$ or memory or cerebr$ or mental$) NEAR/3 (declin$ or impair$ or los$ or deteriorat$ or degenerat$ or complain$ or disturb$ or disorder$))	
11	TS = (MCI or aMCI or CIND or non-aMCI)	
12	TS = "cognitive impair*"	
13	Y	313381
14	TS=lipid*	623475
15	TS=lipoprotein*	188675
16	TS=cholesterol	268455
17	TS=hypercholesterol*	46269
18	TS=hypocholesterol*	4146
19	TS=triacylglycerol	15348
20	TS=lipemia*	2882
21	TS=dyslipid?emia	4881
22	TS=hyperlipid?emia*	3324
23	TS=hypolipid?emia	45
24	TS=HDL	63203
25	TS=LDL	76399
26	TS=VLDL	10962
27	TS=triglyceride*	108266
28	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	920847
29	TS=statin*	54504
30	TS=atorvastatin	14422
31	TS=fluvastatin	2547
32	TS=pravastatin	8327
33	TS=rosuvastatin	5171
34	TS=simvastatin	15753
35	TS=lovastatin	6299

Table A.8: Web of Science search strategy - Full list of search terms used to identify relevant records in the Web of Science bibliographic database. The number of records returned per search term is also displayed. *(continued)*

#	Search term	Hits
36	TS=fibrat*	6972
37	TS=("fibric acid" NEAR/3 derivat*)	313
38	TS=bezafibrate	1926
39	TS=fenofibrate	4194
40	TS=gemfibrozil	2606
41	TS=clofenapate	31
42	TS=clofibrate	3037
43	TS=ciprofibrate	608
44	TS=(bile NEAR/3 sequest*)	790
45	TS=colestyramine	64
46	TS=colestipol hydrochloride	73
47	TS=colesevelam hydrochloride	190
48	TS=nicotinic acid*	11925
49	TS=inositol nicotinate	49
50	TS=niacin	6199
51	TS=ezetimibe	3875
52	TS=acipimox	372
53	TS=evolocumab	723
54	TS=alirocumab	551
55	TS=lomitapide	179
56	TS=(omega-3-acid NEAR/2 "ethyl ester*")	112
57	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR # 53 OR # 54 OR # 55 OR # 56	108179
58	#13 and #28	18165
59	#13 and #57	2038
60	#58 or #59	19123
61	TS=((epidemiologic or prospective or retrospective or cross-sectional or "case control*" or cohort or longitudinal or followup or follow-up) NEAR/3 (study or studies))	1065411
62	TS=(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population)	4896813
63	TS=(cohort* NEAR/2 (analys* or compar* or data or study or studies))	235118
64	TS=(population NEAR/2 (based or data* or study or studies or register? or survey? or surveillance))	326505
65	#61 OR #62 OR #63 OR #64	4948637
66	TS=controlled clinical trial	267207
67	TS=randomized controlled trial	412461
68	TS=(randomi?ed or randomi?ation or randomi?ing)	843224
69	TS=(RCT or "at random" or (random* NEAR/3 (administ* or allocat* or assign* or class* or cluster or crossover or cross-over or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or subsitut* or treat*)))	706888
70	TS=placebo	240446
71	TS=trial	1533550
72	TS=(control* NEAR/3 group*)	462747
73	TS=(control* and (trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) NEAR/2 usual)))	20886
74	TS=((single or double or triple or treble) NEAR/2 (blind* or mask* or dummy))	268471
75	#66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74	2393217
76	#65 or #75	6616705
77	TS=Mendelian randomisat*	273

Table A.8: Web of Science search strategy - Full list of search terms used to identify relevant records in the Web of Science bibliographic database. The number of records returned per search term is also displayed. *(continued)*

#	Search term	Hits
78	TS=(RCT? or (randomi?ed NEAR/2 (control* or intervention* or experiment* or trial* or study or studies)))	654068
79	TS=((random* or comparative or intervention? or treatment?) NEAR/3 (efficacy or effect*))	196151
80	TS=(clinical NEAR/0 (intervention? or trial?))	242109
81	#78 OR #79 OR #80	975661
82	#77 AND #81	40
83	TS=instrument* variab*	55089
84	TS=((causal* or causative) NEAR/3 (associat* or infer* or implicat* or effect* or predict* or factor? or risk? or relat*))	67811
85	TS=((gene* NEAR/2 (associat* or risk? or varia* or determinant?)) or risk variant?)	394086
86	TS=(disease* NEAR/3 (expos* or associat* or etiolog* or pathogenesis or risk?))	257979
87	TS=risk factor?	841646
88	TS=(confound* or nonconfound* or non-confound*)	116352
89	TS=(statistics or epidemiolog* or ((genetic* or molecular) and medicine))	898995
90	#83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89	2342704
91	#82 and #90	36
92	#76 or #91	6616705
93	#60 and #92	4874

A.3.4 Code to search preprints

As detailed extensively in the main text, the inclusion of preprinted literature was a key aspect of the review presented in Chapters 3 & 4. Using the `medrxivr` tool presented in Chapter 2.

Given the relatively small number of records contained in the preprint server, no study design filters were employed. For the same reason, the number of search terms is smaller compared with the main database searches, as terms returning no records have been removed.

```
library(medrxivr)


# Define exposure search terms
topic1 <- c(mx_caps("statin"),
            mx_caps("ldl"),
```

```r
            mx_caps("hdl"),
            mx_caps("TG"),
            mx_caps("triglycer"),
            paste0("\\b",mx_caps("TC"),"\\b"),
            mx_caps("ezetim"),
            mx_caps("fibrate"),
            mx_caps("bile acid"),
            mx_caps("lipoprotein"),
            mx_caps("lipid"),
            mx_caps("cholesterol"))

# Define outcome search terms
topic2 <- c(mx_caps("dementia"),
            mx_caps("alzheim"),
            mx_caps("MCI"),
            mx_caps("mild cognitive"))

# Combine search topics using Boolean AND
query <- list(topic1, topic2)

# Run search in bioRxiv
bx_data <- mx_api_content(server = "biorxiv",
                          to_date = "2019-08-01")
bx_results <- mx_search(bx_data, query)

# Run search in medRxiv
mx_data <- mx_api_content(server = "medrxiv",
                          to_date = "2019-08-01")
mx_results <- mx_search(mx_data, query)
```

A.3.5 Calculating Gwet's AC1

Gwet's agreement coefficient, $AC1$ is defined as:

$$AC1 = \frac{observed\ agreement - chance\ agreement}{1 - chance\ agreement} \tag{A.1}$$

In reference to a two-by-two table with cells A, B, C and D, it is calculated using the following:

$$AC1 = \frac{\frac{A+D}{N} - e(\gamma)}{1 - e(\gamma)} \tag{A.2}$$

where $e(\gamma)$ is the chance agreement between raters, given as $2q(1-q)$, where

$$q = \frac{(A+C) + (A+B)}{2N} \tag{A.3}$$

A.3.6 Risk-of-bias assessment tool for Mendelian randomisation studies

A copy of the risk-of-bias tool used to assess Mendelian randomisation studies is presented in Table A.9, below.

Table A.9: Mendelian randomisation risk-of-bias assessment tool - A copy of the tool used to assess risk of bias in Mendelian randomisation studies, adapted from that developed by Mamluk et al.[166]

		Risk of bias judgement		
Bias domain	**Question**	**High**	**Moderate**	**Low**
Weak instrument bias	Strength of association between instrument and exposure F statistic < 10 in the same sample ($F < 10$ indicating a weak instrument)	F<10	F missing or F~10	F»10
Genetic confounding bias	Reported test on association between confounders and IV (testing the assumption that the instrument is associated with the outcome only via the exposure)	Yes AND there is an obvious association	Not presented or Yes presented AND there is some degree of association	Presented and no obvious association
'Other' confounding bias	Included confounders in the IV analysis	Yes		No

Table A.9: Mendelian randomisation risk-of-bias assessment tool - A copy of the tool used to assess risk of bias in Mendelian randomisation studies, adapted from that developed by Mamluk et al.[166] *(continued)*

		Risk of bias judgement		
Bias domain	**Question**	**High**	**Moderate**	**Low**
Additional direct effects between IV and outcome (exclusion restriction assumption)	Presence of pleiotropy for genetic IVs	Genetic IVs with no knowledge of mechanism for genetic variant-lipid association (e.g. GWAS hit, could be acting through any pathway?)	Biologically plausible lipid-specific mechanism of association for genetic variant-lipid (e.g. lipid metabolising genetic variants)	Same as moderate AND checks that there is no other known effect of genetic variants on outcome or its risk-factors
Bias due to selection of participants	Homogenous population or similar ancestry? If no: Stratified by ethnicity or adjusted for population stratification (yes/no)?	Non-homogenous population (e.g. black and white together, etc.)	Population described as homogenous (e.g. whites only) BUT not corrected for ancestry informative markers like principal components derived from GWAS	?Population described as homogenous (e.g. whites only) AND corrected for ancestry informative markers like principal components derived from GWAS

A.4 Chapter 4

A.4.1 PRISMA Checklist

Table A.10: PRISMA Checklist - Following best practice guidelines, the Section/Table/Figure number where important details on the systematic review can be found are listed.

Topic	No.	Item	Location
TITLE			
Title	1	Identify the report as a systematic review.	Page 43
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	Not applicable
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section 3.1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section 3.1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Section 3.2.3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Section 3.2.4

Table A.10: PRISMA Checklist - Following best practice guidelines, the Section/Table/Figure number where important details on the systematic review can be found are listed. *(continued)*

Topic	No.	Item	Location
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Tables A.4-A.8
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Section 3.2.5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Section 3.2.7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Section 3.2.7

Table A.10: PRISMA Checklist - Following best practice guidelines, the Section/Table/Figure number where important details on the systematic review can be found are listed. *(continued)*

Topic	No.	Item	Location
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Section 3.2.7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Section 3.2.8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Specified in individual forest plots
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Section 3.2.9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Section 3.2.8

Table A.10: PRISMA Checklist - Following best practice guidelines, the Section/Table/Figure number where important details on the systematic review can be found are listed. *(continued)*

Topic	No.	Item	Location
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Section 3.2.9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Section 3.2.9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Section 3.2.9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Section 3.2.8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable
RESULTS			

Table A.10: PRISMA Checklist - Following best practice guidelines, the Section/Table/Figure number where important details on the systematic review can be found are listed. *(continued)*

Topic	No.	Item	Location
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Section 4.2.1, and Figure 4.1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Section 4.5.1
Study characteristics	17	Cite each included study and present its characteristics.	Table 4.3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figures 4.3-4.15
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figures 4.3-4.15
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Section 4.3

Table A.10: PRISMA Checklist - Following best practice guidelines, the Section/Table/Figure number where important details on the systematic review can be found are listed. *(continued)*

Topic	No.	Item	Location
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figures 4.3-4.15
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Section 4.4.2
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figures 4.3-4.15
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section 4.5.1
	23b	Discuss any limitations of the evidence included in the review.	Section 4.5
	23c	Discuss any limitations of the review processes used.	Section 4.5.6

Table A.10: PRISMA Checklist - Following best practice guidelines, the Section/Table/Figure number where important details on the systematic review can be found are listed. *(continued)*

Topic	No.	Item	Location
	23d	Discuss implications of the results for practice, policy, and future research.	Section 4.5, Section 8.3 & 8.4
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not applicable
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Section 3.2.1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Appendix A.3.1
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgements
Competing interests	26	Declare any competing interests of review authors.	Acknowledgements
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Section 4.5.5

A.4.2 Funnel plots

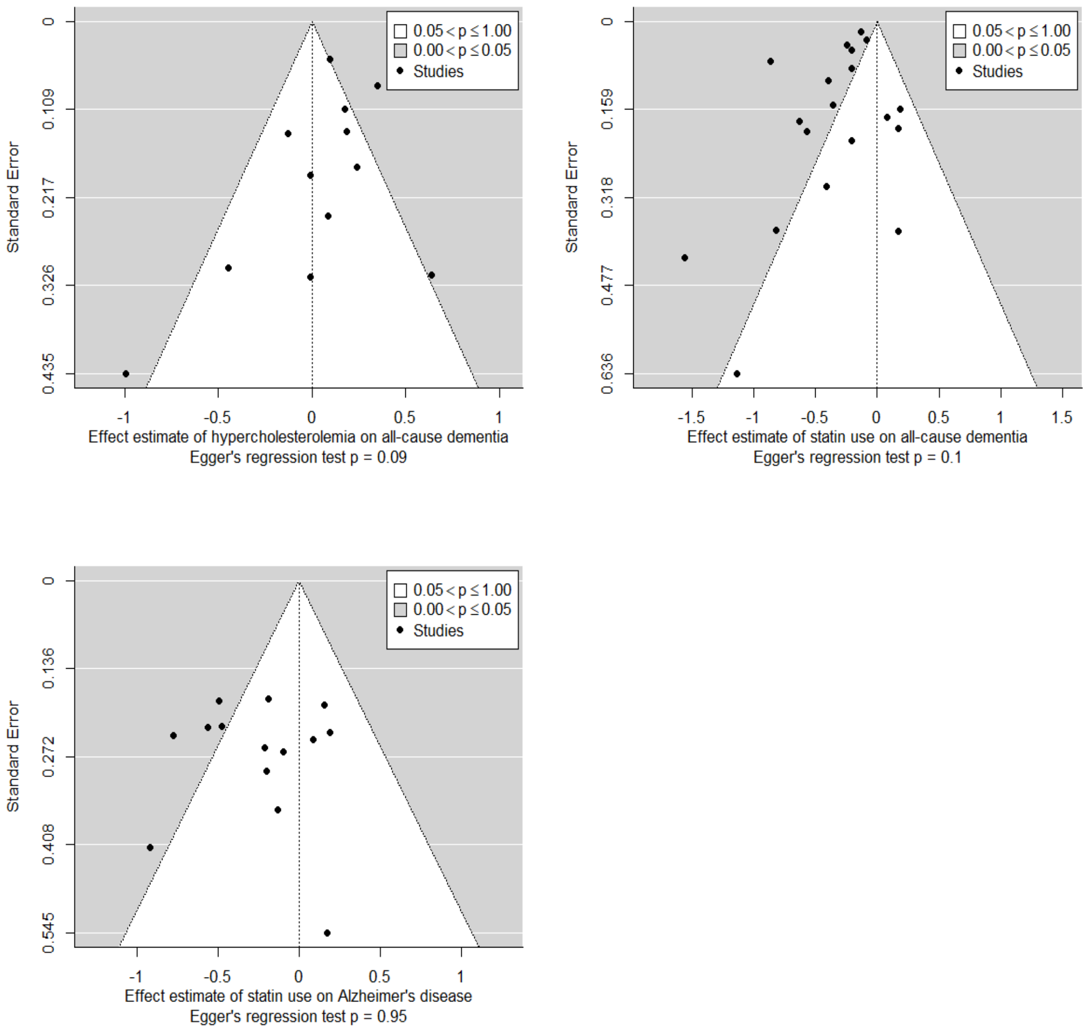

Figure A.1: Funnel plots - To assess the potential for small study effects, funnel plots were produced for the three meta-analyses reported in Chapter 4 that contained more than 10 results. Visual inspection of the plots did not indicate the presence of small study effect, which was supported in each case by the result of Egger's regression test for funnel plot asymmetry.

A.4.3 Dose response plots by fraction

In addition to examining a non-linear relationship between LDL-c and Alzheimer's disease (see Figure 4.16), I performed a dose response analysis for two other exposure-outcome pairs. The results of these analyses are presented below.

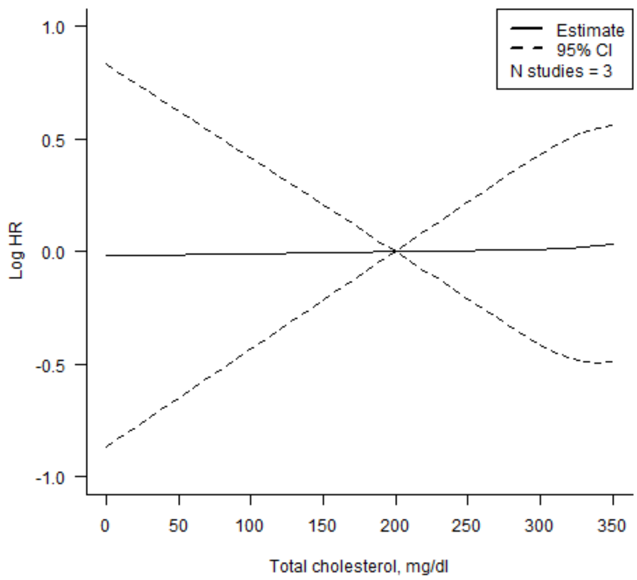

Figure A.2: Dose-response meta-analysis of total cholesterol on all-cause dementia - Non-randomised studies examining the association of total cholesterol with all-cause dementia across several categories or "doses" of exposure were synthesised using a dose response meta-analysis. The reference dose was defined *a priori* as 200 mg/dL, the cut-off of the "Normal"/"Optimal" category for total cholesterol as detailed in Table 1.2.

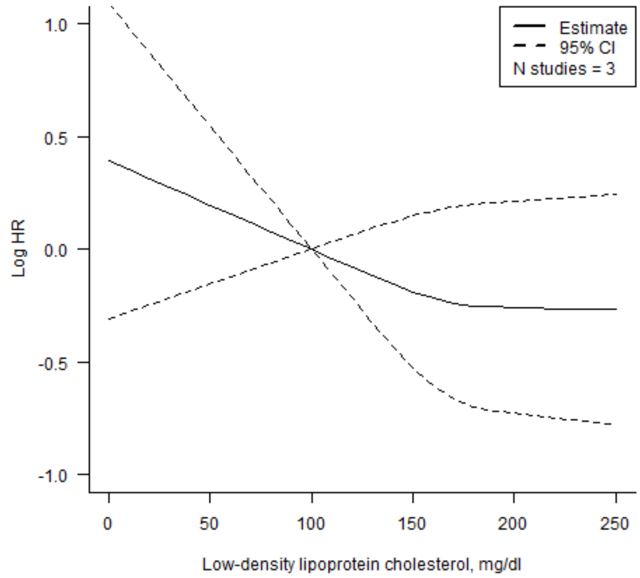

Figure A.3: Dose-response meta-analysis of low-density lipoprotein cholesterol on Alzheimer's disease - Non-randomised studies examining the association of LDL with Alzheimer's disease across several categories or "doses" of exposure were synthesised using a dose response meta-analysis. The reference dose was defined *a priori* as 100 *mg/dL*, the cut-off of the "Normal"/"Optimal" category for LDL as detailed in Table 1.2.

A.5 Chapter 5

A.5.1 Amendments to protocol

Any changes made to the approved protocol are "Minor amendments" as per the ISAC criteria, specifically falling under the category of "Additional methods to further control for confounding or sensitivity analysis provided these are to be reported as secondary to the main findings".

Changes include:

- Use of a time-varying treatment indicator, to correctly classify time-at-risk.
- Inclusion of additional covariates that are adjusted for in the main model.

A.5.2 Minimum follow-up period

Enforcing a minimum period of follow-up is normally used to reduce the risk of reverse causation in an analysis by excluding events occurring within a certain time-frame post exposure. With respect to dementia outcomes, which have a long prodromal period, enforcing a minimum period of follow-up can add biological validity to an analysis. Incident cases of dementia that occur within a few years of starting a drug may already be beyond effective preventive treatment at the time the drug was started, and so restricting the analysis to those with longer exposure to treatment may provide a more reliable estimate of the effect.

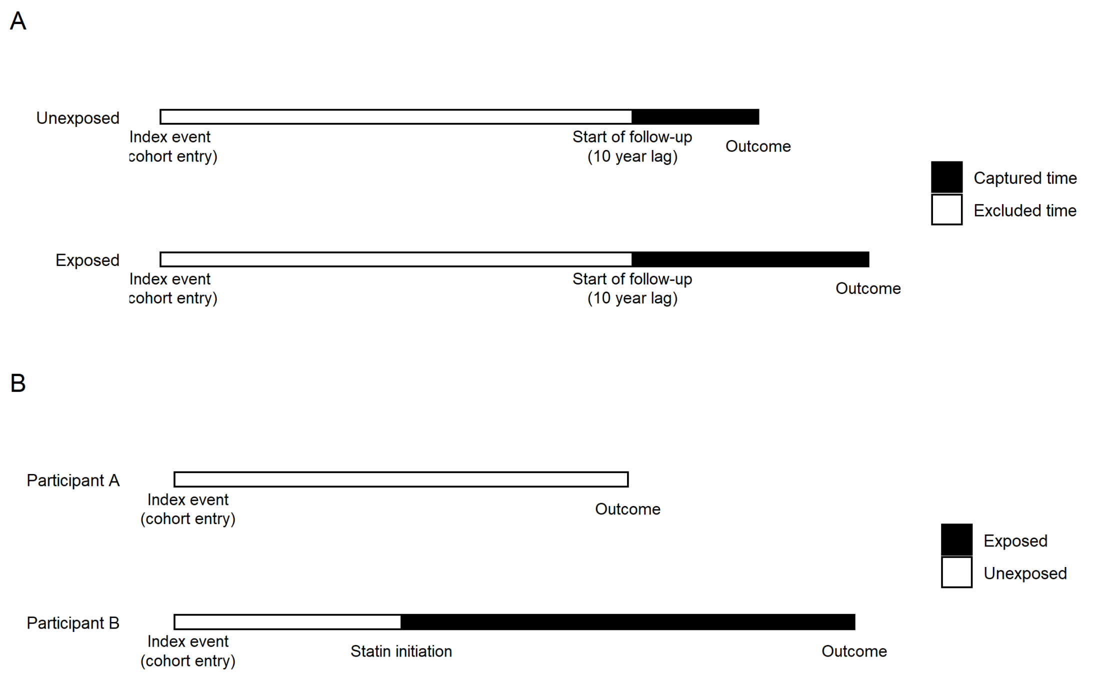

Figure A.4: Illustration of minimum follow-up period in two study designs - Panel A shows a study in which all participants enter the study and are assigned an exposure group at the same time, making it easy to define a minimum period of follow-up. In contrast, Panel B illustrates the time- varying analysis used in Chapter 5, which makes it challenging to define an unbiased minimum period of follow-up.

Panel A of Figure A.4 describes a standard analysis of an exposure with a minimum enforced follow-up period (in this case, 10 years). Participants enter the cohort and are classified at that point as either exposed or unexposed, for example, on the basis of a total cholesterol measurement. Participants are followed-up over time, but events occurring before the minimum period of follow-up are discarded.

However, applying a similar approach to the analysis performed in Chapter 5, illustrated in Panel B of Figure A.4, is challenging. The use of a time updating treatment indicator results in two potential starting points for the 10-year lag: entry into the cohort or initiation of statin therapy. As the purpose of this analysis is to investigate the impact of statin treatment, starting the minimum period of follow-up from cohort entry is not helpful as it does not ensure that participants have been exposed to the drug for 10 years. Alternatively, defining the minimum period of follow-up from statin initiation cause issues around the treatment of time-at-risk before statin initiation and around the start point for the follow-up period in those never prescribed a statin. In summary, either approach is likely to be substantially biased, and so an analysis using a minimum follow-up period was not performed.

A.6 Chapter 6

A.6.1 Covariate matrix

Table A.11: Overview of missing data in the IPD analysis - Missing variables/values across cohorts included in the IPD analysis. Missing variables are denoted using a "-", while missing values are described as N (%). Note that LDL is missing completely for the Whitehall and CaPS datasets as this measure was derived from the measures for TC, HDL and TG following multiple imputation of missing values in these variables.

Variable	Whitehall II	Epic	CaPS
Age group	182 (2.2%)	Complete	Complete
Male	Complete	Complete	Complete
BMI	30 (0.4%)	60 (5.4%)	X
Education	Complete	1 (0.1%%)	969 (38.6%)
Smoke ever	1454 (17.7%)	7 (0.6%)	10 (0.4%)
Alcohol ever	1344 (16.4%)	26 (2.3%)	129 (5.1%)
Ethnicity	30 (0.4%)	6 (0.5%)	X
IHD	Complete	1 (0.1%)	X
Diabetes	372 (3.3%)	1 (0.1%)	9 (0.4%)
TC	82 (1%)	114 (10.2%)	55 (2.2%)
LDL-c	*	140 (12.6%)	*
HDL-c	108 (1.3%)	141 (12.6%)	98 (3.9%)
TG	82 (1%)	114 (10.2%)	115 (4.6%)

Values shown are N (Percentage) unless otherwise stated.
Key: Complete - No missing values; X - Variable not recorded/available in this cohort; * - LDL values derived from total cholesterol, HDL and triglycerides.
Abbreviations: BMI - Body mass index; IHD - Ischemic heart disease; HDL - Low-density lipoprotein cholesterol; LDL - Low-density lipoprotein cholesterol; TG - Triglycerides.

A.6.2 Dementia definitions across cohorts

Table A.12: Definition of dementia outcomes in IPD meta-analysis - The criteria used to define dementia outcomes across cohorts included in the individual participant data meta-analysis are listed below. Note the codes used to define dementia and related outcomes in the HES data as part of the Whitehall II cohort were taken from a previously published analysis.[374]

Cohort	Primary detection methods	Identification of dementia	Identification of AD	Identification of VaD
CaPS	DPUK derived variable from Phase V (2002-2004) data	Assessment at clinic by a combination of interviewers and clinicians.	NA	Not reported
EPIC Norfolk	Self-reported during 5th Health Checkup (2016-2018)	Has your doctor ever told you that you had any of the following: Dementia (Alzheimer's, Vascular Dementia, Lewy Body or other)? YES/NO	NA	NA
Whitehall II	Electronic health records, via the Hospital Episodes Statistics database	ICD-9: 290.0-290.4, 331.0-331.2,331.82,331.9 ICD-10: F00,F01,F03,G30,G31	ICD-9: 331.0 ICD-10: F00, G30	ICD-9: 290.4 ICD-10: F01

A.7 Chapter 7

A.7.1 Calculation of average adjustment values from previous expert elicitation exercise

The paper describing the bias/indirectness-adjusted meta-analysis method used expert elicitation to define a distribution for bias and indirectness across eight studies examining the effectiveness of routine anti-D prophylaxis in Rhesus negative women.[346] The authors consider five sources of bias (selection bias, performance bias, attrition bias, detection bias and other bias) and four sources of indirectness (population, intervention, control, outcome). For each domain of bias/indirectness, four experts were asked to define the 67% interval around the effect expected due to bias/indirectness in the absence of a true effect. Additive or multiplicative scales were used to capture the intervals for additive and proportional bias/indirectness, respectively. The authors then derived a mean and variance for each on the log scale. The resulting data for two domains of bias (attrition and detection) in one study are shown in Table A.13.

Table A.13: Elicited bias distributions - Distributions of bias, defined by position and variance terms, assigned by four independent experts to attrition and detection bias in a single study. This data was obtained from a previous publication,[346] and represents an illustrative subset of the larger dataset.

Study	Domain	Assessor	Position	Variance
1	Attrition bias	1	-0.11	0.01
1	Attrition bias	2	-0.08	0.01
1	Attrition bias	3	-0.11	0.01
1	Attrition bias	4	-0.05	0.00
1	Detection bias	1	-0.09	0.02
1	Detection bias	2	-0.32	0.14
1	Detection bias	3	-0.23	0.02
1	Detection bias	4	0.00	0.01

In an attempt to inform the prior distributions used in the triangulation exercise presented in Chapter 7, I first averaged the position and variance values across the four experts for each source of bias/indirectness within each study. I took the average of the absolute of the position value, as I wanted to obtain the average adjustment regardless of direction. The results of this process for the example data presented below are shown in Table A.14.

Table A.14: Elicited bias distributions, averaged across experts - The expert-averaged position and variance values for two example bias domains (attrition and detection) are shown. These values were obtained by averaging the absolute of the values contained in A.15 across the four experts.

Study	**Domain**	**Position**	**Variance**
1	Attrition bias	0.0875	0.0075
1	Detection bias	0.1600	0.0475

I then took the average and maximum of the expert-averaged position and variance values. The results of this for the example data are presented in Table A.15.

Table A.15: Mean and maximum bias distributions, using example data - The mean and maximum of position and variance values described in Table A.15 were calculated to give the average and maximum bias adjustment across studies and domains of bias.

Mean position	**Mean variance**	**Max position**	**Max variance**
0.12375	0.0275	0.16	0.0475

This two-step approach (averaging across assessors before taking the average and maximum across domains/studies) was important. While the final average values will be the same whichever approach is taken, in a one-step process, the maximum value can be artificially inflated by a single expert's estimate. For example, in the illustrative data subset above, Assessor 2 assigns a distribution of N(-0.32,0.14), which would double the maximum position (0.16) and triple the maximum variance (0.0475) obtained when first averaging across experts.

The distributions arising from this applying this approach to the entire dataset, stratified by bias/indirectness and additive/proportional effects, are presented in Table A.16.

Table A.16: Mean and maximum distributions for bias and indirectness, using full data - Using all data resulting from the elicitation exercise reported in *Turner et al*[346], I calculated mean and maximum distributions for bias and indirectness using the method described above. Note I did not calculate values for additive indirectness, as in my analysis, all indirectness was assumed to be proportional.

	Mean	**Max**
Bias (Additive)	N(0.09, 0.06)	N(0.42, 0.29)
Bias (Proportional)	N(0.03, 0.02)	N(0.31, 0.21)
Indirectness (Proportional)	N(0.07, 0.02)	N(0.26, 0.16)

The mean values shown were used to define the distributions assigned to "Moderate" bias/indirectness judgements in my analysis (see Tables 7.3 & 7.4).

A.7.2 Comparison of two scenarios of bias

As discussed in the main text, I defined two sets of additive bias distributions as a sensitivity analysis. The results for the two case studies under the two scenarios are presented in the figures below. Under the first, shown on the left of the subsequent forest plot, the difference in the position value between the distributions assigned to "High" and "Moderate" bias levels is the same as between the "Moderate" and "Low" levels. Under the second scenario, the difference in the position value between the distributions assigned to "High" and "Moderate" is twice that between "Moderate" and "Low".

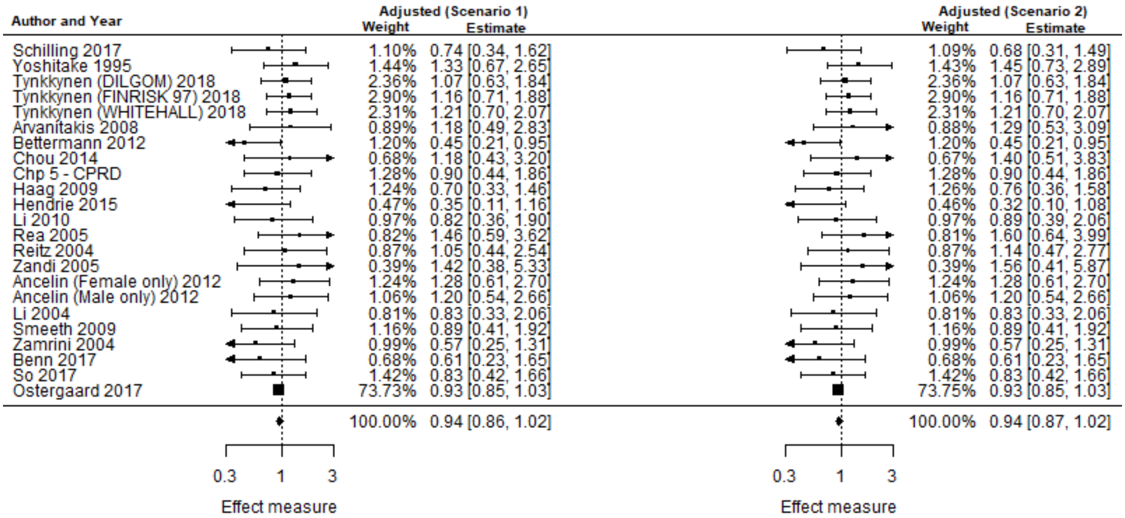

Figure A.5: Comparison of bias-/indirectness-adjusted meta-analyses of LDL-c/Alzheimer's disease under two different scenarios of additive bias - Scenario 1: position value between the additive distributions assigned to "High" and "Moderate" bias levels is the same as between the "Moderate" and "Low" levels. Scenario 2: position value between the additive distributions assigned to "High" and "Moderate" bias levels is twice that between "Moderate" and "Low" levels. See Section 7.4.1 for more details.

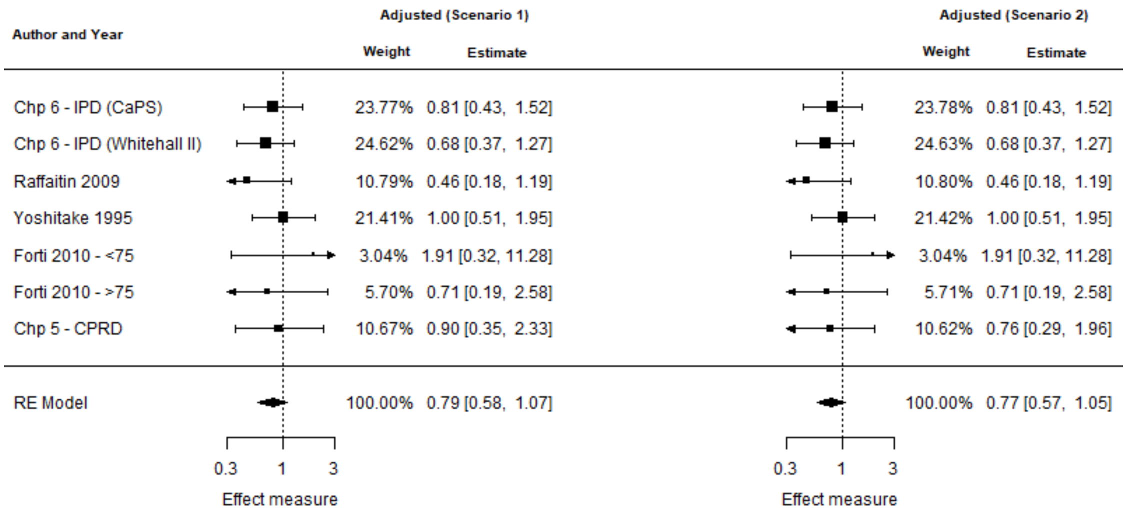

Figure A.6: Comparison of bias-/indirectness-adjusted meta-analyses of triglycerides/vascular dementia under two different scenarios of prior distributions of bias - Scenario 1: position value between the additive distributions assigned to "High" and "Moderate" bias levels is the same as between the "Moderate" and "Low" levels. Scenario 2: position value between the additive distributions assigned to "High" and "Moderate" bias levels is twice that between "Moderate" and "Low" levels. See Section 7.4.1 for more details.

A.8 Chapter 8

A.8.1 Reproducible research

Reproducible research has been a key theme running through this thesis, as reflected by the development of an open-source tools to search preprinted literature, create visualisations of risk-of-bias data and to preform quantitative triangulation. In line with this, an open-source copy of the code used to produce this thesis is available on GitHub, as is the code used to perform the analysis contained within it.

Unfortunately, given the nature of the data underpinning the CPRD (Chapter 5) and IPD (Chapter 6) analyses, it is not possible to make it publicly available. Access to the CPRD data is dependent on an application to its managing body, while access to the cohorts within the DPUK requires approval from both the DPUK and individual cohort owners. In the absence of data sharing, the best option to enable review and increase transparency is the open sharing of the code used to perform the analysis.[136]

Finally, all software projects in these thesis attempt to conform to minimal best practices for research computing.[375,376]

A.8.2 Catalogue of failures

As part of a reflective process, I kept a record of things (analytical mishaps, failed experiments, and unsuccessful grant applications) I attempted during the course of my PhD but which did not work. These are summarised briefly here:

- Prior to the analysis performed in Chapter 5, I attempted an analysis using physicians prescribing preference as an instrumental variable to compare different lipid-regulating agent classes for dementia prevention. However, this analysis was not pursued due to the very small number of patients prescribed a lipid-regulating agent other than statins.

- I initially failed to realise that a code list I was using for the positive control outcome of ischemic heart disease (IHD) in the CPRD analysis (Chapter 5) included only very severe IHD outcomes. This resulted in the positive protective control analysis giving substantially inflated hazard ratios (HR > 4) and led to substantial confusion in the study team.

- For the IPD analysis in Chapter 6, I had to be reminded that (a) BMI can be calculated from weight and height, and (b) that whether you ask at 45 or 50, the age at which someone left school will be the same.

- I was involved in unsuccessful grant applications to the NIHR (with Andrew Beswick), to the Jean Golding Institute (with James Byrne and Chris Penfold) and to the PGR Hub (with Matthew Lee).

B
Other Appendices

Contents

B.1 Software used to create this thesis

This thesis was written in RMarkdown using the RStudio integrated development environment. Several R packages were used as part of this project.[174,377–405] The version number of these packages is shown below:

```
## R version 3.6.1 (2019-07-05)
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 10 x64 (build 19043)
##
## Matrix products: default
##
## locale:
## [1] LC_COLLATE=English_United Kingdom.1252
## [2] LC_CTYPE=English_United Kingdom.1252
## [3] LC_MONETARY=English_United Kingdom.1252
## [4] LC_NUMERIC=C
## [5] LC_TIME=English_United Kingdom.1252
##
## attached base packages:
## [1] stats     graphics  utils     datasets  grDevices methods   base
##
## other attached packages:
##  [1] DiagrammeR_1.0.5    readxl_1.3.1        networkD3_0.4
##  [4] ggdag_0.2.3         dagitty_0.3-1       sf_0.9-8
##  [7] flextable_0.6.4     data.table_1.14.0   kableExtra_1.3.1
## [10] medrxivr_0.0.5.9000 robvis_0.3.0.900    png_0.1-7
## [13] metafor_3.0-2       Matrix_1.2-17       patchwork_1.1.1
## [16] ggplot2_3.3.5       dplyr_1.0.6         magrittr_2.0.1
```

```
##
## loaded via a namespace (and not attached):
##   [1] colorspace_1.4-1        ellipsis_0.3.1          class_7.3-15
##   [4] rio_0.5.16              rprojroot_2.0.2         snakecase_0.11.0
##   [7] base64enc_0.1-3         rstudioapi_0.13         farver_2.0.1
##  [10] graphlayouts_0.5.0      ggrepel_0.9.1           fansi_0.4.2
##  [13] lubridate_1.7.9         mathjaxr_1.4-0          xml2_1.3.2
##  [16] extrafont_0.17          cachem_1.0.3            knitr_1.36
##  [19] polyclip_1.10-0         jsonlite_1.7.2          Rttf2pt1_1.3.7
##  [22] rgeos_0.5-5             ggforce_0.3.1           readr_1.3.1
##  [25] compiler_3.6.1          httr_1.4.1              fastmap_1.0.1
##  [28] cli_2.5.0               tweenr_1.0.1            visNetwork_2.0.9
##  [31] htmltools_0.5.1.1       tools_3.6.1             igraph_1.2.6
##  [34] gtable_0.3.0            glue_1.4.2              rnaturalearthdata_0.1.0
##  [37] rsvg_1.3                V8_3.0.1                PRISMA2020_0.0.1
##  [40] Rcpp_1.0.6              rbiorxiv_0.2.0          cellranger_1.1.0
##  [43] vctrs_0.3.6             debugme_1.1.0           nlme_3.1-140
##  [46] extrafontdb_1.0         DiagrammeRsvg_0.1       ggraph_2.0.0
##  [49] conflicted_1.0.4        xfun_0.22               stringr_1.4.0
##  [52] ps_1.3.0                openxlsx_4.1.4          rvest_0.3.5
##  [55] lifecycle_1.0.0         MASS_7.3-51.6           scales_1.1.0
##  [58] tidygraph_1.1.2         hms_0.5.2               RColorBrewer_1.1-2
##  [61] yaml_2.2.1              curl_4.3                gridExtra_2.3
##  [64] gdtools_0.2.3           stringi_1.5.3           highr_0.8
##  [67] e1071_1.7-3             boot_1.3-22             zip_2.1.1
##  [70] rlang_0.4.10            pkgconfig_2.0.3         systemfonts_1.0.1
##  [73] evaluate_0.14           lattice_0.20-38         purrr_0.3.4
##  [76] htmlwidgets_1.5.1       labeling_0.3            processx_3.5.2
##  [79] tidyselect_1.1.0        here_1.0.0              plyr_1.8.5
##  [82] bookdown_0.21.6         R6_2.5.0                magick_2.2
```

```
##  [85] generics_0.1.0        DBI_1.1.1            pillar_1.5.1
##  [88] haven_2.3.1           foreign_0.8-71       withr_2.3.0
##  [91] units_0.6-6           sp_1.3-2             tibble_3.1.0
##  [94] janitor_2.0.1         crayon_1.4.1         uuid_0.1-4
##  [97] KernSmooth_2.23-15    utf8_1.2.1           rmarkdown_2.7.4
## [100] officer_0.3.17        viridis_0.5.1        rnaturalearth_0.1.0
## [103] grid_3.6.1            callr_3.7.0          cranlogs_2.1.1
## [106] forcats_0.5.1         irrCAC_1.0           digest_0.6.27
## [109] classInt_0.4-2        webshot_0.5.2        tidyr_1.1.3
## [112] munsell_0.5.0         viridisLite_0.3.0    utilities_0.3.0
```

B.2 robvis: producing risk-of-bias visualisations

The `robvis` package provides functions to visualise risk-of-bias assessments, with the resulting plots formatted based on the specific risk-of-bias assessment tool used. The tool is documented extensively online at `https://mcguinlu.github.io/robvis/`. As such, it is not described in detail here, other than to illustrate the data structures required for the figures presented in this thesis and to describe its reception in the evidence synthesis community.

B.2.1 Data setup

For the paired forest plots presented in Chapter 4, the tool expects a "Study" column, followed by one column per domain of bias and one column for the overall risk of bias judgement. To illustrate this, the `data_rob2` dataset which is available via the `robvis` package and contains example risk-of-bias assessments performed using the RoB2.0 tool for randomised controlled trials, is shown in Table B.1.

For the bias direction plots illustrated in Chapter 7, additional details on each domain of bias are required by the tool, namely the direction and type of bias in each domain. An example of the data required by `robvis` in order to produce the bias direction plots is shown in B.2.

B.2.2 Reception

The tool has been well received by the systematic review community. As of December 2021, the `robvis` R package has been downloaded more than 6100 times and the paper introducing the tool had been cited more than 450 times. A copy of this publication is available in Appendix B.3. Development of the tool is ongoing, as evidenced by the new bias direction plot functionality, and there are now a number of contributors to the package.

Table B.1: Example `robvis` dataset - First five assessments contained in `data_rob2`, an example dataset for the Risk of Bias 2 tool for randomised controlled trials available via the `robvis` package.

Study	**D1**	**D2**	**D3**	**D4**	**D5**	**Overall**
Study 1	Low	Low	Low	Low	Low	Low
Study 2	Some concerns	Low	Low	Low	Low	Low
Study 3	No information	Low	Some concerns	Low	Low	Some concerns
Study 4	Low	Low	High	Low	Some concerns	High
Study 5	High	High	Low	Low	Some concerns	Low

Table B.2: Example bias direction dataset - Example risk-of-bias data illustrating the structure required for bias direction plots. d_ij, d_id, and d_it define the extent (Serious, Moderate, Low), direction (right or left), and type (additive or proportional) of bias in the ith domain, respectively Note that, because of the wide nature of the data, I have abbreviated the data in order to display it. A key for interpreting the data can be found below the table.

ID	**d1j**	**d1d**	**d1t**	**d2j**	**d2d**	**d2t**	**d3j**	**d3d**	**d3t**	**d4j**	**d4d**	**d4t**	**d5j**	**d5d**	**d5t**	**d6j**	**d6d**	**d6t**	**d7j**	**d7d**	**d7t**	**overall**
1	H	L	A	L	-	-	M	U	P	L	-	-	L	-	-	L	-	-	M	L	P	H
2	M	R	A	M	L	A	L	-	-	L	-	-	L	-	-	M	U	A	M	L	P	M
3	H	L	A	H	L	A	L	-	-	L	-	-	L	-	-	M	U	A	M	L	P	H
4	H	L	A	M	U	A	L	-	-	L	-	-	L	-	-	L	-	-	M	R	P	H
5	H	L	A	L	-	-	L	-	-	L	-	-	M	U	P	L	-	-	M	L	P	H

Abbreviations: H - High risk of bias; M - Moderate risk of bias; L - Low risk of bias; R - Right; L - Left; U - Unpredictable; A - Additive; P - Proportional

B.3 Copies of papers arising from this thesis

The following pages contain copies of the following publications:

- ***McGuinness L. A.***, *Higgins J. P. T., Walker, V. M., Davies, N. M., Martin, R. M., Coulthard, E., Davey-Smith, G., Kehoe, P. G., and Ben-Shlomo, Y. (2021) Association of lipid-regulating drugs with dementia and related conditions: an observational study of data from the Clinical Practice Research Datalink. medRxiv. DOI: 10.1101/2021.10.21.21265131*

- ***McGuinness, L. A.***, *and L Schmidt. (2020) medrxivr: Accessing and searching medRxiv and bioRxiv preprint data in R. Journal of Open Source Software 5.54 2651. DOI: 10.21105/joss.02651*

- ***McGuinness, L. A.***, *and Higgins J. P. T. (2020) "Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments." Research Synthesis Method). DOI: 10.1002/jrsm.1411*

- ***McGuinness, L. A.***, *and Sheppard A. L. 2020. "A Descriptive Analysis of the Data Availability Statements Accompanying Medrxiv Preprints and a Comparison with Their Published Counterparts." PLOS ONE 16(5): e0250887. DOI: 10.1371/journal.pone.0250887*

- *Hennessy, E. A., Acabchuk, R., Arnold, P. A., Dunn, A. G., Foo, Y. Z., Johnson, B. T., Geange, S. R., Haddaway, N. R., Nakagawa, S., Mapanga, W., Mengersen, K., Page, M., Sánchez-Tójar, A. Welch, V.,* ***and McGuinness L. A.*** *(2021). Ensuring Prevention Science Research is Synthesis-Ready for Immediate and Lasting Scientific Impact. Prevention Science . DOI: 10.1007/s11121-021-01279-8*

These manuscripts arose from work performed as part of this thesis, as discussed more fully in Section 1.7.1.