Science knows it doesn't know everything; otherwise, it'd stop.

1 Background

1.1 Lay summary

This thesis is

1.2 Introduction

This Chapter will provide an overview of the key exposures, outcomes and methods used throughout this thesis.

This Chapter will provide an overview of the thesis, introducing the core concepts used throughout and providing some background context on each. It will briefly discuss the natural history of dementia, it's public health importance and the .IN this context it will highlihg the importance of identifying easily modified treatm

It will also introduce the primary exp, covering their biological role, meausrement and

Finally, it will outline the theoretical framework used in this thesis.

1.3 Dementia

1.3.1 Definition and Subtypes

Dementia is major neurocognitive disorder, with symptoms including impairment of executive cognitive functions such as speech, judgement and memory. The most common causes of dementia are Alzheimer's disease and vascular dementia, accounting for ~60-80% and ~10% of cases respectively. The remaining 10-30% of cases are caused other dementia subtypes (e.g. Lewy Body dementia) or by progression of other neurological diseases (e.g. Parkinson's disease).

1.3.2 Diagnosis

Dementia is difficult to diagnose, primarily due to the absence of a gold standard test for the condition (is this true, or would it be better to say that there is no gold standard test without an autopsy). Information from multiple diagnostic tools are utilised, from medical history examination, through assessment of patients mental ability (e.g. the Mini-Mental State Examination), to clinical tests (e.g. Magnetic Resonance Imaging (MRI) scans).

1.3.3 Criteria

Several scales are commonly used to diagnose dementia and associated diseases for research purposes. Two of the most commonly used include the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR)1 and the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS–ADRDA).[@dubois2007] [**Need first NINCDS-ADRDA citation and DSM-IV citations**

Note important differences between the scales and whether they affect results. Could cross-reference with an exploratory analysis in Chapter ??

1.3.4 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,6 an ageing population looks set to create a dementia epidemic, particularly in Westernised countries. In the UK, there are estimated to be 800,000 people currently living with dementia, with this figure expected to double by 2040.7 Globally, the prevalence of dementia is expected to reach 75 million by 2030.8 Despite the number of dementia cases and decades of research, there remains much unknown about the pathogenesis and progression of the disease.

1.3.5 Challenges in the study of dementia using traditional study designs

Speak to the

Historically, studies on dementia have faced a range of challenges. As a range of determinants (genetic, environmental and lifestyle) are thought to jointly influence the risk, progression and outcomes of dementia, any individual association is likely to have only a small effect. Therefore, the statistical power need to detect these associations will often require sample sizes that are unfeasible using primary data collection. This fact is further complicated by the long latency of dementia, which necessitates a costly long-term approach to patient follow-up. Furthermore, dementia studies often have limited generalisability to the target population, as certain subgroups (e.g. the very old) are frequently under-represented in study cohorts due to difficulties associated with their recruitment.9 Finally, studies employing a case-control design are further limited by the high potential for differential recall bias between those who have and have not developed dementia.10

Fortunately, these limitations may potentially be addressed through the use of routinely collected health data, and the electronic health record databases in which they are stored.

Cognitive impairment not dementia (CIND) is another term used to described those with cognitive impairment but who fall below the diagnostic criteria for dementia.

A further clinical subtype that is of particular import the

And MCI

And different scales

1.3.6 History

> Two major clinical trials are often cited as providing evidence that statins do not have an effect on the incidence ofdementia: the Prospective Study ofPravastatin in the Elderly (PROSPER) and the Medical Research Council/British Heart Foundation Heart Protection Study; however, because of methodologic limitations in relation to dementia outcomes in these two trials, the results of these trials are difficult to evaluate. Dementia incidence or cognitive outcomes were not preplanned endpoints in either of them, neither study included a clinical cognitive evaluation, and numbers of patients with follow-up information for cognitive evaluations were not reported in either study manuscript. In PROSPER a post hoc analysis compared changes in cognitive scores over a 3-year period between statintreated and placebo patients and found no significant differences. In the MRC/BHF HPS trial,27 similar percentages of participants (0.3% in each—statin vs placebo—group) developed dementia during the 5-year follow-up period. The report did not state how the outcome of dementia was determined (e.g., reported as an adverse event or by follow-up phone interview). *Taken from Cramer 2008 - included in review*

There exist only two large scale randomized controlled trials of the effect of statins on dementia risk - in fact these studies are the only two trials included in a 2016 review of statins for the prevention of dementia produced by the Cochrane [@mcguinness2016b]. Both showed no effect of

However, while being widely cited,

Queries around how the data were collected, along

1.3.7 Economic impact

The economic impact of dementia is enormous, but in terms of the direct care required

Patients with dementia stay in hospital for longer,[@mollers2019]

Patients are more prone to falls and other con

1.3.8 Risk factors

1.3.9 Treatments

1.3.10 Preventative measures

1.4 Serum lipids

1.4.1 Range of lipids

The blood profile has a range of lipid fractions to it. However, for the sake of this thesis, we will only consider the three most important fractions, namely total cholesterol, low density lipoprotein cholesterol (LDLc), high density lipoprotein cholesterol (HDLc) and trigylcerides (TG).

1.4.2 HDL-c

1.4.3 LDL-c

Include formula for working out total cholesterol and the ranges.

LDL-c levels are not directly measured but instead are estimated from using the Friedewald formula,[@friedewald1972] where the :

$$LDLc \approx TC - HDLc - kTG$$

where k is 0.20 if measurements are in mg/dl and 0.45 if in mmol/l.

Limitations to the method include a requirement to fast for 12-14hrs prior to measures, an inability to estimate LDLc if TG levels are high

Measurement error is a big deal for this thesis, as will discuss measurement error regarding how different codelists/measurement of AD vs vascular dementia affect results in later chapters.

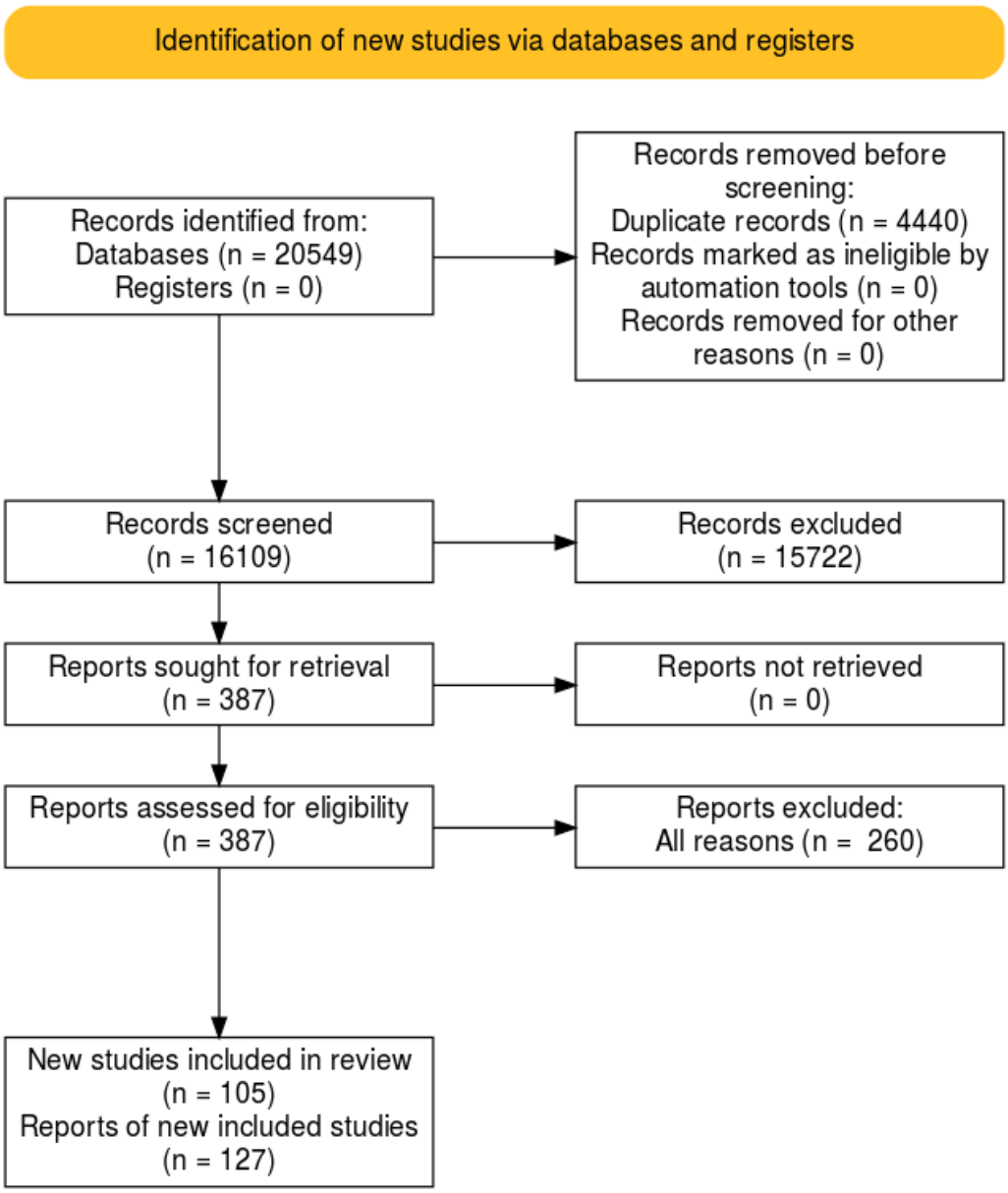

Figure 1.1: Statin mechanism of action:

1.4.4 Triglycerides

1.4.5 Total cholesterol

1.5 Serum lipid interventions

1.5.1 Statins

Statins are the primary

Lipophilic

Hydrophilic

1.6 Other lipid regulating agents (LRA)

1.7 Methods used in the thesis

1.7.1 Evidence synthesis

The main theoretical framework used in this thesis is evidence synthesis - the identification, critical assessment, and integration of all available evidence on a research question in order to either: a) provide a more definitive answer to that question; or b) highlight gaps in the existing evidence base.

While this thesis does include a research tool (Chapter 2 - systematic searching of preprint) and a primary evidence generation element (Chapter 5 - observational analysis of CPRD data), this was performed with the intention of providing a further source of evidence for the evidence synthesis/triangulation aspect of the thesis.

1.7.2 Involvement of patients and the public

Lay summaries appear at the beginning of each chapter, reviewed by the Patient and Public Involvement panel. They provide a plain language summary

1.7.3 Primary cohort analysis

1.7.4 Triangulation

1.7.5 Individual patient data meta-analyis

1.8 Summary

1.9 Aims and Objectives of the thesis

1.9.1 Hypothesis

1.9.2 Aim

1.9.3 Objectives

- To review the published literature with respect to the effec tof lipids and lipid regulating agents

- 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
- To meta-analyze the

1.10 Theoretical framework

The main theoretical framework used in this thesis is evidence synthesis - the discovery and critical integration of all available evidence on a research question in order to either: a) provide a more definitive answer to that question or; b) highlight gaps in the existing evidence base, so that future research address questions that have yet to be answered, or explores the same question in a way that increases our confidence in the result.

All elements of this thesis are based around this framework.