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

1 Background, Theoretical framework, Aims & Objectives

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 context on each. It will briefly discuss the underlying pathologies and diagnosis of dementia, its public health importance, and the current state of treatment and prevention therapeutics. In this context, it will highlight the importance of identifying easily modified risk factors and introduce blood lipids, and blood lipid-modifying treatments such as statins, as the primary exposures considered by this research.

The central theoretical framework used - the synthesis of diverse sources of evidence - is introduced, and the research presented in this thesis is then framed in terms of three types of diverse evidence, with opposing viewpoints for each being discussed.

Finally, it will outline the aims, objectives and structure of this thesis, and briefly summarise the contributions to the scientific literature that arose from this research.

1.2 Dementia

Dementia is major neurocognitive disorder, with symptoms including impairment of executive cognitive functions such as speech, judgement and memory.

1.2.1 Underlying pathologies

Dementia is a collective umbrella term for a range of conditions each with different clinical presentations and disease courses, and is generally defined as "".

Alzheimer's disease, named after Dr. Alois Alzheimer who presented the first recorded case in 1907, is the most common cause of dementia, accounting for approximately 60-80% of cases. Characterised by substantial cognitive impairment and diffculty with high level executive function to the extent that it interferes with, it is an insidious disease, within initial onset thought to occur up to 15 years prior to symptomatic presentation. Much remains unknown unknown about Alzheimer's pathogenesis, despite research implicating the accumluation of amyloid plaques and neurofibrillary tangles, or alternatively the cholingeric nervous system, as potential mechanisms of disease.

Vascular dementia (VaD) is the second largest underlying pathology of dementia, accounting for ~10% of cases and is caused by a range of cerebrovascular disorders. Presentation can vary widely based on the underlying cause, and due to the varied underlying pathopysiology, VaD can onset quite rapidly following a cerbrovascular event such as a stroke or over a long period due to series of small infarcts. VaD is diagnosed using the NINCDS-AIREN criteria.[@roman1993vascular]

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).

Where more than one underlying dementia pathologies co-occur, this is termed mixed dementia. It is common for patients to present with mixed dementia, as the occurrence of one underlying cause weakens overall brain health and increases the likeliness of occurrence of the other.

1.2.2 Diagnostic criteria

Dementia is difficult to diagnose, primarily due to the absence of a gold standard test for the condition. There exist several diagnostic criteria for dementia and related disease, many of which have existed for quite some time and have more recently been updated to reflect current understanding in dementia pathology. In all cases, dementia is diagnosed on the basis of behavioural and congitive changes as assessed by an experience clinician.

Two of the most commonly used criteria include the the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR) criteria and the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS-ADRDA) criteria.[@dubois2007]

While these define the overall parameters for a assinging a dementia diagnosis, they are informed using practical scales to measure patients cognitive health, with two of the best known of these scales 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 a tool for assessing cognitive impairment, but does not by itself indicate the absence or presence of dementia, instead merely indicating congitive impairment which could be due to another cause (for example, temporary delerium as a result of an infection or surgery). A low score on the MMSE should feed into the diagnostic process, potentially as a screening tool to help identify which patients require further assessment by a trained clinician. Studies that use a memory scale alone are likely to be biased.

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,[@prince2016] an ageing population looks set to create a dementia epidemic, particularly in Westernised countries. 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.[@baker2019] Globally, the prevalence of dementia is expected to reach 75 million by 2030.[@prince2016]

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.[@wittenberg2019] . Based on the implications of a dementia diagnosis, this is perhaps unsurprising. Patients living with dementia are more prone to falls and other conditions that necessitate admission to hospital. Once admitted, patients with dementia are more likely to be stay in hospital for longer.[@mollers2019]

The urgent need to reduce the burden of dementia, both at the personal and system (national health systemic) level, is clear. As such, the systematic assessment of easily modifiable targets (such as blood lipid levels) for their utility in the prevention of dementia should be prioritized.

1.2.4 Treatments

Developing treatments for dementia is regularly deemed to be one of the hardest markets in the pharmaceutical world, with trials of seemingly promising therapeutics, such as BACE inhibitors, being regularly abandoned due to futility.[@cummings2020]. At present, there are no known curative treatments for dementia, regardless of the underlying cause, though several 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.[@hampel2018] Commonly prescribed ACE inhibitors include donepezil and galantamine.[@pariente2008] ACE inhibitors increase the availability of the neurotransmitter, and has shown clinical effect is easing the behavioural and

memeory-related symptoms of Alzheimer's disease.[@marucci2020] ACE inhibitors are only a stop-gap treatment, treating the symptoms rather than the underlying pathology which may continue to progress.

Several cardiovascular elements have been identified as potential risk factors for dementia, and of these, lipid levels represent a promising target for preventative treatment due to the availability of lipid-modifying treatments. In this context, determining whether variations in lipid levels are causative for dementia may prove critical in reducing the future burden of the condition. The next section provides an overview of blood lipid fractions and therapeutic interventions that modify them.

1.3 Serum lipids

1.3.1 Lipid fractions

The blood lipid profile contains a range of fractions. However, for the sake of this thesis, we will only consider the two most important fractions, trigylcerides (TG) and cholesterol, which are either absorded from food (exogenouse lipids) or produced internally (endogenous lipids).

Triglycerides are the simplest and most common type of lipids found across the body. They are used to store unused calories from food, and to move energy around the body. In contrast, cholesterol is primarily used to create cell walls and certain sex hormones. As lipids are not water soluble, within the blood stream, cholesterol is transported in lipoprotein structures of varying densities. Low-Density-Lipoprotein-cholesterol (LDL-c), commonly know as the "bad" cholesterol, transports fat to cells. In contrast, High Density-Lipoprotein-cholestel (HDL-c), transports cholesterol to the liver to be broken down and excreted.

Total serum cholesterol is a commonly used summary measure to estimate the total lipid burden in a patients blood, and derived from the HDL-c, LDL-c and TG fractions using the Friedewald formula:[@friedewald1972]

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

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

Elevated cholesterol in the bloodstream via high LDL-c levels leads to atherosclerosis, the build-up of fatty deposits in the blood vessels, which 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 attach or stroke. Globally, the prevalence of elevated total cholesterol, or hypercholestoreolemia, was estimated by the World Health Organisation to be approximately 40%.

1.3.2 Statins

Statins are by far the most common method of lipid regulation currently prescribed. Statins inhibit the conversion of 3-Hydroxy-3-Methylglutaryl-Coenzyme-A (HMG-CoA) into mevalonic acid, by compeitivlely binding with HMG-CoA Reductase (HMG-CoA-R). This conversion is the key rate limiting step in the biochemical pathway that produces cholesterol (see Figure **??**), allowing statins to reduce the production of LDL cholesterol.

Statins can either be lipophilic or hydrophilic, with several of the common brands falling into each category. The distinction between the two is of particular importance in the assessment of their impact on dementia, as only lipophilic statins can cross the blood brain barrier. However, this is only applicable if the relationship between statins and dementia risk is independent of their impact on circulating blood levels.

1.3.3 Other lipid regulating agents (LRA)

There are a range of other interventions that can be used to modify a persons lipid profile, though each act is slightly different ways. Most commonly though, these treatments are either used as adjunct (additional) treatments with statins therapy, or are used in situations where statins are contra-indicated or not tolerated.

The most commonly used non-statin therapeutic is ezetimbibe, 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/ezetimbe therapies (both compounds contained in a single pill, as opposed to complimentary treatemnts).

A second example are fibrates, used to treat hypertriglyceridaemia 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.[@chaudhary2017] 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.

1.4 Evidence for the association between blood lipids and dementia

In this section I provide 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 [CITE], while the most established genetic risk factor for late-onset dementia, apolipoprotein E (ApoE), is involved in cerebral cholesterol transport. Several other genes involved in cholesterol transport have also been found to be robustly associated with increased AD susceptibility [CITE].

Despite these encouraging results, evidence from the diverse range of epidemiological studies on this topic has to date been been contradictory.

1.4.2 Observational studies

Several observational studies have examined the relationships between concentrations of serum lipids (total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c) and triglycerides) and both Alzheimer's disease and vascular dementia and reported widely different results. A high serum cholesterol concentration has been found to be associated with an increase in susceptibility to AD [8-13], though other studies have shown no association [14-17], or a reduced susceptibility [18,19]. With regards VaD, decreased levels of HDL-c appear to be associated with increased risk [18,20,21], while for LDL-c, studies have reported both positive and negative association [18,22].

1.4.3 Randomised controlled trials

Meta-analyses of randomised controlled trials are commonly seen as the gold standard in terms of epidemiological evidence. Indeed in the "evidence pyramid", meta-analysis of trials sit proudly on top. However, there included several potential limitations to this trial-only approach. In terms of the central research of this theis, RCTs of statin therapy can be used to provide indirect evidence for 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 prodomal period, such as dementia (see Section @()), as they would require extremely long and costly follow-up.[@ritchie2015] Additionally randomised trials require clinical equipoise - something that is unlikely in the case of statins, as while equipose may exist, it would be unethical to randomised patients to statins or not given their proven protective effect against coronary disease. It is no surprise then that the two know existing trials providing evidence on the effect of statins on dementia risk, identified by a recent Cochrane review,[@mcguinness2016a] are in fact trials of statins for the prevention of coronary related outcomes. The Prospective Study of Pravastatin in the Elderly (PROSPER) examined the protective effect of pravastatin on coronary outcomes.

While being widely cited and indeed included in a Cochrane review on this topic (ironically, the lead author on this Cochrane review is), these studies have major limitations that their utility to provide evidence on the effect of statin treatment on in assessing the impact of lipid-lowering treatment on dementia risk. Firstly, there was no clinical cognitive evaluation of patients to determine a dementia outcome. In fact, the PROSPER trial reported not on dementia outcomes, but on the change in cognitive scores over a mean of 3.2 years. As highlighted in Section @() , change in scores alone is insufficient to diagnose a dementia outcome. The second trial, the Medical Research Council/British Health Foundation Protection Study found no effect of simvastatin on dementia (OR: 1.0 (95% CI:0.6-1.6)), but did not report how the outcome was assessed/recorded within the trial.

Additionally, the two trials, while putatively examining all-cause dementia subject to the limited applicability of change in cognitive scores as described above, do not make any effort to assign an underlying pathology to each case. As discussed in Section @ref(), the different underlying pathology of dementia have different mechanisms of action, and so it is not given that the effect of statins would be consistent across them.

Additionally, both trials were limited by the relatively short follow-up period examined, expected when the primary outcome of the trials were coronary related conditions rather than dementia [24,25]. 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 leg time between non-symptomatic onset of dementia and clinical presentation. Finally, as they included only patients at high vascular risk, their generalisability to other settings is limited [23].

1.4.4 Mendelian randomisation

Newer methodological approaches, such as Mendelian randomisation (MR),[@daveysmith2014] have also been used to examine the effect of varying lipid levels on dementia risk. 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 [26]. The analytic method relies on several assumptions about the instrumental variable (IV),[@davies2018] as shown in Figure **??**, namely that:

1. the IV is associated with the exposure of interest (the relevance assumption);
2. the IV and outcome do not share a common cause (the independence assumption); and
3. the IV does not affect the outcome other than via the exposure (the exclusion restriction assumption).

This approach relies on the results of genome wide association studies (GWAS) to identify appropriate instruments, and as such, analysis of this type are restricted by the availability of relevant GWAS. As the cost of genome sequence falls, more and more GWAS are being performed, and so number of MR studies had increased in tandem.

A recent MR study indicated that low levels of LDL-c may cause a reduction in AD risk.[27] However, this study was widely criticised as it did not exclude the region surrounding the ApoE gene, the strongest know risk factor for Alzheimer's disease. This invalidated the exclusion exclusion restriction criteria (Assumption 3, above), as the risk reduction observed in this study could be driven by variants in this region via a pathway independent of lipid levels.

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

1.5 Theoretical framework: Evidence synthesis

The central 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.

This thesis applies seeks to use an evidence synthesis framework to assess the relationship between lipids/statins and dementia. Of particular interest is the synthesis of evidence from a range of diverse sources. This thesis considers three sources of diversity in the evidence base:

- Diverse study designs (and sources of bias)
- Diverse publication status (preprints vs published articles)
- Diverse sources of data (summary level data vs individual-level data)

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

1.5.1 Study designs

As illustrated in Section 1.4, each individual epidemiological approach taken to examine the central research question of this thesis is subject to distinct biases and short-comings that limit our ability to infer a causal relationship between blood lipids and subsequent dementia risk.

However, as each approach will be subject to distinct biases, these differences in design can be advantageous. If all approaches point, or triangulate, towards the same answer, this strengthens the evidence of a causal link between lipid levels and dementia risk.[26] In this context, systematically identifying, assessing and integrating all available evidence in a "aetiological triangulation" framework,[@lawlor2016a] regardless of study design or approach taken, may help to increase our confidence that a causal relationship truly exists.

As such, this thesis aims to find all existing evidence on the relationship between lipids/statins and dementia via the comprehensive review in Chapter **??**, and then triangulate the different sources of evidence along with the primary analyses performed in this thesis (Chapters **??** and **??**) in Chapter **??**.

1.5.2 Preprints versus peer-reviewed articles

Defined by the Committee on Publication Ethics (COPE) as 'scholarly manuscript[s] posted by the author(s) in an openly accessible platform, usually before or in parallel with the peer review process'[@committeeonpublicationethicscope2018], preprints serve several purposes. They are used to establish primacy when submitting to a journal where the peer-review process may take several months;[@vale2016] to rapidly disseminate research findings, as occurred during the COVID-19 pandemic;[@fraser2020a] and to make available publications that may not have been accepted elsewhere in an attempt to combat publication bias or the "file-drawer" effect.[@rosenthal1979]

Preprint repositories have existed in certain fields for many years, such as the aRxiv for preprints in physics and mathematics, but have recently expanded into other fields. Repositories now exist for everything from ecology (EcoEvoRxiv) to meta-research (metaArXiv). There is much ongoing debate, particularly in light of the explosion of preprints following their widespread use to disseminate research related to the COVID-19 pandemic, about how preprints should be handled in the context of an evidence synthesis.

One of the major criticisms of using preprints as an evidence source is that they have not yet undergone formal peer review. Some researchers recommend treating preprints as a separate category to peer-reviewed publication, using a flag or marker to indicate that certain evidence was sourced from. However, this approach assigns a lot of weight to peer-review as a indicator of "quality". Given the rise of predatory journals, and the (anecdotally) variable quality of peer-review across legitimate journals depending on the reviewer selected for a paper, peer-review is not always a reliable indicator.

Meta-studies of the concordance between preprints 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 overwhelming majority of cases.[@shi2021a] This indicates that preprints

should be considered a reliable reflection of the study, though these analyses are by necessity limited to preprinted studies that were subsequently published - the effect of peer review in limiting the publication of poorly design or executed studies is harder to assess. However, in the absence of any information on the subsequent publication, the preprint contains the best available evidence on a given research study, and so should be included in the review.

The inclusion of non-peer-reviewed preprints substantially increases the need for thorough and detailed risk-of-bias assessment as part of the systematic review, in lieu of formal peer review. Risk-of-bias assessments provide a structured and transparent way to assess the internal validity of a study across several domains of bias. In theory, risk-of-bias assessments should be performed as part of systematic reviews, regardless of whether they included preprints, but several of the existing highly cited reviews of observational studies of the relationship between statins and dementia did not perform any risk-of-bias assessment.

Accepting that preprints represent an import source of information, their inclusion in systematic reviews is limited in practical terms by the absence of a replicable and transparent search tool for performing systematic searches in preprint repositories. The tool presented in Chapter **??** aims to address this, and enables the inclusion of health-related preprints as evidence sources in the systematic review presented in Chapter **??**.

1.5.3 Summary level results vs individual patient data

If lipids are found to have a causal role in development of dementia, evidence-based preventative strategies would be informed by identifying the types of individuals who are most likely to receive benefit from treatment with lipid-modifying agents. Analysis of summary level data, that is the data extracted from publications describing primary studies, can only take investigators so far in this regard. Due to a lack of primary studies readily presenting results stratified by covariates of interests, for example sex and ethnicity (see Section @ref()), meta-analyses

of summary-level data often have limited ability to examine exposure-covariate interactions (for example, sex and ethnicity.

An individual participant data (IPD) meta-analysis is therefore the best option to examine the modification of dementia risk by individual-level covariates. This analytical approach has the added benefit of allowing a common set of inclusion criteria and statistical model to be applied across all dataset, potentially eliminating some important sources of heterogeneity. It also allows for the incorporation of relevant, previously un-analysed datasets, available via new initiatives such as the Dementia Portal UK, which aim to provide access to several dementia-related datasets via a single simplified application process.

This thesis will attempt to obtain the raw data from relevant primary studies identified by the systematic review in Chapter **??** and combine this with previously unanalysed data from the DPUK portal as part of an individual participant data meta-analysis in Chapter **??**.

1.6 Aims and Objectives of the thesis

1.6.1 Hypothesis

Circulating blood lipid levels, and by extension treatments that modify blood lipid levels such as statins, affect the risk of subsequent dementia.

1.6.2 Aims and Objectives

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 meta-analyse previously unexplored datasets as part of a individual participant data (IPD meta-analysis)

1.6.3 Thesis Structure

Chapters are self-contained, presenting the methods and results of that specific research project. The are bookended by introductory and discussion sections which place the methods and results in context. Each chapter is prefaced by a "Lay" or plain English summary, developed with input from the Patient and Public Advisory Group (see Section **??** for a discussion of the group's involvement and Appendix **??** for more detail on the group).

- **Chapter 1:** Background information on dementia and blood lipid levels. This chapter provides an introduction to the topics covered in this thesis to non-subject area experts, and discusses the motivation for the remainder of the thesis.
- **Chapter ??:** This Chapter introduces a new tool, the `medrxivr` R package, which was used to developed to allow for systematic searches of the health-related preprint repositories.
- **Chapter ??:** This Chapter describes a comprehensive systematic review and meta-analysis of all available evidence on the relationship between blood lipids, and interventions that modified blood lipids, and dementia.
- **Chapter ??:** 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, based in England.
- **Chapter ??:** This Chapter describes an individual patient data analysis of several previously unanalysed longitudinal cohort studies, to describe the relationship between blood serum lipids and dementia outcomes.

1.7 Outputs from this thesis

The outputs of this thesis are detailed below, and include published peer review papers, presentations at conferences, open source evidence synthesis tools.

1.7.1 Contributions to the scientific literature

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

***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 short paper introducing the open-source preprint search tool described in Chapter **??**.

*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., **McGuinness L. A.** (2020). Ensuring Prevention Science Research is Synthesis-Ready for Immediate and Lasting Scientific Impact. MetaArXiv. DOI: 10.31222/osf.io/ptg9j*

The experience of extracting data for the systematic review in Chapter **??** inspired a practical guide for researchers in prevention science is currently under review at Prevention Science. This piece was co-written with Dr. Emily Hennessy (see author declarations).

***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*

The tool used to visualise the risk-of-bias assessments in Chapter **??** has been published in Research Synthesis Methods. See Appendix **??** for more details on this tool.

***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." MetaArXiv. DOI: 10.31222/osf.io/p75xe*
Using the tool described in **??**, I performed a "research-on-research" study, comparing the concordance between the 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 **??**.

1.7.2 Presentations/Talks

- Abstract accepted to the Cochrane Colloquium 2019
- ARUK abstract on systematic review (I hope!)
- Presentation to the Evidence Synthesis and Meta-Analysis in R Conference (ESMARConf)
- Invited seminar series on the RoB2 risk-of-bias assessment tool for randomised controlled trials to for Evidence Synthesis Ireland
- Presentations to internal department wide seminar series, including the Methods in Evidence Synthesis Salon (MESS) and the MRC-IEU seminar series.

1.7.3 Software

`medrxvir`

An R package and associated `shiny` web application that allows users to easily search and retrieve bibliographic data from the medRxiv[@rawlinson2019] and

bioRxiv[@sever2019] preprint repositories. See Chapter **??** 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:

`robvis`

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

1.8 Summary

This Chapter has provided background information on the core elements of the central research question, framed the research presented in this thesis in the context of an evidence synthesis framework, and described the contributions of the research in this thesis to the scientific literature.