**Chapter 1 – Background**

**Key take-aways:**

* **Dementia is a pressing public health concern.**
* **Evidence-based prevention, using readily modifiable risk factors, will be important as the population ages.**
* **Current evidence on lipid-dementia relationship is contradictory**

**Favourite/most interesting aspect:**

* Defining a theoretical framework - wasn't something I had done before, and so it was interesting to have to formally define how my research interests fit together.

**Chapter 2 - medrxivr**

**Key take-aways:**

* **Preprints can contain important information.**
* **Developed a new tool to search medical/health-related preprints, published in Journal of Open Source Software**
* **Also allows for access to preprint data, enabling two case studies:**
  + Journal policies affect the availability of data.
  + Two-thirds of the preprints published allowing for a two-year lag.

**Strengths:**

* Transparent and reproducible searching, enabling the systematic review in Chapter 3 & 4.
* Advantages over previous tools:
  + Allows for searching of preprints, rather than just summarising social media engagement
  + Allows historical searching, not just most recent

**Weaknesses**

* Only searches metadata, not the full text of the preprint.
* Doesn't fully address publication bias, as preprints still represent a prepared manuscript.

**Favourite/most interesting aspect:**

* A large proportion of preprints are not formally published after a two-year lag.
* The peer review process for software is great.

**Chapter 3/4 - Systematic Review**

**Key takeaways:**

* **Review sought to identify all evidence, regardless of study design or publication status.**
* **Most studies:**
  + were non-randomised studies (Figure 4.17)
  + examined all-cause dementia and Alzheimer's disease (Table 4.1)
  + were published (Figure 4.1)
  + were based in Western countries (Figure 4.2)
  + were poorly reported.
* **Some indication of protective effect of statins on ACD/Alzheimer’s in NRSI but not in RCT/MR:**
  + Presence of bias in NRSI
  + Different exposure windows are important
* **Risk of bias was generally high, and ROB-ME was also high.**
* **For Mendelian randomisations studies:**
  + Lots of overlap between those using two-sample approach
  + Lack of search filter/risk-of-bias tool
  + Strong potential for missing evidence due to multiple comparisons
  + Substantial attenuation following adjustment for ApoE4
* **Suggestion of heterogeneity (high I2), but could only investigate for sex (no effect) because:**
  + Small number of meta-analyses had 10 or more results
  + Reporting of important variables was poor
* **Weak evidence of dose-response (Figure 4.16) or publication bias (Appendix A.4.2)**

**Strengths:**

* Comprehensiveness of review, above existing reviews
* Structured approach to risk-of-bias assessment, including novel ROB-ME assessment
* Inclusion of preprints as an evidence source
* Piloting of new methodologies (preprint searching, ROB-ME assessment, and robvis)

**Weaknesses:**

* Only a sample of records were dual screened
* Search may be out of date (Summer 2019)
* Preliminary version of ROBINS-E used
* Strong potential for missing evidence

**Favourite/most interesting aspect:**

* Opportunity to experiment with visualisation methods (map, paired forest plots, etc.)
* Risk of bias due to missing evidence - interesting to see how blatant it often is.

**Chapter 5 - CPRD**

**Key takeaways:**

* **Aimed to address two issues identified in review:**
  + Absence of evidence on vascular dementia
  + Bias due to immortal time, as per risk-of-bias assessments
* **Examined 1.6 million participants, with median follow-up of 6 years.**
* **Fully adjusted Cox PR model with time-varying treatment indicator suggested:**
  + No association of treatment with probable/possible Alzheimer's disease
  + Harmful association of treatment with all-cause, vascular and other dementia
* **For specific treatments:**
  + Main effect driven by statin group
  + Ezetimibe with increased risk of vascular and other dementia
  + Fibrates with increased risk of all-cause dementia and probable Alzheimer’s
* **Control outcomes (IHD, Backpain, Type 2 Diabetes – Figure 5.7) showed strong potential for confounding by indication, likely related to vascular factors (Figure 5.12)**
* **Sensitivity analyses:**
  + Results robust to **imputation**, **covariate list** and **pregnancy status**
  + Entry period - variation in prob AD group, but not due to different diagnosis by period
  + Statin properties
    - Hydrophilic pulled effect estimates to the left vs lipophilic (Figure 5.11)
    - Contrary to idea that lipophilic is better as can cross blood-brain barrier
  + Smeeth
    - Comparison of code list didn't help (Figure 5.13)
    - Obtained harmful results using their code list, in contrast with their paper

**Strengths:**

* Provides evidence on vascular dementia
* Size of the CPRD - one of the largest available studies, as per review
* Use of time-updating treatment covariate

**Weaknesses:**

* Differential misclassification of the outcome based on treatment
* Challenging comparing across studies using different code lists
* Uncontrolled confounding due to ApoE4
* Potential for reverse confounding

**Favourite/most interesting aspect:**

* Value of including control outcomes to illustrate confounding
* Comparison with published work using target trial approach

**Chapter 6 - Individual patient data analysis**

**Key takeaway:**

* **Aimed to collect and combine multiple cohorts to:**
  + Identify participants most likely to benefit from lipid lowering (age/sex)
  + Produce more evidence on lipids and vascular dementia
* **Applied for access to cohorts from the review and the DPUK (Figure 6.1):**
  + Some cohorts identified but not approached as didn’t have relevant covariates
  + 3 (8%) of 37 cohorts approached provided data
  + Even within the DPUK, just over half responded at all.
  + Within DPUK cohorts, some excluded following data access (Table 6.1)
* **Three included studies were all based in the UK: Caerphilly, EPIC Norfolk, Whitehall II**
* **Presented results for two models (results robust between them, Figure 6.4):**
  + *Minimally adjusted (M1):* age, sex, smoking, alcohol, education and diabetes
  + *Maximally adjusted (M2):* M1 + ethnicity, prevalent ischemic heart disease, and BMI
* **Using M1 across 11,000 participants to assess main effects:**
  + 1 mmol/L increase had no effect on any lipid/outcome pair
  + *except* for *(tentative)* harmful association of triglycerides and vascular dementia (Figure 6.3)
* **Interaction analysis:**
  + All-cause dementia – none except protective effect of male on LDL-c/all-cause dementia
  + Vascular dementia - could only investigate age, and no evidence for an interaction.
* **Qualitative difference between previous analysis of Whitehall II for triglycerides (Figure 6.8/6.9), potentially due to use different handling of missing data and ApoE4 adjustment**

**Strengths:**

* Used systematic approach to collect data from cohorts
* Incorporates previously unanalysed cohorts w.r.t this question
* Provides new evidence on vascular dementia
* Examined interaction between age/sex and lipid-dementia relationship

**Weaknesses:**

* Low response rate to requests for data (not unexpected, given previous studies)
* Uncontrolled confounding (ApoE4, etc.)

**Favourite/most interesting aspect:**

* Minimal impact of adjustment, similar to that observed in Chapter 5 (Figure 6.4)
* Low response rate from DPUK, despite it being a managed application process

**Chapter 7 - Triangulation**

**Chapter 8 - Discussion**

**Key takeaway:**

* **Summary of findings**
  + No consistent evidence of effect of lipids at midlife on dementia outcomes
  + At odds to published literature demonstrating the protective effect of statins
* **Two recent big studies recently published:**
  + Iwagami - 1 million CPRD patients
    - Slight increased risk of Alzheimer's disease with increased LDL-c
    - No adjustment for ApoE4, and simulation illustrates this would explain this
    - Reportedly studied TG-vascular dementia relationship, but not reported
  + Gong - 500000 UK BioBank patients
    - No association between lipids and dementia outcomes in 500,000 UK Biobank
    - Similar to Iwagami, may be subject to residual confounding due to ApoE4
* **Implications for clinical practice**
  + No clear guidance
  + Clinicians should be aware of uncertainty and be prepared to communicate it to patients
* **Methodological contributions**
  + Inclusion of pre-printed evidence
  + Assessing and visualising risk of bias
  + Triangulation framework
* **Suggestions for future research**
  + Long-term follow-up of existing trials of statins
  + Focus on obtaining additional evidence on vascular dementia (e.g. VaD GWAS)
  + Guidance on handling discrepancies between preprinted and published records
  + Tools for reviewing MR studies (search filter/ROB tool/duplication of TSMR)
  + Expansion of triangulation methods (empirical priors, incorporation of ROB-ME)

**Strengths:**

* Identification and triangulation of multiple sources of evidence
* Production of new evidence:
  + from previously unanalysed data (EPIC, Caerphilly)
  + on understudied outcome (vascular dementia)
* Production of software to support new ES techniques

**Weaknesses:**

* Absence of well-understood mechanism for Alzheimer's disease
* Reliance on secondary data sources - no primary data collected
* Missing evidence was common (reported results/vascular dementia/data access in IPD)
* Geographical focus - lots of UK/Western based evidence, so may not generalise