**Notes**

* **Corrections are highlighted in blue in the document.**

**General corrections (provided in the Word document)**

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| **Abstract** | 1. The rationale is not very clear. What was the existing evidence before the study/thesis? Previous evidence of associations and causal effects? Are there uncertainties? | I am somewhat limited in what I can add to the abstract given the 350-word limit. However, I have:   * Added text to highlight the existing uncertainty in the literature regarding the effect of lipids on dementia outcomes * Expanded the LDL/HDL abbreviations on first use. * Added text to clarify that meta-analyses were performed as part of the systematic review * Reported the results of the association between triglycerides and vascular dementia. * Updated the text to ensure that the description of the CPRD results presented in the Abstract agrees with the main text   I have not reported the results of the systematic review (Point 3, left), as to maintain the word limit, I would have to cherry-pick a subset of results from the many presented across Chapter 4 which might mislead readers.  Note that some of these changes reflect suggestions made as comments on the PDF of my thesis [see the next table for a list of these comments]. |
| 2. Report results of the association between triglycerides and vascular dementia |
| 3. Report results of systematic review of MR studies |
| 4. Results of your CPRD analysis are not consistent with that in the main text. Please revise |
| **Chapter 1** | The section on “Public health importance” only touched on the incidence, prevalence and economic costs. What about the morbidity and mortality associated with dementia? Please expand. | Fixed. Added additional paragraph to describe the impact of dementia on comorbidity incidence and management. |
| Revise text on AD and VaD to reflect the evidence base from population-based studies, including that from epidemiological neuropathology in which it is clear that dementia at older ages is mixed in aetiology and how this influences the study of all-cause dementia and its currently used subtypes. | Fixed. Added an additional paragraph and reworked existing text to discuss the validity of specific dementia subtypes vs a mixed/all-cause outcome. |
| What was the rationale/motivation for choosing lipid levels as your exposures of interest (Page 7; Paragraph 2 of section on Risk Factors)? This wasn’t communicated clearly in your thesis. There was mention of reducing the prevalence of the seven most important risk factors for dementia (obesity, hypertension, diabetes, smoking, physical inactivity, and low educational attainment) which could reduce the prevalence of dementia. Then you started the next paragraph with “In this context, lipid levels represent a promising target….” Make clearer how you arrived at lipid levels being a promising target for preventative treatment, given that there was no previous mention or discussion of this. Furthermore, you stated seven most important risk factors, but you only reported six. | Fixed. Text has been added and the paragraphs reordered to make the rationale for the focus on lipids clearer. I have also added the missing risk factor (depression) to the list. |
| Section on “Randomised controlled trials”: Need to mention that another limitation of RCTs of statins in being unable to assess the causal effect of LDL-c lowering on dementia risk is due to the pleiotropic effects of statins. They modify levels of other markers such as C-reactive protein, which are also associated with dementia risk, hence difficult to attribute any changes to LDL-c alone. | Fixed. An additional paragraph discussing this point has been added. |
| The last paragraph of the section “Individual participant data meta-analysis” was written in the future tense (page 19). Please revise | Fixed. Reworded to the correct tense. |
| **Chapters 3 & 4** | You did perform meta-analyses in these chapters. Not sure why you did not include the term “meta-analysis” in the title; title should rather be “Systematic reviews and meta-analyses of existing evidence on the association between blood lipids and dementia outcomes” to reflect what was done. | Fixed. Add “and meta-analyses” to the titles of Chapters 3 & 4. |
| Tables of baseline characteristics do not report duration of follow-up especially for the non-randomised studies. This is very relevant in the context of the outcome dementia and biases such as reverse causation and regression dilution bias. Please include another column for these. | Fixed.  **Note:** This correction is not highlighted in the corrected PDF, due to incompatibility between the highlighting and table-rendering packages. |
| Provide rationale for reporting RR as per SD increase. | Fixed. Added additional text to the analysis overview related to this point. |
| **Chapter 5** | Page 143: Not sure what these results refer to “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).” | Fixed. Added text to clarify where these results were sourced from. |
| Your original results showed that statin use was associated with increased risk of all-cause dementia, vascular dementia and other dementia. Please rephrase statement as not clear. | Fixed. Additionally, inconsistencies between the abstract and main text in relation to these findings have been addressed. |
| **Chapter 6** | Regarding the findings of the associations of triglycerides with all-cause dementia using Whitehall cohort II, you found a harmful effect and Tynkkynen et al found a protective effect. Your potential reasons for the discrepancy include handling of missing data, difference in number of events, adjustment for ApoE status. Could the fact that you used ORs and the other study used HRs be responsible for the difference? Add a sentence or two for this. | Fixed. Added an additional sentence related to this point. |
| Regression dilution bias was never mentioned as a potential source of bias. It is an important source of bias in observational cohort studies and could be responsible for some of the null findings. It should be mentioned/discussed. | Fixed. Add additional section to the discussion of limitations describing the potential impact of this bias. |
| **Discussion** | Discussion section – this needs to reflect the text that will have been inserted and modified in the background introduction to dementia in ageing populations with a critique of the emphasis on specific subtypes and how this can lead to curious findings because of diagnostic processes. | Fixed. Added an additional paragraph to the “Limitations” section of the final discussion chapter to highlight the problems introduced from the focus of existing evidence on dementia subtypes. |

**Line edits (provided as comments in the PDF)**

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| **Abstract** | **Background:** Expand LDL-c/HDL-c abbreviations the first time they are used. | Fixed. See comments in the *General corrections* tableabove for a fuller discussion of changes made. |
| **Background:** What is new and what is the existing evidence before this study? Would have liked to see a brief discussion/statement on the existing evidence in the background. |
| **Methods:** State that thesystematic review included meta-analyses |
| **Results:** Results of CPRD analysis not consistent with that in main text. |
| **Chapter 1** | **Lay summary:** Your aim was to infer causality. I don't think this term [risk factor] captures your real aim. | Fixed. The last sentence of the lay summary now reads: “The aim of this thesis is to use all available evidence to assess whether raised blood lipid levels are in fact a cause of dementia.” |
| **Section 1.2.1:** Two additional references needed:   * “Alzheimer’s disease is the most common cause of dementia, accounting for approximately 60-80% of cases” * “Vascular dementia (VaD) is the second largest underlying pathology of dementia, accounting for ~10-25% of cases” | Fixed. |
| **Section 1.2.3:** Needs more discussion on morbidity and mortality. | Fixed. See related point in *General corrections* above for a fuller discussion of changes made. |
| **Section 1.2.5: Relating to risk factors:**   * What are these risk factors? * Only six risk factors are listed [text states there will be seven] * Not quite sure how you arrived at lipid levels as a promising target, given that it hasn't been previously mentioned! | Fixed. See related point in *General corrections* above for a fuller discussion of changes made. |
| **Section 1.5.1:** Typo, “the” -> “they” | Fixed. |
| **Section 1.5.2 (last paragraph):** This section is reported in the future tense. Has this not been done already? | Fixed. |
| **Chapters 3** | **Titles:** Include "meta-analysis" in title as you did pool the evidence. | Fixed. |
| **Section 3.2.3 (& throughout):** You have previously abbreviated [LDL & HDL] as HDL-c and LDL-c. Please be consistent! | Fixed. I have also corrected similar inconsistencies in other sections of the thesis. |
| **Section 3.2.3 (“Studies of any duration were included”):** Does this apply to observational cohort studies that assessed the associations between blood lipid levels and dementia outcomes? | Fixed. Added parenthetical statement clarifying this point. |
| **Section 3.2.9:** Define rare outcome. | Fixed. |
| **Chapter 4** | **Section 4.2.4:** Of the 81 studies, how many are observational cohorts, RCTs, MR studies etc? Useful to indicate this. | Fixed. |
| **Figure 4.16:** Please provide a p-value for non-linearity. | Fixed. The has been added to the figure caption. |
| **Chapter 5** | **Section 5.4.1:** This statement [“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.”] is not consistent with your abstract and lay summary. | Fixed. See related point in *General corrections* above for a fuller discussion of changes made. |
| **Section 5.5:** [Same as above] Inconsistent with what is reported in the abstract. | Fixed. See related point in *General corrections* above for a fuller discussion of changes made. |
| **Chapter 8** | **Section 8.1.1:** Indicate that they were comprehensive systematic reviews and meta-analyses | Fixed. |