# Triangulation Panel

This report contains an agenda and supporting materials for a panel discussion on the results of a doctoral research project to examine the relationship between blood lipids, and interventions that modify them such as statins, with dementia and related outcomes. The project consisted of three elements (Figure 1):

* Comprehensive systematic review (search conducted in July 2019)
* Analysis of statin use in CPRD participants
* Analysis of lipids levels across three previously unanalysed cohorts, obtained via the DPUK

The purpose of this panel is to obtain feedback and suggestions on approaches for triangulating the data obtained from these different evidence sources.

## Agenda

* Welcome (and thanks for attending!)
* Summary of evidence sources contributing to the triangulation exercise
* Summary of results for three endpoints: dementia, Alzheimer’s disease, and vascular dementia
* Key discussion points
  + Options for combining presented results beyond a qualitative summary
  + Competing sources of bias within a single result (e.g. immortal time bias vs misclassification expected to bias result in different directions)
  + Incorporating different lipid categorisation (hypercholesterolemia vs per 1-SD increase)
  + Incorporating heterogeneity within a given evidence strata (e.g. statin-dementia cohorts had substantial heterogeneity)
  + Handling missing evidence within each synthesis
  + Presentation of results of triangulation
* AOB

## Analysis methods used in this report

To enable easier comparison between different sources of evidence, the results obtained from the three approaches listed above were initially stratified by study design and exposure, and then further by risk of bias level, assessed using a design-appropriate risk-of-bias tool: ROB2 for RCTs/ROBINS-I for NRSI/ ROBINS-E for NRSI /Mamluk et al for MR). For each result, a summary of the key sources of bias was created (see Table 1 for a summary), and where possible, the predicted impact of each bias on the result. To note, the primary analyses performed as part of my project (statin use in the CRPD, lipid levels in three cohorts) have been included in the relevant strata.

Each strata was then meta-analysed using a random effects model (via the *metafor* R package). For each meta-analysis, I extracted the number of studies, overall point estimate, confidence intervals, prediction intervals and heterogeneity statistic. Where only one study result was available for a given strata, this was not meta-analysed and is denoted by a transparent point estimate box in the Figures.

For the purposes of this panel, I have selected the exposure/outcome pairings with the largest evidence base for discussion: statins/lipids on all-cause dementia, Alzheimer’s disease, and vascular dementia. The results for these are shown in Figures 1-3.

## All-cause dementia

The all-cause dementia outcome had several distinct sources of evidence, drawing from two randomised controlled trials, a Mendelian randomisation studies, and several prospective cohorts at varying levels of risk of bias.

**Figure 1 –** Summary of meta-analysis results for all-cause dementia, stratified by study design, specific exposure, and risk of bias level. The number of studies included in the meta-analysis and an estimate of the heterogeneity (I2) are also shown.

Table

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**Table 1 –** Summary of common sources of bias across all outcomes

|  |  |
| --- | --- |
| Study design | Common sources of bias |
| Cohort - Statins (NRSI) | Insufficient adjustment for/low validity of confounders; Immortal time bias; Missing outcome data; Non-differential misclassification of outcome |
| Cohort – Lipids (NRSE) | Insufficient adjustment for/low validity of confounders; Missing outcome data; Non-differential misclassification of outcome; Selection of the reported result (key example is different methods of categorizing lipid levels) |

## Alzheimer’s disease

The Alzheimer’s disease outcome also had several distinct sources of evidence, drawing from Mendelian randomisation studies (including the only two-sample MR result available for lipid levels on any dementia outcome), and several prospective cohorts at varying levels of risk of bias.

**Figure 2 –** Summary of meta-analysis results for Alzheimer’s disease, stratified by study design, specific exposure, and risk of bias level. The number of studies included in the meta-analysis and an estimate of the heterogeneity (I2) are also shown.

Table

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***Notes****: Prediction intervals are denoted by the dashed grey lines. Where only one study was available for a given “design-exposure-bias” strata, this is denoted with a transparent point estimate. Observational studies at “Critical” risk of bias have been excluded.*

## Vascular dementia

The vascular disease outcome had a similar number of evidence sources to the previous two outcomes, but substantially less studies/results per design-exposure-bias strata.

**Figure 3 –** Summary of meta-analysis results for vascular dementia, stratified by study design, specific exposure, and risk of bias level. The number of studies included in the meta-analysis and an estimate of the heterogeneity (I2) are also shown.

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***Notes****: Where only one study was available for a given “design-exposure-bias” strata, this is denoted with a transparent point estimate. Observational studies at “Critical” risk of bias have been excluded.*