Next on my list of features to be specially considered I would place the consistency of the observed association. Has it been repeatedly observed by different persons, in different places, circumstances and times?

1

Aetiological triangulation across evidence sources

1.1 Lay Summary

Triangulation is the practice of using multiple sources of evidence to provide more reliable answers to a research question. Different sources of evidence will have different limitations. If the result from each source points towards the same answer, this improves our confidence in the conclusion.

1.2 Introduction

This chapter will attempt to triangulate the evidence identified by the systematic review in Chapter **??**sys-rev-heading-results), with the the results from the analysis of CPRD data (Chapter **??**cprd-heading) and IPD **??**ipd-heading).

1.2.1 Overview of triangulation

1.2.2 Terminology

Different types of triangulation

Qualitative triangulation is describing the different results.It has been widely used in the literature, and is comparable to Bradford-Hill's criteria of "consistency", that is the replication of an observed relationship across several different "contexts". In this framework.

However, previous attempts at triangulation ignore the potential for varying and opposing sources of bias within a evidence source. For example,

The terminology used in describing different mechanisms by which an observed result may complicate interpretation. This section clearly defines how each are used in h

Here, internal bias is used in terms of

In contrast, external bias (also called indirectness, or)

Additionally, potential biases can be additive or proportional. Pro

1.3 Methods

1.3.1 Data sources

This chapter builds on the comprehensive systematic review presented in CHapter @re(sys-rev-heading), and incorporates the results of the analyses presented in Chapters **??** (statins on dementia outcomes in the CPRD) & **??** (lipids on dementia outcomes in IPD).

Table **??** illustrates the causal question each approach attempted to answer, along with the exposures and outcomes for each.

Table 1.1: triSummary

	mpg	cyl	disp	hp	drat	wt	qsec	vs	am	gear	carb
Mazda RX4	21.0	6	160.0	110	3.90	2.620	16.46	0	1	4	4
Mazda RX4 Wag	21.0	6	160.0	110	3.90	2.875	17.02	0	1	4	4
Datsun 710	22.8	4	108.0	93	3.85	2.320	18.61	1	1	4	1
Hornet 4 Drive	21.4	6	258.0	110	3.08	3.215	19.44	1	0	3	1
Hornet Sportabout	18.7	8	360.0	175	3.15	3.440	17.02	0	0	3	2
Valiant	18.1	6	225.0	105	2.76	3.460	20.22	1	0	3	1
Duster 360	14.3	8	360.0	245	3.21	3.570	15.84	0	0	3	4
Merc 240D	24.4	4	146.7	62	3.69	3.190	20.00	1	0	4	2
Merc 230	22.8	4	140.8	95	3.92	3.150	22.90	1	0	4	2
Merc 280	19.2	6	167.6	123	3.92	3.440	18.30	1	0	4	4
Merc 280C	17.8	6	167.6	123	3.92	3.440	18.90	1	0	4	4
Merc 450SE	16.4	8	275.8	180	3.07	4.070	17.40	0	0	3	3
Merc 450SL	17.3	8	275.8	180	3.07	3.730	17.60	0	0	3	3
Merc 450SLC	15.2	8	275.8	180	3.07	3.780	18.00	0	0	3	3
Cadillac Fleetwood	10.4	8	472.0	205	2.93	5.250	17.98	0	0	3	4
Lincoln Continental	10.4	8	460.0	215	3.00	5.424	17.82	0	0	3	4
Chrysler Imperial	14.7	8	440.0	230	3.23	5.345	17.42	0	0	3	4
Fiat 128	32.4	4	78.7	66	4.08	2.200	19.47	1	1	4	1
Honda Civic	30.4	4	75.7	52	4.93	1.615	18.52	1	1	4	2
Toyota Corolla	33.9	4	71.1	65	4.22	1.835	19.90	1	1	4	1
Toyota Corona	21.5	4	120.1	97	3.70	2.465	20.01	1	0	3	1
Dodge Challenger	15.5	8	318.0	150	2.76	3.520	16.87	0	0	3	2
AMC Javelin	15.2	8	304.0	150	3.15	3.435	17.30	0	0	3	2
Camaro Z28	13.3	8	350.0	245	3.73	3.840	15.41	0	0	3	4
Pontiac Firebird	19.2	8	400.0	175	3.08	3.845	17.05	0	0	3	2
Fiat X1-9	27.3	4	79.0	66	4.08	1.935	18.90	1	1	4	1
Porsche 914-2	26.0	4	120.3	91	4.43	2.140	16.70	0	1	5	2
Lotus Europa	30.4	4	95.1	113	3.77	1.513	16.90	1	1	5	2
Ford Pantera L	15.8	8	351.0	264	4.22	3.170	14.50	0	1	5	4
Ferrari Dino	19.7	6	145.0	175	3.62	2.770	15.50	0	1	5	6
Maserati Bora	15.0	8	301.0	335	3.54	3.570	14.60	0	1	5	8
Volvo 142E	21.4	4	121.0	109	4.11	2.780	18.60	1	1	4	2

1.3.2 Qualitative triangulation

As a first step to assessing the evidence, all evidence sources were grouped by outcome and compared and contrasted. Potential reasons for heterogeneity were examined with specific reference to the risk of bias assessments performed.

1.3.3 Quantitative triangulation

In addition to the qualitative discussion of evidence, I attempted to integrate the . This approach incorporated advancements in the way that bias in results is assessed to illustrate both how causal questions could be addressed under this quantitative triangulation framework, and

Definition of the causal questions of interest (case-studies)

This chapter will consider two questions

Firstly, an ter

Secondly an

Background to the causal question

Following best practice guidance, three

Table with columns describing exposure, outcome, time-point, other aspects (cumulative), and

This was also guided by the forthcoming ROBINS-E tool, which has

- One interventional: Effect of average exposure to LDL-c during midlife on AD
- One aetiological: Effect of cumulative LDL-c from birth

As outlined in the thesis overview presented in Section **??**, the triangulation draws on the research produced in the preceding chapters.

a) Proposed method for this chapter
b) Example: LDL-c at midlife on Alzheimer's disease risk

ii) Specific causal effect of interest using ROBINS-E framework: • Population of interest: General population • Exposure of interest: Low density lipoprotein cholesterol • Exposure window of interest: Midlife (45-60) • How exposure over time should be summarized: Cumulative exposure

iii) Identify relevant studies from evidence base • LDL-c assessed at midlife • MR of LDL-c • Statin use at midlife

iv) Assess risk of bias in each result, define expected directions of each bias and plot

v) Assign additive value to each level of bias (High = 0.2, Some concerns =0.1, Low = 0), assign sign to these values based on predicted direction and sum across result

vi) E.g. for effect estimate 0.71 (0.57-0.89):

Element D1 D2 D3 D4 D5 D6 D7 Overall Bias High Some concerns Low Low Low Some concerns Some concerns Serious Direction Left Away from null - - - Towards null Away from null
Modifier -0.2 -0.1 0 0 0 0.1 -0.1 -0.3

vii) Assign a proportional value representing the indirectness for each result • Statin studies would give smaller proportion (e.g. 0.7) of effect observed for generally lower lipids, as they would reduce cumulative exposure • SNPs predict quite strongly LDL-c and so would have minimal indirectness
viii) Combine in a bias-adjusted meta-analysis

Identify relevant studies

Once the causal question of interest had been defined, studies related to it were

Assess risk of bias in each result, define expected directions of each bias

In addition, the tool also aim to capture the potential direction of bias for each result. Possible responses included: "Favours experimental", "Favours comparator", "Towards null", "Away from null", and "Unpredictable". Highlight that this is slightly different for the confounding domain in non-randomised studies.

These levels only apply to existing tools, not the MR tool. However, a similar approach was employed.

Visually inspect results and bias

Within our framework and as part of the risk-of-bias assessments reported in **??**, I attempted to records the direction of the bias, so that it could feed into the triangulation.

Talk about new visualisation method here, and the different

For the graphs, the direction of bias is important.

Where the direction of bias was unclear/could not be determined from the report, this is indicated

In order to aid with the triangulation exercise, a new method of presentation of these results was developed to enable detailed comparison across different studies contributing to the causal question. The level of bias in each study is reported using coloured blocks, while the predicted direction of bias in that domain, categorised as towards or away from the null, is indicated using an arrow

Of note, a different approach was required for the confounding domains in the assesment tools used for non-randomised studies. Confounding in a study will either pull to the left or right, regardless of where the effect estimate is, while other domains will pull towards/away from the null (e.g. non-differential misclassification). In this case, the program accounted for the position of the effect estimate when assigning a directional arrow in relation to the positon of the effect estimate. For example, see Figure @ref(), which shows an example study under the same confounding structure (protective), but with protective and harmful effect estimates. In this case, when the estimated effect is protective (Study 1), the arrow for the confounding domain indicates that the bias is pulling it away from the null. If the estimated effect is harmful, the arrow indicates that the results is being biased towards the null.

These graphs were built using the risk of bias tool described in Appendix **??**)

Assign modifying values to risk/direction of bias

One key feature of the domain-based risk-of-bias domains is that the domains are considered interchangeable - i.e. a high risk of bias in one domain is equivalent to a high risk fo bias in any other. This runs contrary to the idea put forward in some previous tools where certain domains

However, this also allows us to a priori define common modifying values across all domains of bias. In a bias-adjusted meta-analysis using this approach, a high risk of bias in the will have the same modifying effect on the results.

As such, a simulation approach was taken to explore the impacts of several different strategies

Assign modifying values to risk/direction of bias

"One important difference between these approaches that will need to be addressed in the triangulation is that RCTs relate to short-term modification of lipid levels, whereas Mendelian randomisation studies typically refer to lifelong exposures; and traditional observational epidemiology approaches may refer to short or longterm exposure (although are often not explicit about this). The triangulation will take these into account, for example by superimposing the studies on a hypothetical model for exposure-outcome relationship across the life course."

Combine in a bias-adjusted meta-analysis

1.4 Results

1.4.1 Intro

Summary of risk-of-bias/triangulation results

Percentage of domains for which a direction of bias could be assigned?

Compare bias-adjusted and

See what happens if using additive (l=1,m=2,s=3,c=4) vs multiplicative/log scale (l=1,m=2,s=4,c=8). Present adjusted results and meta-analysis of adjusted results.

Applicability/indirectness as an issue Compare with GRADE and cite George's example of 40% of effect predicted by MR seen when using statins for 5 years

1.4.2 Qualitative triangulation

All-cause dementia

Statins and all-cause dementia

This conflicts with the findings of our analysis, where statin use was associated with an increased risk of all-cause dementia (HR:1.17, 95%CI:1.14-1.19). Some of the included studies in the meta-analysis specifically exclude vascular dementia from the definition of all-cause dementia,[2] which may limit the ability for comparison with our findings for the all-cause dementia outcome.

Additionally, a previous analysis of the THIN EHR database using a propensity-score matched analysis found a protective effect of statins on all-cause dementia (HR:0.81, 95%CI:0.69-0.96)[3].

Alzheimer's disease

Statins and Alzheimer's disease

Our results are broadly in line with the findings of two distinct approaches examining the effect of statin treatment on subsequent Alzheimer's disease. No randomized trials of statins for the prevention of Alzheimer's disease have been reported, but a recent meta-analysis of 20 observational studies found statins were associated with a reduced risk of Alzheimer's disease (RR 0.69, 95% CI 0.60–0.80) with stronger evidence than observed in our analysis.[4] This review included case-control studies and analyses likely to be at risk of immortal time bias, which may account for the discrepancy with our findings. Additionally, a recent Mendelian randomization study examining the effect of genetic inhibition of HMGCR on Alzheimer's disease (a genetic proxy for statin treatment) provided equivocal evidence (OR: 0.91, 95%CI: 0.63-1.31) but was consistent with our results.[5]

Our additional analyses stratified by statin properties found little evidence of differences in associations of lipophilic and hydrophilic statins and incidence of Alzheimer's disease, consistent with a recent meta-analysis of observational studies.[6]

Vascular dementia

Statins and vascular/other dementia

Far fewer studies have tested the association between lipid-regulating agents and vascular dementia or other dementias. A recent review found four observational studies examining the association of statins and vascular dementia found limited evidence for an effect (RR:0.93, 95% CI 0.74–1.16).[4] This contrasts with the harmful association found in our analysis (HR:1.81, 95%CI:1.73-1.89). When stratifying by lipid properties, lipophilic statins were more harmful than hydrophilic statins in vascular dementia, potentially due to their ability to cross the blood brain barrier.

Other drug classes

Apart from statins, few studies examining a lipid-regulating agent have been reported (Chapter **??**/**??**).

One of the few classes for which a evidence was available were fibrates, which found little evidence of an association with all-cause dementia was identified,[7] inconsistent with our finding that patients prescribed fibrates had higher all-cause dementia risk than those prescribed other lipid lowering agents.

A previous Mendelian randomization study found little evidence that genetic variants that proxy for ezetimibe affect risk of Alzheimer's disease (OR: 1.17, 95%CI: 0.73-1.87),[5] consistent with our findings. Note that this study was published in 2020 and so was not included in the review.

Impact of patient characteristics

1.4.3 Quantitative triangulation

1.4.4 Standardisation across study designs

Standardising across different measures of ex

Want best information across lipids, and so standardised across differnt measures

Fixing directions of effect - get everything pointing the same way

1.5 Discussion

Future quantitative triangulation should move beyond the concept of comparing results at the approach leve, and instead focus on the inherent threats to internal validity present in each specific result relevant to the causal question.

While this makes the process both more labour intensive and complex, to assume that, for example, all retro-spective studies are equally at risk is to overlook. While ti could be true thtat all retrospective studies share some *minimal level* of bias, there are several opportunities. Failing to seperate these out results in a lack of information.

In this chapter, I have presented a new visualistion fo the bias inherent to each result, and suggested hwo. While this work is largely illustrative, as the correst distributions of modifying values in each risk-of-bias domain should be driven by meta-epidemiologic studies, these do not yet exist.

1.5.1 Problems with quantitative triangulation approach

Missing natural variation obtained from elicitation approach. Trade-off between systematic approach presented here and personal variation obtained from several reviewers.

A potential combination between the two would be to use the variation in risk-of-bias assessments

Eliciation and bias-adjusted not as favoured versus weighting[8] though weighting at the overall risk of bias level loses some of the information contained in domain-level based assessments.

No good information on what the potential biases should be.

Meta-epidemiological studies on the effect of different methodological issues on results exist for randomised controlled trials,[9,10] suggesting that X, Y and Z.

However, there is substantially less , arguably because of the absence of clear Many meta-epi studies of non-randomised studies assume bias at the study-design level, similar to the early triangulation frame-work, rather than considering the actual biases deemed to be present in a given result. In this scenario, study

Potential future meta-epidemiology studies should begin to create these datasets.

A key example of a useful future study in this domain would be the mining of maximally adjusted vs. unadjusted estimates from abstracts from primary studies to assess the impact of insufficient confounding by topic. However, these datasets could also be built from systematic reviews of a topic, as they would already be gruped by reserach domain and provided the risk of bias data is shared, provide a ready source of information

For example, if it was . New software for performing risk of bias assessments, being developed by the Bristol Appraisal and review of Research group has this as a secondary methodological aim.

1.5.2 Limitations

In previous attempts at bias/indirectness-adjusted meta-analysis, the extent to each was assessed via a elicitation process using a number of experts.

Ideally, the modifying values)

i) Ideally modifying values (both internal and external) would be based on empirical research, but in absence of this, sufficient to model multiple values (High = 0.1, Some concerns =0.05, Low = 0) and relationships (High = 0.3, Some concerns =0.1, Low = 0)? Need range around modifying values, as total variance of the biases is added to the total variance of the studies (elicitation on scale presented above asks for range rather than single estimate

1.5.3 Discussion of E-values

Present as an alternative to putting priors on the level of bias due to confounding. E-values work the other way around - get result then work out how strong a biasing factor would have to be to negate the result. One major problem is that they can only be used to evaluate negating biases, not other biases.

How strong unmeasured confounding would have to be in order to explain the observed effect.

Heavily criticised in a range of papers.

Also, no useful to focus on a specific bias in the context of risk of bias domains

1.5.4 Challenges of real-life data

Compare and contrast with the nice example presented in the triangulation paper - realities of non-exemplars is that it is very hard to get this right. ALso highlight the issue with assigning a direct of bias in many studies

I hope this presents step forward in how researchers think about and visualise triangulation at the result level, rather than simply saying that certain

1.5.5 Need for new methods

Can I suggest any empirical studies that need to be performed? Average strength of immortal time bias/etc?

1.6 Conclusion

Triangulation is a promising developing field, somewhat hamstrung by the limited understanding of the impact of biases at the meta-epidemiological level.

References

001. Hill, A. B. The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine* **58**, 295–300 (1965).

2. Chao, T.-F. *et al.* Statins and the risk of dementia in patients with atrial fibrillation: A nationwide population-based cohort study. *International Journal of Cardiology* **196**, 91–97 (2015).

3. Smeeth, L., Douglas, I., Hall, A. J., Hubbard, R. & Evans, S. Effect of statins on a wide range of health outcomes: A cohort study validated by comparison with randomized trials. *British Journal of Clinical Pharmacology* **67**, 99–109 (2009).

4. Poly, T. N. *et al.* Association between Use of Statin and Risk of Dementia: A Meta-Analysis of Observational Studies. *Neuroepidemiology* **54**, 214–226 (2020).

5. Williams, D. M., Finan, C., Schmidt, A. F., Burgess, S. & Hingorani, A. D. Lipid lowering and Alzheimer disease risk: A mendelian randomization study. *Annals of Neurology* **87**, 30–39 (2020).

6. Chu, C.-S. *et al.* Use of statins and the risk of dementia and mild cognitive impairment: A systematic review and meta-analysis. *Scientific Reports* **8**, 5804 (2018).

7. Ancelin, M.-L. *et al.* Lipid lowering agents, cognitive decline, and dementia: The three-city study. *Journal of Alzheimer's Disease* **30**, 629–637 (2012).

8. Stone, J. C., Glass, K., Munn, Z., Tugwell, P. & Doi, S. A. R. Comparison of bias adjustment methods in meta-analysis suggests that quality effects modeling may have less limitations than other approaches. *Journal of Clinical Epidemiology* **117**, 36–45 (2020).

9. Amer, M. A. *et al.* A meta-epidemiological study of bias in randomized clinical trials of open and laparoscopic surgery. *British Journal of Surgery* **108**, 477–483 (2021).

10. Page, M. J. *et al.* Empirical Evidence of Study Design Biases in Randomized Trials: Systematic Review of Meta-Epidemiological Studies. *PLOS ONE* **11**, e0159267 (2016).