The epidemiology is promising, but the trial evidence is weak. Why pharmacological dementia risk reduction trials haven't lived up to expectations, and where do we go from here?

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Abstract

There is an urgent need for interventions that can prevent or delay cognitive decline and dementia. Decades of epidemiological research have identified potential pharmacological strategies for risk factor modification to prevent these serious conditions, but clinical trials have failed to confirm the potential efficacy for such interventions. Our multidisciplinary international group reviewed seven high potential intervention strategies in an attempt to identify potential reasons for the mismatch between the observational and trial results. In considering our findings, we offer constructive recommendations for the next steps. Overall, we observed some differences in the observational evidence-base for the seven strategies, but there were several common methodological themes that emerged. These themes included the appropriateness of trial populations and intervention strategies, including the timing of interventions and other aspects of trials methodology. To inform the design of future clinical trials, we provide recommendations for the next steps in finding strategies for effective dementia risk reduction.
Reducing the risk of dementia remains a significant global challenge. The ageing of the world's population means that, unless we can reliably reduce the incidence of dementia, the absolute number of cases will continue to rise to an estimated 131.5 million by 2050 [1]. The Organisation for Economic Co-operation and Development's (OECD) 2018 report on dementia reiterates the continuing need in this area but also notes that whilst ‘dementia has stayed high on the policy agenda’, 'progress in addressing dementia has not kept up with the scale of the challenge' [2].

Progress requires both an understanding of biological pathways or pharmacological targets and a population health perspective on risk reduction. Borrowing an example from public health and the story of Dr John Snow [3], we now need to know how to turn off the water pump (acting on risk factors to reduce population-level risk if we can), alongside gaining an understanding of the detailed mechanisms and therapeutic targets behind the different disease pathways. In the accompanying article (…reference to add…), an international panel of experts focuses on the role of risk factors and risk reduction and considers why, despite decades of research on modifiable risk factors for dementia, the evidence for risk reduction due to pharmacological risk factor modification remains weak. Specifically, the strong epidemiological evidence for the association between risk factors and greater risk of later dementia or cognitive decline is not matched by clinical trial evidence for pharmacological risk reduction and risk factor modification. We argue that to build dementia risk reduction programmes, we need to do more than identify the modifiable risk factors. We also need evidence for risk reduction.

Recent years have yielded a library of comprehensive systematic reviews summarising the evidence on dementia risk factors and risk reduction. The reviews have variously focused their attention on the risk factor associations (the epidemiological evidence) [4-6], the risk factor interventions (the clinical trial evidence) [7-9], or both [5, 6, 8, 10-13], and sit alongside further work estimating the potential gain from risk reduction [5, 14-16]. This thorough synthesis of the available evidence has served to highlight that (despite some notable
exceptions); conclusive clinical trial results are, in general, lacking in this field. This is also evident in the recent World Health Organisation dementia risk reduction guidelines [9] and the 2017 National Academy of Science review [7]. Until we have a greater understanding of what works for dementia risk reduction, and what does not work, we cannot usefully develop further guidelines or targeted risk reduction strategies above and beyond existing health guidelines. Before we embark on another generation of costly pharmacological clinical trials, we need to take a step back and to examine in-depth the potential reasons for this gap between the epidemiology and clinical trial data and to derive recommendations for ways forward. In short, this provides us with an opportunity to re-examine our understanding of the relationships between risk factor exposure, its modification, impact on pathology, and clinical expression of dementia and our methodological approaches so far. We need to build our understanding and think about what we might be missing.

Using a multidisciplinary, international expert review group and seven exemplar risk factors, we focus on pharmacological interventions, identify and highlight potential reasons for the mismatch and make constructive recommendations for the next steps. The risk factors were selected to be those supported by plausible mechanisms or pathways for their impact on cognition, have an evidence base in both the epidemiology and clinical trial literature, and be modifiable by means of pharmacological intervention, meaning that trials could be double-blind. Non-pharmacological interventions were beyond the scope of this review. The seven risk factor/intervention pairs were: type 2 diabetes and treatment, high cholesterol/statins, high blood pressure/antihypertensives, inflammation/non-steroidal anti-inflammatories, hormone regulation/hormone replacement therapy, hyperhomocysteinemia/B-vitamins, and omega 3-fatty acid levels/supplementation. These are well-established risk factors in the literature and may arguably have commonalities in their underlying pathways, including but not limited to vascular risk [17-25] and inflammation [26, 27], although this may not be the whole story [20, 28-32].
We found that whilst the evidence base differed in maturity and complexity per risk factor/intervention, similar methodological issues emerged across all seven. Three themes were evident, population selection, intervention and methodology, specifically;

(i) issues of population heterogeneity/lack of sufficiently targeted populations for trials or where the trial populations did not match those indicated by the epidemiology (particularly concerning age and timing and the dementia prodrome but also, sex, genetic profile, pathological burden, clinical history),

(ii) lacking understanding or appropriate selection of intervention (e.g., therapeutic dose, duration (particularly given potential real-life exposure to risk factors over long periods), suitable target biomarkers and biomarker level, drug class or combination),

(iii) methodological issues, insufficient adjustment for confounding including potential complex relationships with and change in confounding factors over time (e.g., body mass index); a lack of awareness of mediating factors; risk of reverse causality; competing risks; insufficiently sensitive measures of cognition; variation in diagnostic criteria, attrition.

We thus make three broad recommendations to inform the next generation of clinical trials.

We propose;

(i) re-analysis of existing trial data to be used to drive insight into who might benefit (even if the overall trial group differences were null). Note: the sensitivity of statistical assumptions should be evaluated.

(ii) re-analysis of epidemiology to be used to drive insight into the timing and age, dose, duration, and risk profiles at baseline and over time.

(iii) greater methodological rigour and understanding of dementia aetiology, including the development and validation of brain-specific biomarkers that can precede and predict changes in clinical outcomes and are modifiable by the proposed intervention.
An associated guide provides practical suggestions for the operationalisation of our recommendations (figure 1).

**Consolidated results and study design**

Full details of the evidence reviews are published in a companion article, Peters et al., *Dementia risk reduction, why haven't the pharmacological risk reduction trials worked? (Reference to be confirmed)*, an in-depth exploration of seven established risk factors from where the above recommendations were drawn. Evidence reviews were drafted by experts in the field and subsequently appraised by the full review panel. Figure 2 shows the issues identified for each risk factor/intervention pair and the extent of overlap across the risk factors. Challenges and opportunities associated with target population selection and intervention were explored and used to derive a 9-point guide to support operationalisation of recommendations and drive the next steps. (Figure 1). Using one risk factor (cholesterol) as a worked exemplar, we can show where questions remain.

**Using the 9-point guide to operationalise the recommendations and identify the next stages for research.**

In general, given the difficulty of long term trials, future research requires sufficiently sophisticated cognitive assessment allowing measurement of subtle and short term change (figure 1, point 9) with subsequent modelling and supplementation by longer-term planned follow-up as part of ongoing observational studies, similar to the longer-term follow-up seen in some cardiovascular trials[33]. For cholesterol in particular: we know that raised cholesterol is likely to have its impact in midlife (figure 1, point 1). This would indicate a preference for us to select a population for future trials that had raised cholesterol in midlife and potentially to stratify later life populations by midlife cholesterol level. However, questions remain about what other characteristics we should take into account. Should we also recruit by sex or genetic risk profile, by cholesterol change since midlife, or select those with demonstrated Alzheimer pathology? (Figure 1, points 2,4).
Moreover, what level of cholesterol is important? We also need a greater understanding of the relationship between cholesterol and cognition (figure 1, point 3). For example, is the relationship between cholesterol and cognitive function linear, 'u' or 'n' shaped and are there thresholds above which risk increases? Consequently, what goal or target level of cholesterol should we aim for when we treat? And how would changes in blood cholesterol affect the brain? For the intervention (figure 1, point 5), is it cholesterol-lowering that matters or the drug type, or particular drug, or dose, and should we be combining treatment, for example, with an antihypertensive (figure 1, point 6)? Finally, does cholesterol across the life course matter? How much does cholesterol change matter, is there a risk of reverse causality? Should we recruit a group that is homogeneous for their prior exposure to cholesterol? How do we factor in related risk factors/confounding factors that vary across time (figure 1, points 7,8)? Re-interrogation of existing data or, if necessary, collection of new data is needed to answer these questions and generate the estimates required to support power calculations for future trials.

**Future directions**

We propose furthering our understanding with new analyses across and between cohorts and clinical trials. Specifically, we suggest taking a structured approach. This would include examining the similarities and differences between samples and using one and two-stage individual participant data meta-analyses. Added to this is a cautious application of causal inference methodology, potentially as a sensitivity analysis (acknowledging the assumptions this requires), followed by trial emulation, trial simulations, and replication studies to identify patterns, population-level target engagement, and a robust body of evidence to support intervention choice. Using the results of this process can then help drive trial design for the next generation of risk reduction trials. Finally, we acknowledge the different levels of maturity in the clinical trial evidence across the risk factors. That the potential risk factor modification may not work for all risk factors, that there may be additional yet uncovered complexity and variation in possible pathways for pathology and expression. Real-life
scenarios are also likely to include multiple risk factors and influences across the life-course and the potential for earlier risk reduction, more effective treatment and/or the prevention of risk factors themselves, all of which are important but beyond our review’s scope. There remains a need to continue unravelling this. Our structured approach may also be useful for risk factors beyond those we have considered above. Alternatively, there may also be insights in areas specific to one risk factor rather than common to several, all of which require further evaluation. Without taking these careful next steps, we risk further money and time spent on inconclusive research and a continued lack of understanding about what may, and crucially, what may not help with dementia risk reduction.

Research into dementia risk reduction is at a critical juncture. We encourage new trials to factor in the recommendations discussed in this review.
Figure 1 A practical guide to support clinical trial planning and identifying the evidence gaps in dementia risk reduction
• Consider the relationship between age, risk factor exposure and cognitive outcomes. I.e. are we selecting the most appropriate at risk population based on age?

• Are there other characteristics that may have an influence and which need to be taken into account? (e.g. should we be looking by sex or by genetic risk profile)

• Consider the relationship between the risk factor, risk reduction and the outcome. Do we know what level of exposure to the risk factor confers risk? And do we know what level of the risk factor is hypothesized to confer protection or risk reduction? I.e. what level is bad for cognition, what level is good?

• Understanding the intervention: the mechanism. Is the targeted pathology justified by the hypothesized biological framework? How will we be sure that our target population has the pathology? Does the trial population need to be enriched for pathology?

• Selecting the intervention: are there benefits to the selection of one treatment over another? Is it important that the treatments cross the blood brain barrier? What dose is required to achieve the required concentration/to have the hypothesized impact?

• Take other treatments into account, is combination treatment required?

• Consider timing, duration and causality, is the duration of exposure to the risk factor or its trajectory over the life-course important?[13]

• Similarly, consider accounting for related risk factors, their influence, their trajectories over time (e.g. if body mass index rises and falls and blood pressure follows?)

• Consider assessment tools, including using a sufficiently sophisticated cognitive assessment tool where shorter term cognitive change can be measured reliably and be validated for the association with translational effects to daily functions (i.e., clinically meaningful).