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 urgent need for interventions that can prevent or delay dementia and cognitive decline. Decades of epidemiological research have identified potential pharmacological strategies for risk factor modification for prevention of dementia, but clinical trials have failed to show efficacy for these interventions. Our multidisciplinary, international group reviewed seven such intervention strategies and attempted to identify potential reasons for the mismatch between observational study and trial results. In consideration of 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 a number of common methodological themes emerged. These themes included appropriateness of trial populations and intervention strategies, including timing of interventions, and other aspects of trials methodology. To inform the design of future clinical trials we provide recommendations and suggestions for next steps in finding methods for 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, to 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. Each risk factor was appraised by an expert in the field. The risk factors were selected to be those supported by plausible mechanisms or pathways for their impact on cognition, to have an evidence base in both the epidemiology and clinical trial literature and to 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, hypertension/antihypertensives, inflammation/non-steroidal anti-inflammatories, hormone/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 with regard to age and timing and the dementia pro-drome 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), appropriate 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;

(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).

(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 to 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 there a linear, ‘u’ or ‘n’ shaped relationship between cholesterol and cognitive function or 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 also, (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 are homogeneous for their prior exposure to cholesterol? How do we factor in related risk factors/confounding factors that also vary across time (figure 1, points 7,8)? Re-interrogation of existing data or, if necessary, collection of new data is needed now to answer these questions and to 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 propose taking a structured approach, examining the similarities and differences between samples and using one and two stage individual participant data meta-analyses and application of causal inference methodology followed by trial emulation and even trial simulations to identify patterns and population level target engagement and to 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, the potential that risk factor modification may not work for all risk factors, that there may be additional as yet uncovered complexity and variation in potential pathways for pathology and expression and that there remains a need to continue unravelling this alongside the epidemiology. 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.

References

1. Prince M, W.A., Guerchet M, Ali G-C, Wu, Y-T, Prina M. , *World Alzheimer Report 2015 The Global impact of dementia*, in *World Alzheimer Report*. 2015.
2. *Renewing priority for dementia:Where do we stand?*, in *Policy Brief*. 2018.
3. Ramsay, M.A.E., *John Snow, MD: anaesthetist to the Queen of England and pioneer epidemiologist.* Proceedings (Baylor University. Medical Center), 2006. **19**(1): p. 24-28.
4. Anstey, K.J., et al., *A Systematic Review of Meta-Analyses that Evaluate Risk Factors for Dementia to Evaluate the Quantity, Quality, and Global Representativeness of Evidence.* J Alzheimers Dis, 2019. **70**(s1): p. S165-s186.
5. Livingston, G., et al., *Dementia prevention, intervention, and care.* The Lancet, 2017. **390**(10113): p. 2673-2734.
6. Livingston, G., et al., *Dementia prevention, intervention, and care: 2020 report of the Lancet Commission.* The Lancet, 2020. **396**(10248): p. 413-446.
7. Kane RL, B.M., Fink HA, Brasure M, Davila H, Desai P, Jutkowitz E, McCreedy E, Nelson VA, McCarten JR, Calvert C, Ratner E, Hemmy LS, Barclay T. , *Interventions To Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia. Comparative Effectiveness Review*, in *AHRQ Publication No. 17-EHC008-EF. Rockville, MD: Agency for Healthcare Research and Quality;* . 2017.
8. Williams, J.W., et al., *Preventing Alzheimer's disease and cognitive decline.* Evidence report/technology assessment, 2010. **193**(1): p. 1-727.
9. *Dementia_Guidelines_Evidence_Profiles*. Available from: https://www.who.int/mental_health/neurology/dementia/guidelines_risk_reduction/en/.
10. Xu, W., et al., *Meta-analysis of modifiable risk factors for Alzheimer's disease.* J Neurol Neurosurg Psychiatry, 2015. **86**(12): p. 1299-306.
11. Yu, J.-T., et al., *Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials.* Journal of Neurology, Neurosurgery & Psychiatry, 2020: p. jnnp-2019-321913.
12. Daviglus, M.L., et al., *Risk Factors and Preventive Interventions for Alzheimer Disease: State of the Science.* Archives of Neurology, 2011. **68**(9): p. 1185-1190.
13. Plassman, B.L., et al., *Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life.* Ann Intern Med, 2010. **153**(3): p. 182-93.
14. Barnes, D.E. and K. Yaffe, *The projected effect of risk factor reduction on Alzheimer's disease prevalence.* The Lancet. Neurology, 2011. **10**(9): p. 819-828.
15. Norton, S., et al., *Potential for primary prevention of Alzheimer's disease: an analysis of population-based data.* Lancet Neurol, 2014. **13**(8): p. 788-94.
16. Oliveira, D., et al., *Reducing the Number of People with Dementia Through Primary Prevention in Mozambique, Brazil, and Portugal: An Analysis of Population-Based Data.* Journal of Alzheimer's Disease, 2019. **70**: p. S283-S291.
17. Feinkohl, I., et al., *The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors.* Alzheimers Res Ther, 2015. **7**(1): p. 46.

18. McGuinness, B., et al., *Statins for the prevention of dementia.* Cochrane Database of Systematic Reviews, 2016(1).
19. Iadecola, C. and R.F. Gottesman, *Neurovascular and Cognitive Dysfunction in Hypertension.* Circ Res, 2019. **124**(7): p. 1025-1044.
20. Iadecola, C., et al., *Impact of Hypertension on Cognitive Function: A Scientific Statement From the American Heart Association.* Hypertension, 2016. **68**(6): p. e67-e94.
21. Walker, K.A., M.C. Power, and R.F. Gottesman, *Defining the Relationship Between Hypertension, Cognitive Decline, and Dementia: a Review.* Curr Hypertens Rep, 2017. **19**(3): p. 24.
22. Smith, A.D. and H. Refsum, *Homocysteine, B vitamins, and cognitive impairment.* Annu Rev Nutr, 2016. **36**: p. 211-39.
23. Smith, V., et al., *Methodology in conducting a systematic review of systematic reviews of healthcare interventions.* BMC Med Res Methodol, 2011. **11**(1): p. 15.
24. Obeid, R. and W. Herrmann, *Mechanisms of homocysteine neurotoxicity in neurodegenerative diseases with special reference to dementia.* FEBS Lett, 2006. **580**(13): p. 2994-3005.
25. Zhuo, J.M., H. Wang, and D. Pratico, *Is hyperhomocysteinemia an Alzheimer's disease (AD) risk factor, an AD marker, or neither?* Trends Pharmacol Sci, 2011. **32**(3): p. 562-71.
26. Au, A., et al., *Estrogens, inflammation and cognition.* Frontiers in Neuroendocrinology, 2016. **40**: p. 87-100.
27. Sierra, S., et al., *Dietary eicosapentaenoic acid and docosahexaenoic acid equally incorporate as decosahexaenoic acid but differ in inflammatory effects.* Nutrition, 2008. **24**(3): p. 245-54.
28. Sasaki, N., et al., *Advanced glycation end products in Alzheimer's disease and other neurodegenerative diseases.* Am J Pathol, 1998. **153**(4): p. 1149-55.
29. Gottesman, R.F., et al., *Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition.* JAMA, 2017. **317**(14): p. 1443-1450.
30. Petrovitch, H., et al., *Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study.* Neurobiol Aging, 2000. **21**(1): p. 57-62.
31. Palmer, J.C., et al., *Zibotentan, an Endothelin A Receptor Antagonist, Prevents Amyloid-β-Induced Hypertension and Maintains Cerebral Perfusion.* Journal of Alzheimer's Disease, 2020. **73**: p. 1185-1199.
32. Geifman, N., et al., *Evidence for benefit of statins to modify cognitive decline and risk in Alzheimer's disease.* Alzheimers Res Ther, 2017. **9**(1): p. 10.
33. Zoungas, S., et al., *Follow-up of Blood-Pressure Lowering and Glucose Control in Type 2 Diabetes.* New England Journal of Medicine, 2014. **371**(15): p. 1392-1406.

Figure 1 A practical guide to support clinical trial planning and identifying the evidence gaps in dementia risk reduction

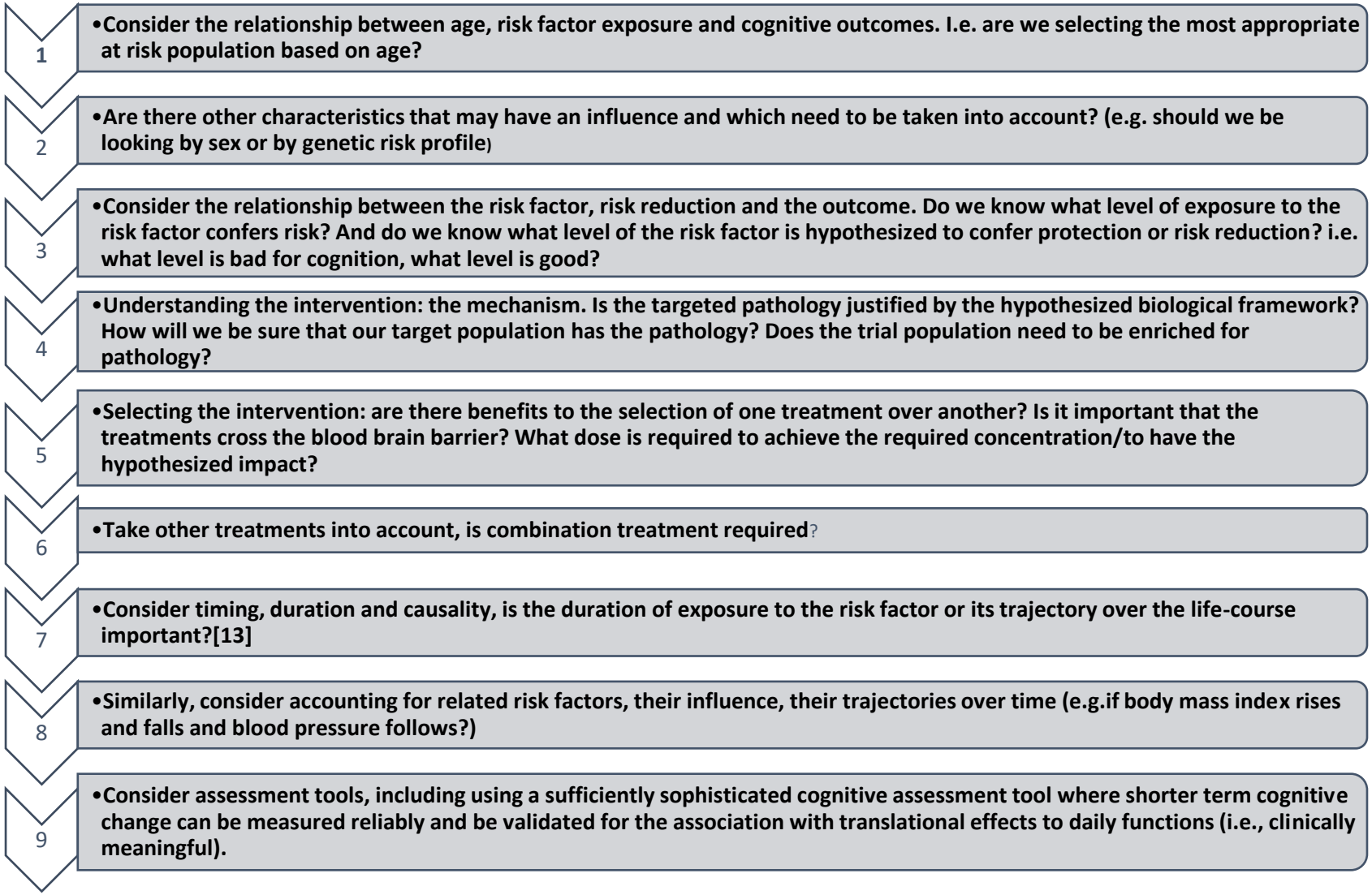

Figure 2 Showing details of the issues identified by expert review for each of the seven risk factors