Author's response to reviews

Title: Cognitive Health Begins At Conception: Addressing dementia as a lifelong and preventable condition

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Author's response to reviews: see over
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Dear Dr D'Souza,

Many thanks to yourself and the reviewers for the very helpful comments on our manuscript ‘Cognitive health begins at conception: Addressing dementia as a lifelong and preventable condition’.

In response to the comments raised, we have made the following changes.

With respect to the review by Dr Aisen:

While the aim of the paper is to further the hypothesis that prevention is possible, we absolutely accept Dr Aisen’s comments that epidemiological association does not demonstrate causality and have changing the wording at several points throughout the paper to tone down our inferences and to reiterate this point. In particular we have added the following:

“Moreover, the disease processes that result in dementia develop over several decades, implying that attempts to ameliorate them need to start early in life.” (Abstract).

“The epidemiological evidence described above provides strong evidence of associations between lifestyle factors and risk for dementia but these associations do not prove causality. Nonetheless, the existence of these associations does suggest that some risk for dementia could be reduced through the protection of cognitive health throughout the lifespan (Figure 2).” (Page 7, line 1)

“As yet there is little evidence from largescale studies about the efficacy of individual or combined lifestyle interventions in preventing dementia, but in the absence of disease-modifying therapies, the prevention of dementia should be prioritised by clinicians and healthcare policy, and by more ambitious research efforts.” (Page 7, line 33).

With respect to Dr Fratiglioni’s review:

1) We have increased the emphasis on metabolic risk factors by adding the following statement “Evidence is particularly strong for a cluster of metabolic factors including hypertension, serum lipids, diabetes, and obesity and exposure to these factors during midlife (as opposed to late-life) seems particularly predictive of later dementia risk [17–20].” (page 4 line 10). We have also redrawn Figure 2 as requested to better emphasise this point.
2) We have included altered the section dealing with early-life risk to acknowledge the important point that there is considerably less evidence for this than for midlife exposure to risk. Specifically, we have made the following changes:

“While the evidence for association between lifestyle factors and dementia risk is strongest for exposure in midlife, lifestyles in middle age usually reflect lifelong patterns of behaviour, so individuals who eat well and exercise in midlife are likely to be benefiting from the cognitively-protective effects of a lifetime of such behaviours. For many adult diseases, substantial risk can be traced to early childhood and, in some cases, back to the womb. The ‘Barker hypothesis’ that suboptimal prenatal and early life environment increases risk for adult disease, has been convincingly demonstrated for conditions including stroke, heart disease, insulin resistance, and hypertension[31]. Although considerably less research has addressed this, there are a number of ways which this is probably true also for dementia.” (page 5).

3) We have replaced reference 12 with the Lobo et al (2000) paper as suggested (page 3).

In addition, I have included the email addresses of the other authors on the title page and clarified the author contribution statements, and I can confirm permission to reproduce the figures.

We hope that in the light of these changes you are now able to accept the paper for publication.

With best wishes,

Jenny Barnett, Vladimir Hachinski and Andrew Blackwell.