J Prev Alz Dis 2023;4(10):746-747
Published online June 6, 2023, http://dx.doi.org/10.14283/jpad.2023.66

Editorial

Dietary Cholesterol and Dementia Risk

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Despite recent evidence of a decline in the incidence and prevalence of the late-onset Alzheimer's disease (LOAD) and other related dementia forms (ADRD), the numbers of sufferers continue to grow exponentially, world-wide. Hence, AD and ADRD represent expanding major socio-economic and healthcare challenges, unless effective therapeutic or preventive solutions become available. These diseases are known to be of multifactorial aetiology, involving complex interactions, over the entire life-course, between a variety of potentially modifiable and non- modifiable factors (1.3). As new knowledge continues to emerge on several of these factors (and their interactions), we are still far from having a comprehensive and precise understanding of the nosology and aetiological complexity of these diseases (1). Non modifiable factors include age and several genetic susceptibility variants, with the APOE4 allele being the strongest and most validated one (2). In the absence of proven curative therapies, there is increasing emphasis on potentially modifiable risk factors, recently reported to account for 40% of worldwide dementias (3). They include factors related to cardiovascular health (CVH), such as hypertension, obesity, diabetes, smoking and dyslipidaemias (3).

In this issue, Wang et al present findings of their analysis, using data from the Framingham Offspring Study, on an association between high intake of dietary cholesterol with lower risk of AD and ADRD (4). Their sample included 3,249 participants who had valid dietary data from the Harvard Food Frequency Questionnaire (FFQ) at baseline (cycle 5) between 1991 and 1995 (mean age 54.7 years), over a follow up period of 20.2 years and reported 312 dementia events, with 211 reported as AD. Participants were classified in tertiles of cholesterol intake. The relative risk of disease was adjusted for several potential confounders, including low density lipids (LDL-C), although their values and timing of sampling were not reported. Furthermore, there was no information on other blood-based lipids and lipoproteins or the content of unsaturated, highly saturated, unsaturated or trans fatty acids, all highly relevant for the evaluation of a potential independent effect of dietary cholesterol (5). The authors acknowledge the methodological limitations and challenges of such analyses and the inconsistencies of previously reported animal-based and clinical epidemiological studies on the relationship between dietary cholesterol and dementia risk.

Conflicting results are common amongst the plethora of clinical observational and interventional studies exploring such associations with dementia and, importantly, with cardiovascular disease and stroke; many of these studies are summarized in the American Heart Association (AHA) Science Advisory 2020 report (6). The report alludes to the marked variability in study design and populations, methodological challenges in statistical analyses, with an emphasis on the role of potential residual confounding related to other dietary components. A meta-regression analysis of fifty-five dietary interventional RCTs found a dose-response relationship between dietary cholesterol and LDL-C and this relationship persisted, after adjustment for dietary fat type (7). However, another meta-regression analysis of controlled feeding RCTs indicated that dietary cholesterol significantly increased total blood cholesterol but there was no significant association with HDL-C and LDL-C, the latter being a stronger predictor of CVD risk (6). The AHA report concludes that dietary guidance to achieve cardiovascular health should focus on healthy dietary patterns, such as the Mediterranean-style diet, rather than providing specific dietary cholesterol targets.

APOE is also known to be involved in cholesterol transport and metabolism, hence a potentially relevant factor to account for, when attempting to explore the role of dietary cholesterol on late-onset dementia risk. In 2020, Peloso et al. investigated the role of cardiovascular health and genetic risk with risk of dementia, also based on the same Framingham Offspring Cohort data (8). For genetic risk, they used APOE4 and a genetic risk score (GRS) that also included twenty-three common smaller-effect variants. For CVH, they applied the AHA Life's Simple 7 formula (including cholesterol blood levels) to compare favourable vs unfavourable CVH scores, at baseline (cycle 5).They found that a high GRS (>80th percentile) was associated with a 2.6-fold risk of dementia and carrying at least one APOE4 allele was associated with a 2.3-fold risk. A favourable CVH score had a 0.4-fold lower hazard of dementia, compared to an unfavourable CVH, when all three components were included in the model. Although

Received April 30, 2023
Accepted for publication May 5, 2023

these results suggest that genetic and lifestyle related metabolic factors carry similar relative risk for dementia, as the prevalence of higher genetic risk is much lower than the prevalence of lifestyle related metabolic factors in the general population, the absolute number of cases of dementia attributable to the latter may be much higher.

In view of the methodological pitfalls and complexities of evaluating individual dietary nutrients, extreme caution is warranted when interpreting results of such analyses. The AHA recommendation to adopt a "healthy dietary pattern" is in line with several observational studies that investigated the relationship between diet and dementia risk. In view of the available evidence from epidemiological studies and results of non-pharmacological multi-domain lifestyle RCTs (9), the focus of primary and secondary prevention for late onset dementias should remain in agreement with the public health strategy of targeting multiple modifiable risk factors, both at the population level and at the level of personalized health and lifestyle profiles of individuals.

Conflict of interest: Dr. Middleton reports grants from Janssen , Merck, Takeda, GATES Ventures, Eisai and NIHR, outside the submitted work; Dr Riboli report no conflicts to declare.

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How to cite this article: L.T. Middleton, E. Riboli. Editorial: Dietary Cholesterol and Dementia Risk. J Prev Alz Dis 2023;4(10):746-747; http://dx.doi.org/10.14283/jpad.2023.66