



Gene-environment interactions determine risk for dementia: the influence of lifestyle on genetic risk for dementia

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Modifiable lifestyle factors such as diet, exercise, alcohol intake, and smoking, have well-established associations with risk of dementia. A poor diet, insufficient exercise, excessive alcohol intake, and smoking are individually associated with increased risk for dementia, while adhering to a healthy diet, abstaining from smoking, exercising regularly, and consuming alcohol in moderation have all been associated with decreased risk. However, there is a paucity of research regarding the cumulative impact of these factors on dementia risk. Moreover, studies of lifestyle typically have not taken into account an individual's overall genetic predisposition for dementia. This is a significant confound given that genetic background is thought to play a predominant role in much of dementia. Large genome-wide association studies (GWAS) have made substantial progress in unearthing susceptibility loci for dementia, but most of these have not been examined in conjunction with lifestyle (1,2). Thus, prior to the recent *JAMA* study by Lourida *et al.* (3), the extent to which overall lifestyle can offset or exacerbate an individual's genetic risk for dementia had been examined only in small cohorts, and/or in the context of specific genetic risk factors (i.e., *APOE-ε4*). This study is the first to examine the association between lifestyle and dementia using a composite measure of lifestyle and a polygenic measure of genetic risk for dementia. Consequently, it provides strong evidence that modifiable, external factors such as lifestyle can influence dementia risk, regardless of genetic background.

This retrospective study measured incident dementia in 196,383 participants from the United Kingdom. Mean age

of individuals at enrollment was 65.8 years for those who developed dementia (n=1,769), and 64.1 years for those who did not (n=194,614). Participants, who did not have prevalent dementia at study enrollment, were followed for approximately 8 years or until one of the following criteria was met: (I) diagnosis of dementia, (II) death, or (III) loss to follow-up. The authors generated a polygenic risk score based on single nucleotide polymorphisms (SNPs) previously identified in a GWAS (2), ultimately including over 200,000 SNPs associated with Alzheimer's disease (AD). For each individual, the number of risk alleles per SNP was weighted by the strength of that SNP's association with AD, and these were summed to generate an overall risk score. Individuals were then divided into either low, intermediate, or high genetic risk categories.

Individuals were also grouped into either favorable, intermediate, or unfavorable lifestyles, based on self-reported responses to a questionnaire at enrollment on smoking status, physical activity level, diet, and alcohol consumption. One significant limitation to this approach is that lifestyle habits measured at enrollment do not necessarily reflect lifestyle habits throughout life. Since dementia pathogenesis is thought to initiate years or even decades prior to manifestation of symptoms, lifestyle factors in mid-to-early life are arguably more or equally important to those later in life. A long-term prospective cohort study that carefully documents lifestyle habits throughout life and measures incident dementia would be needed to address this issue. Consequently, published prospective cohort studies of incident dementia and lifestyle factors have been restricted

to small sample sizes with limited statistical power. While retrospective studies can be an effective way to circumvent this barrier, it will be important for future studies that enroll elderly patients to establish how well lifestyle metrics ascertained at study entry reflect the lifestyle habits of previous decades. Similarly, preclinical studies using validated animal models of dementia may be useful in identifying therapeutic window(s) during which lifestyle factors effectively influence dementia risk.

The key findings of the Lourida *et al.* study are: (I) an unhealthy lifestyle increases risk for dementia, independent of genetic risk; and (II) a healthy lifestyle can decrease risk for dementia, independent of genetic risk. However, it is important to note that for individuals with a high genetic risk score, following a favorable lifestyle may decrease risk of incident dementia, but it does not completely eliminate their risk for developing dementia. As noted by the authors, in individuals with high genetic risk of dementia, the difference between following a favorable vs. unfavorable lifestyle roughly translates to prevention of dementia in 1/121 individuals over a 10-year period. Whether lifestyle habits also affected the severity or time-to-onset of dementia was not specifically addressed. Considering that this study found that the genetic contribution to dementia risk was decreased, but not eliminated by a healthy lifestyle, it is worth exploring whether therapeutics can amplify the effects of a favorable lifestyle in genetically susceptible individuals.

Given the challenges of conducting a randomized controlled trial (RCT) to evaluate whether lifestyle factors, such as diet and exercise, modify the genetic risk of AD and other dementias, preclinical studies will be critical for generating data regarding the value of various lifestyle factors in influencing genetic risk. To that end, here we comment on recent preclinical and clinical studies of various non-drug interventions, and discuss their potential to be used as therapeutics, or in conjunction with lifestyle changes to mitigate dementia.

Diet

Ketogenic diets and caloric restriction have both been reported to have beneficial effects on cognitive function. These approaches may reflect overlapping mechanisms, since caloric restriction effectively increases ketone bodies (4). Ketones and a ketogenic diet have well-established beneficial effects in the treatment and control of epilepsy; however, their benefit(s) in AD and age-related cognitive

decline is an emerging area of research (5). In rodents, ketogenic studies are typically performed using exogenous ketones, and several studies have demonstrated improved cognitive function and decreased β -amyloid load in AD-transgenic mice administered ketones (6,7). Similarly, a small clinical trial in humans with mild cognitive impairment (MCI) showed that a low-carbohydrate (ketogenic) diet improved verbal memory (8). While these data are promising, there are critical challenges associated with leveraging the beneficial effects of ketones as a therapeutic strategy for treating dementia. These include issues of patient compliance due to poor tolerability of long-term ketogenic diets, although this may be improved by using a different type of ketone body (9,10). Perhaps more problematic is that long-term ketogenic diets and prolonged fasting may lead to or exacerbate nutritional deficits in the elderly (5). Therefore, it will be important to establish the efficacy of ketone supplementation prior to and during the symptomatic period.

Probiotic supplementation

Altered gut microbiota have been observed in multiple neurological conditions including dementia and AD, which has spurred exploration of the microbiome as a therapeutic target (11). Indeed, recent clinical trials of prebiotic or probiotic supplementation to change the microbiome have shown promising results in AD or MCI patients, even with short-term treatment (12-15). For example, one small exploratory study found that a 4-week probiotic treatment resulted in improvements in the Mini-Mental State Examination for cognitive impairment (14), though these results need to be confirmed in a RCT. Moreover, though clinical and preclinical studies agree that there is a general decrease in microbial diversity during AD (16,17), these changes comprise many bacterial species, and probiotic supplementation has not been exhaustively interrogated for all of these. Probiotic supplementation studies typically use *Lactobacillus* and *Bifidobacterium* species, as these are thought to decrease during AD, and are general well-tolerated by patients. However, it is unclear whether other species or more targeted supplementation would have similar beneficial effects. More importantly, it is not clear how probiotics are exerting their effects on dementia or MCI. Gut microbiota have been shown to produce neurotransmitters and peptides involved in blood-brain barrier stability, to alter the immune response, and to increase insulin resistance (11). While all of these pathways have been implicated in AD,

whether the effects of probiotic supplementation on the microbiome composition of the gut influences AD specifically through one of these pathways has yet to be shown. However, one intriguing finding from these studies is that peripheral immune markers of inflammation are often reduced with probiotic administration, suggesting that perhaps probiotics are mediating their effects on the brain via immune pathways. Consistent with these findings from human studies, probiotic administration to AD-transgenic mice reduces oxidative stress and improves AD phenotypes in the brain (18,19).

Overall, probiotics are particularly intriguing as a therapeutic, as they are generally well-tolerated and can be easily administered. However, as with a ketogenic diet, further studies are needed to determine the dose and length of treatment that provide optimized benefits while ensuring tolerability in dementia patients.

Exercise

Exercise is perhaps the lifestyle factor most consistently associated with reduced risk of dementia, and studies have found that the positive effect(s) of exercise hold whether physical activity occurs in midlife, well in advance of dementia symptoms (20), or whether it occurs in elderly patients already diagnosed with dementia (21). Though numerous studies have documented the benefits of exercise in ameliorating dementia, it is important to note that the mechanism by which this occurs differ with age. For example, exercise in midlife may have long-term cardiovascular benefits that ultimately reduce dementia risk (22), while exercise in dementia patients may increase neurotrophic growth factors, or ameliorate depressive symptoms (23,24).

The path forward

As Lourida *et al.* discuss, SNPs associated with AD affect various biological processes including immune function, lipid homeostasis, endocytic processing, and cholesterol transport. Thus, it is possible that stratifying individuals by genetic variant function may reveal more pronounced effects of certain lifestyle factors in mitigating genetic risk. For example, risk variants in *TREM2* and *HLA-DRB5-DBR1* are known to influence microglial function and inflammatory processes. Would probiotics that modulate inflammation be most efficacious in these individuals? *APOE-ε4* is thought to play a role in cholesterol homeostasis and lipid transport.

Would *APOE-ε4* individuals benefit most from a long-term ketogenic diet? Alternatively, perhaps the benefits of a healthy lifestyle are greater than the sum of its parts. Admittedly, the biological pathways implicated in AD and age-related dementias often interact with one another, and many AD risk genes have pleiotropic effects. Over a lifetime, these interactive effects are likely to be magnified, and thus, a single therapeutic targeting a particular pathway (i.e., cholesterol transport) may be ineffective, or only effective when the intervention is administered early in life. Overall, future large-scale cohort studies that stratify by genetic variant function will be important in determining whether particular lifestyle factors should be targeted to specific individuals. Likewise, preclinical studies will be essential for determining the therapeutic window for effective lifestyle interventions, and for determining whether the effects of specific genetic variants on AD can be uniquely targeted by particular lifestyle interventions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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