Structured Abstract

**Objectives:** To assess whether previous research on purported risk or protective factors for Alzheimer’s disease (AD) and cognitive decline is of sufficient strength to warrant specific recommendations for behavioral, lifestyle, or pharmaceutical interventions/modifications targeted to these endpoints.

**Data Sources:** MEDLINE® and the Cochrane Database of Systematic Reviews. Additional studies were identified from reference lists and technical experts.

**Review Methods:** A group of experts in the field developed the list of factors to be evaluated in preparation for an upcoming National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR) State-of-the-Science Conference addressing the prevention of AD and cognitive decline. We grouped the factors into the following categories: nutritional factors, medical conditions and prescription and non-prescription medications, social/economic/behavioral factors, toxic environmental factors, and genetics. Outcomes of interest were the development of AD or cognitive decline. Both observational and intervention studies were evaluated. Studies were evaluated for eligibility and quality, and data were abstracted on study design, demographics, intervention or predictor factor, and cognitive outcomes.

**Results:** A total of 25 systematic reviews and 250 primary research studies were included. Only a few factors showed a consistent association with AD or cognitive decline across multiple studies, including both observational studies and randomized controlled trials (when available). Such factors associated with increased risk of AD and cognitive decline were: diabetes, epsilon 4 allele of the apolipoprotein E gene (APOE e4), smoking, and depression. Factors showing a fairly consistent association with decreased risk of AD and cognitive decline were: cognitive engagement and physical activities. A consistent association does not imply that findings were robust, as the data were often limited, and the quality of evidence was typically low. In addition, the modification of risk for reported associations was typically small to moderate for AD, and small for cognitive decline. Some of the factors that did not show an association with AD or cognitive decline in this review may still play an influential role in late-life cognition, but there was not sufficient evidence to draw this conclusion. Many of the factors evaluated are not amenable to randomization, so rigorous observational studies are required to assess their effect on AD and cognitive decline.

**Conclusions:** The current research on the list of putative risk or protective factors is largely inadequate to confidently assess their association with AD or cognitive decline. Further research that addresses the limitations of existing studies is needed prior to be able to make recommendations on interventions.

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