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COMMENTARY

Clarifying dementia risk factors: treading in murky waters

In light of the growing burden of dementia, continued research into risk factors and potential contributors to disease development is essential. Clearly established risk factors can not only inform our understanding of disease pathophysiology and treatments but also identify potential preventive strategies. While age and the ApoE4 allele have consistently been shown to increase risk of developing dementia (Kukull *et al.*, 2002), other risk factors have been less studied or have had inconsistent findings. The study by Booker and colleagues (Booker *et al.*, 2016) re-examines proposed late-life medical risk factors for incident dementia in a large population-based case-control study. This important contribution is best interpreted in the context of existing research.

The study provides further support for risk of dementia among individuals with diabetes, stroke, Parkinson's disease, and mild cognitive impairment. Mental/behavioral disorders due to alcohol use are also identified as a strong risk factor. Previous data on alcohol misuse and dementia are mixed (Ilomaki *et al.*, 2015). Thus, late-life heavy alcohol use as a risk factor requires further investigation to understand mechanisms and potential confounders, such as education and smoking. Coronary heart disease, interestingly, had a weak association with incident dementia, perhaps due to adjustment for associated conditions, including hypertension, hyperlipidemia, diabetes, and obesity. Intracranial injury was also weakly associated, though prevalence of intracranial injuries was low and severity of intracranial injury was not assessed. Hypertension, obesity, and hyperlipidemia were not found to be independent risk factors. These conditions may exert differential effects in mid versus late life and in Alzheimer's versus vascular dementia (Li *et al.*, 2007; Fitzpatrick *et al.*, 2009; Mielke *et al.*, 2010). It is therefore important to understand exposures over the life course as our understanding of disease processes evolves.

The protective effects of statins, proton pump inhibitors (PPIs), and anti-hypertensive drugs are particularly interesting given ongoing controversy. Despite studies suggesting harmful effects of statins on cognition (Muldoon *et al.*, 2004), meta-analyses have also shown protective effects (Song *et al.*, 2013). Two recent studies of PPI use have demonstrated an increased risk of dementia among PPI users (Haenisch *et al.*, 2015; Gomm *et al.*, 2016). This conflicting result highlights the need to understand methodologic differences between studies and to conduct further high quality observational studies that accurately measure and consider long-term PPI use, covariates, and incident dementia (Kuller, 2016). With regard to anti-hypertensives, accounting for specific class of medication and blood pressure are necessary to fully understand whether and which medications exert a direct protective effect (Sink *et al.*, 2009; Yasar *et al.*, 2013).

This study by Booker and colleagues (Booker *et al.*, 2016) increases the evidence supporting specific medical conditions as risk factors for dementia and, where conflicting results are present, underscores the need for additional investigation of controversial risk factors in large cohorts and other case-control studies. Several aspects of this study are worth highlighting. The sample of over 20,000 older adults is large and drawn from primary care practices representative of the German population. The case-control design allows for examination of multiple exposures, which may be particularly important given increasing evidence that dementia may be multifactorial in etiology. At the same time, it would be important to conduct a similar study in which measures of other risk factors can be included, such as ApoE4 status, education, and physical activity. These factors may in fact modulate the effects of other risk factors and their treatment on incident dementia (Satizabal *et al.*, 2016).

Booker and colleagues (Booker *et al.*, 2016) highlight that dementia is a complex disease. The pathophysiology is still not fully disentangled and understood. Identifying and ultimately addressing risk factors, for different types of dementia and with differential effects over the life course, is equally complex and remains an important task in the efforts to address this devastating disease.

Conflict of interest

None.

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