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Featured Article

Circulating metabolites and general cognitive ability and dementia: Evidence from 11 cohort studies

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Abstract

Introduction: Identifying circulating metabolites that are associated with cognition and dementia may improve our understanding of the pathogenesis of dementia and provide crucial readouts for preventive and therapeutic interventions.

Methods: We studied 299 metabolites in relation to cognition (general cognitive ability) in two discovery cohorts (N total = 5658). Metabolites significantly associated with cognition after adjusting for multiple testing were replicated in four independent cohorts (N total = 6652), and the associations with dementia and Alzheimer's disease (N = 25,872) and lifestyle factors (N = 5168) were examined.

Results: We discovered and replicated 15 metabolites associated with cognition including subfractions of high-density lipoprotein, docosahexaenoic acid, ornithine, glutamine, and glycoprotein acetyls. These associations were independent of classical risk factors including high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, and apolipoprotein E (*APOE*) genotypes. Six of the cognition-associated metabolites were related to the risk of dementia and lifestyle factors.

Discussion: Circulating metabolites were consistently associated with cognition, dementia, and lifestyle factors, opening new avenues for prevention of cognitive decline and dementia.

Keywords: Cognitive function; General cognitive ability; Alzheimer's disease; Dementia; Metabolites; Metabolomics; NMR; Lifestyle factors

1. Background

Cognitive function is an important determinant of health and well-being and a key component of the dementia spectrum, including Alzheimer's disease (AD), the most common cause of dementia [1]. Vascular dysfunction and metabolic dysregulation contribute to impairment in cognitive performance [2]. Clinical and population-based studies suggest a relationship of cognitive function with midlife hypertension, high blood levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides and glucose, and low levels of high-density lipoprotein cholesterol (HDL-C) [3–5]. The recent decrease in incidence of dementia in longitudinal studies has been attributed to improved control of vascular and metabolic factors [6–9]. These findings have fueled speculation that discovery of other circulating metabolites influencing cognition and future dementia may not only improve our understanding of the determinants of cognition but may also facilitate prevention through interventions on lifestyle factors and dedicated medication [10]. Previous studies have shown circulating metabolites in blood (e.g., lipoproteins, amino acids, fatty acids, and other small molecules) to be associated with cognitive function and conversion from normal cognition to dementia or AD [11–17]. However, these studies were relatively small and findings have not been replicated [15,18], emphasizing the need for studies in large well-characterized populations where findings are replicated [10,19].

We performed a comprehensive metabolic analysis to study the role of circulating metabolites in cognitive function. Discovery of novel measures associated with cognitive function was performed in two large population-based studies in the Netherlands—the Rotterdam Study (RS) and the Erasmus Rucphen Family (ERF) study. We determined whether the associations were independent of known vascular and metabolic risk factors. Metabolites independently associated with cognition were replicated in independent cohort studies, and their relation to the risk of dementia and AD was validated in eight cohort studies. Finally, we assessed whether lifestyle factors, including dietary fish intake, smoking, and physical activity, were associated with the identified metabolites.

2. Methods

For a schematic overview of the analysis setup, see Fig. 1.