



## Featured Article

# Association of branched-chain amino acids and other circulating metabolites with risk of incident dementia and Alzheimer's disease: A prospective study in eight cohorts

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## Abstract

**Introduction:** Metabolite, lipid, and lipoprotein lipid profiling can provide novel insights into mechanisms underlying incident dementia and Alzheimer's disease.

**Methods:** We studied eight prospective cohorts with 22,623 participants profiled by nuclear magnetic resonance or mass spectrometry metabolomics. Four cohorts were used for discovery with replication undertaken in the other four to avoid false positives. For metabolites that survived replication, combined association results are presented.

**Results:** Over 246,698 person-years, 995 and 745 cases of incident dementia and Alzheimer's disease were detected, respectively. Three branched-chain amino acids (isoleucine, leucine, and valine), creatinine and two very low density lipoprotein (VLDL)-specific lipoprotein lipid subclasses were associated with lower dementia risk. One high density lipoprotein (HDL; the concentration of cholesterol esters relative to total lipids in large HDL) and one VLDL (total cholesterol to total lipids ratio in very large VLDL) lipoprotein lipid subclass was associated with increased dementia risk. Branched-chain amino acids were also associated with decreased Alzheimer's disease risk and the concentration of cholesterol esters relative to total lipids in large HDL with increased Alzheimer's disease risk.

**Discussion:** Further studies can clarify whether these molecules play a causal role in dementia pathogenesis or are merely markers of early pathology.

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## Keywords:

Dementia; Alzheimer's disease; Metabolomics; Biomarkers; Amino acids

## 1. Introduction

Dementia, including Alzheimer's disease (AD), is a major public health problem with devastating physical, financial, and social consequences for patients, their caregivers, families, and society. Worldwide the cost of AD care in 2010 was \$604 billion or 1% of the global gross domestic product [1]. However, despite over two decades of research on animal models and clinical trials, we still have no effective prevention or disease-modifying therapy for late-onset clinical dementia and AD. Dementia is increasingly recognized as a heterogeneous syndrome that would be best addressed with a multipronged approach to prevention and treatment, analogous to the multipronged and individually tailored use of statins, antihypertensives, antiplatelet agents, and vasodilators in persons with coronary artery disease. Identifying novel biology could suggest new circulating biomarkers for risk prediction and drug targets. Agnostic approaches such as genome wide genetic analyses have identified new biological pathways and molecules mediating microglial inflammation (*TREM2*) and endocytosis (*BINI*, *PICALM*) as having a previously unsuspected key role in AD pathophysiology [2,3].

Blood metabolomics is an attractive tool for agnostic exploration of disease pathways for several reasons. Metabolites are small molecules that reflect the interplay of genetic and environmental factors, readily cross the blood-brain barrier and their levels are modifiable through dietary or pharmacological

interventions. This recognition has spurred interest in using metabolomics as a tool to understand AD. For example, longitudinal studies in mouse models of AD have implicated perturbed polyamine metabolism, disturbances in essential amino acids, branched-chain amino acids (BCAA), and in the neurotransmitter serotonin along with imbalances in phospholipid and acylcarnitine homeostasis in both the brain and the blood [4]. Human studies in cerebrospinal fluid and plasma have to date only compared AD cases to controls in cross-sectional settings or attempted to identify markers predicting conversion from mild cognitive impairment (MCI) to clinical dementia [5–9]. However, in persons with MCI or dementia, it is not possible to determine if the observed metabolite changes are causal or secondary to disease-related processes. There has only been one prior study of preclinical AD that failed to detect any consistently reproducible signal [10].

We conducted a prospective study relating blood metabolites, lipid, and lipoprotein lipids quantified by nuclear magnetic resonance (NMR) or mass spectrometry (MS) metabolomics to risk of incident dementia and AD in eight longitudinal studies with a total of 22,623 participants free of dementia at baseline: the FINRISK 1997 study, the Dietary, Lifestyle and Genetic determinants of Obesity and Metabolic Syndrome (DILGOM) study, the Whitehall II Study, the Estonian biobank study (EGCUT), the Health 2000, the Framingham Heart Study (FHS), the Rotterdam study (RS), and the Erasmus Ruchen Family (ERF) study. The first

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