ELSEVIER

Alzheimer's & Dementia ■ (2018) 1-11

Alzheimer's & Dementia

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

Juho Tynkkynen[a,†], Vincent Chouraki[b,c,d,†], Sven J. van der Lee[e], Jussi Hernesniemi[a], Qiong Yang[c,f], Shuo Li[c,f], Alexa Beiser[b,c,f], Martin G. Larson[c,f], Katri Sääksjärvi[g], Martin J. Shipley[h], Archana Singh-Manoux[h,i], Robert E. Gerszten[j,k,l], Thomas J. Wang[m], Aki S. Havulinna[g], Peter Würtz[n,o], Krista Fischer[p], Ayse Demirkan[e], M. Arfan Ikram[e,q,r], Najaf Amin[e], Terho Lehtimäki[s,t], Mika Kähönen[u,v], Markus Perola[g,o,p], Andres Metspalu[p], Antti J. Kangas[n], Pasi Soininen[n,w,x], Mika Ala-Korpela[w,x,y,z,aa,bb], Ramachandran S. Vasan[c,cc], Mika Kivimäki[h,dd], Cornelia M. van Duijn[e,ee], Sudha Seshadri[b,c,ff,*,‡], Veikko Salomaa[g,**,‡]

[a]*Department of Cardiology, Tays Heart Hospital, Tampere University Hospital and Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland*
[b]*Department of Neurology, Boston University School of Medicine, Boston, MA, USA*
[c]*The Framingham Heart Study, Framingham, MA, USA*
[d]*Lille University, Inserm, Lille University Hospital, Institut Pasteur de Lille, U1167 - RID-AGE - Risk Factors and Molecular Determinants of Aging-Related Diseases, Labex Distalz, Lille, France*
[e]*Department of Epidemiology, ErasmusMC, Rotterdam, The Netherlands*
[f]*Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA*
[g]*Department of Health, National Institute for Health and Welfare, Helsinki, Finland*
[h]*Department of Epidemiology and Public Health, University College London, London, UK*
[i]*INSERM, U1018, Centre for Research in Epidemiology and Population Health, France*
[j]*Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
[k]*Broad Institute of MIT and Harvard, Cambridge, MA, USA*
[l]*Cardiovascular Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
[m]*Vanderbilt Heart and Vascular Institute, Vanderbilt University School of Medicine, Nashville, TN, USA*
[n]*Nightingale Health Ltd, Helsinki, Finland*
[o]*Research Programs Unit, Diabetes and Obesity, University of Helsinki, Helsinki, Finland*
[p]*Estonian Genome Center, University of Tartu, Tartu, Estonia*
[q]*Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, The Netherlands*
[r]*Department of Neurology, Erasmus MC, Rotterdam, The Netherlands*
[s]*Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland*
[t]*Department of Clinical Chemistry, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland*
[u]*Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland*
[v]*Department of Clinical Physiology, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland*
[w]*Computational Medicine, Faculty of Medicine, University of Oulu and Biocenter Oulu, Oulu, Finland*
[x]*NMR Metabolomics Laboratory, School of Pharmacy, University of Eastern Finland, Kuopio, Finland*
[y]*Population Health Science, Bristol Medical School, University of Bristol, Bristol, UK*
[z]*Medical Research Council Integrative Epidemiology Unit at the University of Bristol, Bristol, UK*
[aa]*Systems Epidemiology, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia*

A.J.K., P.W., and P.S. are shareholders and report employment relation for Nightingale Health Ltd, a company offering NMR-based metabolite profiling. The other authors have no conflicts of interest.

[†]These authors contributed equally as first authors.

[‡]These authors contributed equally as senior authors.

*Corresponding author. Tel.: +001 210 450 8426; Fax: +001 210 450 2250.

**Corresponding author. Tel.: +358 29 524 8620; Fax: +358 29 524 8338.

E-mail address: suseshad@bu.edu (S.S.), veikko.salomaa@thl.fi (V.S.)

https://doi.org/10.1016/j.jalz.2018.01.003

[bb]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Faculty of Medicine, Nursing and Health Sciences, The Alfred Hospital, Monash University, Melbourne, Victoria, Australia
[cc]Department of Medicine, Sections of Preventive Medicine and Cardiology, Boston University School of Medicine, Boston, MA, USA
[dd]Clinicum, Faculty of Medicine, University of Helsinki, Helsinki, Finland
[ee]Leiden Academic Center for Drug Reseach (LACDR), Leiden University, Leiden, The Netherlands
[ff]Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, University of Texas Health Sciences Center, San Antonio, TX, USA

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.

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 (*BIN1*, *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