European Society for Paediatric Research
Society for Pediatric Research
www.nature.com/pr

POPULATION STUDY ARTICLE OPEN

Check for updates

Genetic susceptibility to Alzheimer's disease and cardiometabolic risk from childhood

Eero A. Haapala[1,2,3]✉, Saara Heinonen[1,2], Juha Mykkänen[4,5], Harri Niinikoski[5,6], Hanna Lagström[5,7,8], Pia Salo[4,5], Antti Jula[7], Tapani Rönnemaa[9,10], Jorma SA Viikari[9,10], Olli T. Raitakari[4,5,11], Katja Pahkala[4,5,12] and Suvi Rovio[4,5,7]

BACKGROUND: We investigated the associations of genetic risk score for Alzheimer's disease (GRS-AD) with cardiometabolic risk from early childhood over a 20-year follow-up.
METHODS: The STRIP study included 1062 children at baseline. GRS-AD was calculated for 631 participants using 22 independent genetic risk variants, including APOE ε2 and ε4 alleles, and excluding them (non-APOE-GRS-AD). We repeatedly measured waist circumference, high-density (HDL-C) and low-density (LDL-C) lipoprotein cholesterol, triglycerides, glucose, insulin, and blood pressure. The data were analysed with generalised additive mixed models.
RESULTS: GRS-AD was directly associated with serum LDL-C (unstandardised $\beta = 0.140$, 95% CI = 0.084 to 0.195) and inversely with HDL-C ($\beta = -0.026$, 95% CI = −0.044 to −0.009). GRS-AD was inversely associated with serum HDL-C in males ($\beta = -0.044$, 95% CI = −0.070 to −0.018) but not in females ($\beta = -0.010$, 95% CI = −0.032 to 0.012). The associations were diluted when the non-APOE-GRS-AD was applied.
CONCLUSION: A genetic predisposition to AD may alter lipid metabolism from early childhood.

Pediatric Research; https://doi.org/10.1038/s41390-026-04860-5

IMPACT:

- While Alzheimer's disease and cardiometabolic diseases may have shared genetic determinants, the associations between genetic susceptibility for Alzheimer's disease and increased cardiometabolic risk from childhood to young adulthood are poorly understood.
- We investigated the associations of genetic risk score for Alzheimer's disease with cardiometabolic risk from early childhood over a 20-year follow-up.
- We found that a higher genetic risk score for Alzheimer's disease was associated with higher LDL cholesterol, non-HDL cholesterol, and ApoB, and with lower serum HDL cholesterol and ApoA1.
- These findings suggest that a genetic predisposition to Alzheimer's disease may alter lipid metabolism from early childhood.

INTRODUCTION

Along with ageing population, cognitive decline and dementia affect a substantial number of people.[1] Moreover, the prevalence of cardiometabolic morbidities, e.g., obesity[2] and type 2 diabetes mellitus,[3] remains high. Notably, obesity, dyslipidaemia, insulin resistance, and hypertension increase the risk of Alzheimer's disease (AD), the most common cause of dementia.[4,5] While AD and cardiometabolic diseases may have shared genetic determinants, the associations between genetic susceptibility for AD and increased cardiometabolic risk from childhood to young adulthood are poorly understood.[6]

In prior studies in adult cohorts, higher body mass index (BMI) has been associated with an increased risk of dementia during a long follow-up period.[7] In contrast, short-term studies have reported opposite findings,[7] likely due to reverse causation, where AD-related pathophysiological changes lead to lower BMI.[8] Accordingly, genetic susceptibility to AD has been associated with lower adiposity in adults aged ≥53 years but not in younger adults[9] or children.[6] In addition, overweight and obesity may modify the associations of APOE - the strongest genetic risk factor for AD[10] - and genetic risk score for AD (GRS-AD) with cardiometabolic risk factors in children and adults.[6,11]

[1]Institute of Biomedicine, School of Medicine, University of Eastern Finland, Kuopio, Finland. [2]Sports and Exercise Medicine, Faculty of Sport and Health Sciences, University of Jyväskylä, Keskussairaalantie, Jyväskylä, Finland. [3]Children's Health and Exercise Research Centre, Public Health and Sport Sciences, University of Exeter Medical School, University of Exeter, Exeter, UK. [4]Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland. [5]Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland. [6]Department of Pediatrics and Adolescent Medicine, Turku University Hospital, University of Turku, Turku, Finland. [7]Department of Public Health, University of Turku and Turku University Hospital, Turku, Finland. [8]Nutrition and Food Research Center, Faculty of Medicine, University of Turku, Turku, Finland. [9]Department of Medicine, University of Turku, Turku, Finland. [10]Division of Medicine, Turku University Hospital, Turku, Finland. [11]Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, University of Turku, Turku, Finland. [12]Paavo Nurmi Centre and Unit for Health and Physical Activity, University of Turku, Turku, Finland. ✉email: eero.haapala@uef.fi

Received: 24 June 2025 Revised: 3 January 2026 Accepted: 25 January 2026
Published online: 05 March 2026

Recent studies in adults have identified shared genetic risk factors also between AD and dyslipidaemia,[12] hypertension,[13] incident cardiovascular disease[14] and cardiometabolic diseases,[15,16] but the evidence is unclear[14,17,18] and lacks from young and healthy cohorts. In adults, AD-associated APOE allele ε2 has been shown to modulate levels of cardiometabolic risk factors and cardiovascular outcomes.[19] Increasing number of carried ε2 alleles is associated with lower risk for cardiovascular diseases, lower levels of systolic blood pressure, low-density lipoprotein (LDL) cholesterol, and ApoB, and higher levels of high-density lipoprotein (HDL) cholesterol and triglycerides.[19–21] In contrast, ε4 allele of APOE has been associated with an increased levels of LDL cholesterol, ApoB and triglycerides, and lower levels of HDL cholesterol.[19,22]

Furthermore, APOE ε4 is associated with increased risk of dyslipidaemia, type II diabetes, and cardiovascular diseases in adults.[23] At the same time, dyslipidaemia in childhood has been linked with lower cognitive function in midlife,[24] while dyslipidaemia over the life course has been observed to be associated with an increased risk of AD.[25] While increased cardiometabolic risk has been associated with impaired white matter microstructure, a potential mechanism underlying lower cognitive functions and a higher risk of AD,[26,27] understanding the associations between genetic susceptibility for AD and cardiometabolic risk from childhood is important as LDL cholesterol has been found to be more detrimental to the white matter microstructure in APOE ε4 carriers than in non-carriers.[26,27] These findings could be explained by a longer LDL circulation time, increased oxidative stress, and decreased plasma antioxidant capacity, contributing to LDL oxidation.[28]

Because the aetiology of AD extends over decades, prolonged exposure to cardiometabolic disturbances since childhood may contribute to pathophysiological processes in the brain, and thus to the risk of cognitive decline.[29] Accordingly, although AD symptoms typically emerge in late-life, the disease-specific pathophysiological processes begin possibly even decades earlier highlighting the need for life-course preventive strategies[30] which is also acknowledged by the Alzheimer's Association.[31] However, to the best of our knowledge, only one study has examined the associations between genetic susceptibility for AD and cardiometabolic risk factors, two underlying risk factors for AD, in younger cohorts.[6] Therefore, replication of these initial findings[6] in larger cohorts is required, and studies with extended follow-ups spanning from childhood to young adulthood are warranted to strengthen the evidence base. Moreover, previous paediatric study[6] focussed on traditional cardiometabolic risk factors, such as LDL- and HDL cholesterol. However, the main protein components of those lipoproteins, ApoB and ApoA1, also predict cardiovascular endpoints, such as myocardial infarction,[32] and associate with AD risk.[33]

To overcome limitations of previous study in children,[6] we investigated the associations of GRS-AD with waist circumference, body fat percentage, serum LDL, HDL and non-HDL cholesterols, triglycerides, ApoB, ApoA1, glucose, insulin, homeostasis model of insulin resistance (HOMA-IR), and systolic and diastolic blood pressure over a 20-year follow-up from early childhood to young adulthood and whether APOE explains these associations. Moreover, as body adiposity may modify these associations,[6,11] we also investigated these associations in the sex-specific body fat percentage tertiles. Finally, we repeated these analyses using a non-APOE-GRS-AD to study whether the associations between genetic susceptibility for AD and cardiometabolic risk would be independent of APOE.

METHODS

Study design and participants

The current analyses are based on the Special Turku Coronary Risk Factor Intervention Project (STRIP), which is a prospective, randomised intervention trial begun in childhood with the aim to decrease cardiometabolic risk mainly through a healthy diet.[34,35] Briefly, families of 5-month-old infants were recruited to the study at well-baby clinics in Turku, Finland, between 1990 and 1992. A total of 1062 infants were randomised to an intervention group ($n = 540$) or to a control group ($n = 522$) at age 7 months. The intervention group received individualised dietary and lifestyle counselling with the main aim to replace dietary saturated fat with unsaturated fat. The present study cohort comprised those participants who had the data on both GRS-AD ($N = 631$) and cardiometabolic risk factors (N varying between 543 and 626 depending on the cardiometabolic risk factor).

The STRIP study is conducted according to the guidelines of The Declaration of Helsinki, and the study protocol is approved by the Joint Commission on Ethics of the Turku University and the Turku University Central Hospital, and it conforms with Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. Parents provided their written informed consent in the beginning of the study and children provided their written informed consent at ages 15 and 18 years.

Genetic risk scores

Genotyping was performed using the Illumina Custom Metabochip BeadChip (Illumina, San Diego, CA)[36] at the Center for Inherited Disease Research, the Johns Hopkins University. Genotype imputation was performed based on reference haplotypes provided by the Haplotype Reference Consortium. The GRS-AD was calculated using information on 22 AD risk alleles identified by earlier GWAS meta-analyses among adults[37,38] as described previously.[39] The genes and their variants used to calculate the GRS-AD were APOE (ε2/4), rs3818361, rs11218343, rs10838725, rs610932, rs670139, rs3851179, rs17125944, rs10498633, rs8093731, rs3865444, rs744373, rs35349669, rs7274581, rs190982, rs9271192, rs9349407, rs11771145, rs2718058, rs28834970, and rs11136000. Those with missing data, were excluded from the analyses. Briefly, the GRS-AD was calculated by summing log-transformed odds ratios for AD-associated risk alleles reported in earlier GWAS meta-analyses[37,38] weighted by the number of alternative alleles. Because APOE ε4 genotype is the strongest genetic risk factor for AD at the population level and also associated with cardiometabolic risk factors, we calculated a non-APOE-GRS-AD excluding APOE from the score to study if the associations between GRS-AD are independent of APOE. A higher value in the GRS indicates higher genetic risk of AD.

Cardiometabolic risk factors

Body size and composition. Until age 21 months, recumbent length was measured with baby board (Bekvil, Paljerakenne, Helsinki, Finland) and after that, standing height was measured to the nearest 0.1 cm using Harpenden stadiometer (Holtain, Crymych, UK). Weight was measured to the nearest 0.1 kg using mechanical infant scale (Seca 725; Hamburg, Germany) until age 15 months and after 15 months of age using an electronic scale (SoehnleS10; Soehnle, Murrhardt, Germany). BMI was calculated as weight in kilograms divided by height in metres squared (kg/m^2). From the age of 7 years onwards, body fat percentage was assessed using the leg-to-leg bioimpedance apparatus (Tanita body fat analyser, TBF 105, Tanita Corporation, Tokyo, Japan).[40] Waist circumference was measured midway between the iliac crest and the lowest rib at the midaxillary line to the nearest 0.5 cm with an unstretchable measuring tape.

Serum lipids, apolipoproteins, glucose, and insulin. On each study visit, venous blood samples were drawn. The samples drawn before age 5 years were non-fasting, while fasting samples were collected from age 5 years. Serum total cholesterol concentration was measured with a fully enzymatic cholesterol oxidase p-aminophenazone method (Merck, Darmstadt, Germany) by an AU510 automatic analyser (Olympus, Hamburg, Germany) or after January 2001, using an AU400 analyser. We measured HDL cholesterol concentration after precipitation of the ApoB containing lipoprotein particles by dextran sulfate 500000 and $MgCl_2$.[41,42] The interassay (intra-assay) coefficients of variation for total cholesterol and HDL cholesterol were 2.0% (1.5%) and 1.9% (1.2%), respectively. Because the non-fasting samples were obtained before age of 5 years, LDL cholesterol and triglycerides were not assessed before the age of 5 years. We analysed serum triglyceride concentration by the colorimetric glycerol-3-phospate oxidase p-aminophenazone method (Merck) using an automatic Olympus AU510 analyser or after January 2001, an AU400 analyser. We estimated LDL cholesterol using the Friedewald formula in participants with triglyceride levels less than 4.52 mmol/L. Non-HDL cholesterol was

calculated as 'serum total cholesterol – HDL cholesterol'. ApoB and ApoA1 concentrations was determined immunoturbidimetrically (Orion Diagnostica, Helsinki, Finland). The interassay (intra-assay) coefficients of variation for the determination of ApoB were 4.5% (3.3%) and for ApoA1 3.0% (1.8%).

We assessed serum glucose and insulin concentrations for the entire cohort beginning from age 15 years. We measures serum glucose by a hexokinase method (Glucose Olympus System Reagent, Olympus, Ireland; interassay coefficient of variation, 1.8%). For the insulin analyses, the blood samples were centrifuged immediately, and 15 µL enzyme inhibitor antagosan or 30 µL trasylol (since 2008) was added to the 0.5-mL serum sample. We stored the samples frozen until analyses. We measured serum insulin using a microparticle enzyme immunoassay (Insulin IMX system reagent, Abbott, Chicago, IL; interassay coefficient of variation, 6.5%) or with a chemiluminescent microparticle immunoassay (ARCHITECT insulin assay, Abbott; interassay coefficient of variation, 1.8%). We corrected for differences in analytic level between the methods, a correlation equation obtained from standardised principal component analysis of results of samples analysed with both methods was used and the correlation was observed to be very high ($r = 0.997$). We estimated insulin resistance using the homeostasis model of insulin resistance (HOMA-IR; [fasting insulin×fasting glucose]/22.5).[43]

Blood pressure. Blood pressure was measured in a seated position after a ≥ 15 min rest from the right arm using age-appropriate cuff size from the age of 7 months onwards.[44] The blood pressure was measured once until 7 years of age and thereafter at least twice using an oscillometric noninvasive blood pressure monitor (Criticon Dinamap 1846 SX until 2001, thereafter Criticon Dinamap Compact T).[44]

Covariates

We assessed food consumption using a food record for 4 consecutive days including at least 1 weekend day. A dietitian verified the accuracy of food records, and dietary intakes were analysed with Micro Nutrica program,[45] which is based on the Food and Nutrient Database of the Social Insurance Institution, Finland. The program calculates 66 nutrients in commonly used Finnish foods and dishes. The data bank is continuously updated with new foods and recipes. We used a diet score to describe overall diet quality, as described previously.[46]

Leisure time physical activity was assessed with a physical activity questionnaire at the ages of 11 to 19 years. Leisure time physical activity was calculated as metabolic equivalent hours per week (MET h/wk) by multiplying the mean frequency, duration, and intensity of the physical activity.[47]

Pubertal status was assessed using the stages described by Marshall and Tanner (M1–M5/females, G1–G5/males) since the age of 9 years; M1/G1 were considered pre-pubertal and other stages pubertal.[48,49]

Statistical analyses

We performed data analyses using R software (R Core Team, 2022, Vienna Austria, https://www.R-project.org/). First, due to skewed distributions we performed logarithm transformation for triglycerides, insulin, and HOMA-IR. Characteristics were reported sex-specifically using means and standard deviations. Because associations between cardiometabolic risk factors and GRS-AD's were nonlinear, we fitted generalised additive mixed models[50] for all the participants and also separately for males and females. In the models, random smooths adjust the trend of age in a nonlinear way and random effects of individual were modelled by random intercept and random slope for age. Other predictors in the models were sex and study group (intervention and control). Possible effect modification by sex was studied adding a multiplicative interaction term (sex*risk factor) to the models adjusted for study group. Additionally, because body fat percentage and weight status have been found to modify the associations between genetic traits and cardiometabolic risk factors,[6,11] we divided the participants into sex-specific body fat percentage tertiles (≤ 23.5 vs. > 23.5–29.2 vs. > 29.2 for females and ≤ 12.9 vs. > 12.9–18.7 vs. > 18.7 for males). The data were further adjusted for physical activity, diet quality, and pubertal status.

RESULTS

Characteristics of participants

At the age of 20 years, females had a higher body fat percentage and smaller waist circumference than males (Table 1). Females also had higher serum LDL and HDL cholesterol, and lower fasting glucose and systolic blood pressure.

Table 1. Descriptive characteristics of the study population at the age of 20 years.

	Females $n = 240$	Males $n = 225$
Age (years)	20.0 (0.1)	20.1 (0.2)
Height (cm)	167.6 (6.1)	181.1 (6.4)
Weight (kg)	64.1 (12.4)	75.1 (12.5)
Body mass index (kg/m^2)	22.8 (4.2)	22.9 (3.6)
Genetic risk score with APOE	0.41 (0.89)	0.26 (0.83)
Genetic risk score without APOE	−0.16 (0.27)	−0.18 (0.26)
Waist circumference (cm)	74.1 (9.7)	80.7 (8.8)
Body fat percentage (%)	31.3 (8.0)	18.1 (7.9)
LDL cholesterol (mmol/L)	2.7 (0.7)	2.5 (0.7)
HDL cholesterol (mmol/L)	1.5 (0.3)	1.17 (0.3)
Non-HDL cholesterol (mmol/L)	3.1 (0.7)	2.9 (0.7)
Triglycerides (mmol/L)	1.1 (0.5)	1.02 (0.5)
Apolipoprotein B (mmol/L)	0.8 (0.2)	0.8 (0.2)
Apolipoprotein A1 (mmol/L)	1.7 (0.3)	1.4 (0.2)
Glucose (mmol/L)	4.8 (0.4)	4.9 (0.4)
Insulin (mU/L)	7.5 (4.2)	7.3 (4.5)
Homeostatic model assessment for insulin resistance	1.6 (1.0)	1.6 (0.9)
Systolic blood pressure (mmHg)	115.2 (12.1)	126.6 (12.0)
Diastolic blood pressure (mmHg)	66.0 (7.8)	66.0 (8.4)

LDL low-density lipoprotein, *HDL* high-density lipoprotein.

Associations of GRS-AD with cardiometabolic risk factors

GRS-AD was directly associated with LDL cholesterol, non-HDL cholesterol and ApoB and inversely with HDL cholesterol and ApoA1, but not with other cardiometabolic risk factors (Table 2). Furthermore, sex modified the association between GRS-AD and HDL cholesterol ($p < 0.05$ for interaction). In the sex-stratified analyses, GRS-AD was inversely associated with HDL cholesterol and ApoA1 in males ($\beta = -0.044$, 95% CI = −0.070 to −0.018 and $\beta = -0.031$, 95% CI = −0.050 to −0.013, respectively) but not in females ($\beta = -0.010$, 95% CI = −0.032 to 0.012 and $\beta = -0.055$, 95% CI = −0.023 to 0.012, respectively). The inverse association between GRS-AD and HDL cholesterol in males remained similar after adjustment for pubertal status but attenuated after adjustment for diet quality and physical activity ($\beta = -0.015$, 95% CI = −0.037 to 0.008). Further adjustment for physical activity, diet quality, and pubertal status had no effect on these associations. The study group had negligible effects on observed associations.

Associations of non-APOE-GRS-AD with cardiometabolic risk factors

Non-APOE-GRS-AD was not associated with any studied cardiometabolic factors in all participants (Table 2) or in males and females separately.

Associations of GRS-AD with cardiometabolic factors according to body fat percentage

A higher GRS-AD was directly associated with serum triglycerides ($\beta = 0.059$, 95% CI = 0.007–0.111) and inversely associated with serum HDL cholesterol (β = −0.062, 95% CI = −0.103 to −0.020) and systolic blood pressure ($\beta = -2.604$, 95% CI = −4.085 to

Table 2. Associations of genetic risk scores for Alzheimer's disease with cardiometabolic risk factors.

	GRS-AD		Non-APOE-GRS-AD	
	B	95% CI	*B*	95% CI
Waist circumference (cm)	−0.174	−0.860 to 0.511	0.174	−1.991 to 2.339
Body fat percentage (%)	−0.304	−1.129 to 0.522	1.726	−0.871 to 4.323
LDL cholesterol (mmol/L)	**0.140**	**0.084–0.195*****	0.012	−0.169 to 0.193
HDL cholesterol (mmol/L)	**−0.026**	**−0.044 to −0.009****	0.005	−0.050 to 0.060
Non-HDL cholesterol (mmol/L)	**0.167**	**0.112–0.227*****	0.042	−0.145 to 0.230
Triglycerides (mmol/L)	0.0204	−0.006 to 0.047	−0.089	−0.210 to 0.032
Apolipoprotein B (mmol/L)	**0.035**	**0.023–0.046*****	0.002	−0.036 to 0.040
Apolipoprotein A1 (mmol/L)	**−0.017**	**−0.030 to −0.004****	0.006	−0.035 to 0.047
Glucose (mmol/L)	−0.004	−0.010 to 0.003	−0.002	−0.023 to 0.019
Insulin[1] (mU/L, log)	−0.012	−0.042 to 0.017	−0.008	−0.102 to 0.087
HOMA-IR	−0.007	−0.040 to 0.025	−0.031	−0.136 to 0.075
Systolic blood pressure (mmHg)	−0.332	−0.917 to 0.253	0.371	−1.498 to 2.240
Diastolic blood pressure (mmHg)	−0.132	−0.534 to 0.270	0.265	−1.017 to 1.548

The data are unstandardised coefficients and their confidence intervals from the generalised additive mixed models adjusted for age, sex, and the study group (intervention vs. control).
Regression coefficients and their 95% confidence intervals for statistically significant associations are bolded.
**$p < 0.01$, ***$p < 0.001$.
LDL low-density lipoprotein, *HDL* high-density lipoprotein, *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance.
HOMA-IR and triglycerides were log-transformed.

−1.122) in males in the lowest tertile of body fat percentage. In females, a higher GRS-AD was directly associated with serum LDL cholesterol in the highest tertile of body fat percentage ($\beta = 0.156$, 95% CI = 0.038–0.274) but not in other tertiles. There was also a tendency of an inverse association between GRS-AD and serum HDL cholesterol in females in the lowest tertile of body fat percentage ($\beta = -0.031$, 95% CI = −0.031 to 0.003).

DISCUSSION

We found that a higher GRS-AD was associated with higher LDL cholesterol, non-HDL cholesterol, and ApoB, and with lower serum HDL cholesterol and ApoA1 across 20-year follow-up from early childhood to young adulthood. Furthermore, we observed that the associations of GRS-AD wih HDL cholesterol and ApoA1 were modified by sex, with a statistically significant inverse associations observed only in males. We also observed that in males in the lowest body fat percentage tertile a higher GRS-AD associated with higher serum triglycerides and lower HDL cholesterol levels than in males in other body fat percentage tertiles. Furthermore, a higher GRS-AD was directly associated with serum LDL cholesterol in females in the highest body fat percentage tertile. In contrast, non-APOE-GRS-AD was not associated with cardiometabolic risk factors.

In line with prior findings among children,[6] we observed a direct association of GRS-AD with serum LDL cholesterol. In contrast to our prior findings in children[6] and studies in adults,[23] GRS-AD was not associated with indices of glucose metabolism or insulin resistance. Furthermore, our current results indicated that the APOE4 genotype explains the majority of the found associations between GRS-AD and cardiometabolic risk factors, as no associations were found when APOE was excluded from the GRS-AD. This observation is supported by earlier findings in adults,[9,17] indicating that the APOE variant included in the GRS-AD completely explains the association between GRS-AD and cardiometabolic risk factors. Furthermore, we found that one unit increase in GRS-AD increased LDL cholesterol concentration by 0.140 mmol/L and non-HDL cholesterol by 0.167 mmol/L during the first two decades of life. Previous studies suggest that a 0.5–1.0 mmol/L decrease in LDL cholesterol[51] and targeting non-HDL cholesterol levels of <2.2–3.4 mmol/L[52] produces a clinically meaningful reduction in cardiovascular disease incidence but that lowering LDL cholesterol has no effect on cognitive functions in adults.[53,54] Nevertheless, a cumulative burden of higher LDL cholesterol since childhood has been associated with poorer cognitive performance in midlife.[24] Therefore, while the clinical significance of our findings on the direct association between GRS-AD and LDL cholesterol should be elucidated, preventing dyslipidaemia, and lowering LDL and non-HDL cholesterol levels starting in childhood may provide benefits in cognitive function over the life course.

Previous studies also suggest that adiposity may modify the associations of GRS-AD with cardiometabolic risk factors in children and adults.[6,11] In a prior study leveraging a child cohort, GRS-AD and non-APOE-GRS-AD were observed to associate directly with clustering of cardiometabolic risk factors among females in the highest body fat percentage.[6] In this study, we in contrast, observed that GRS-AD was directly associated with serum triglycerides and inversely with serum HDL cholesterol only among males within the lowest body fat percentage tertile. While the reason for these associations is unclear, the increased fat mass may have overdriven the impact of genetic factors for these cardiometabolic risk factors among males with a larger body fat percentage as obesity is considered the most important risk factor for these cardiometabolic disturbances, particularly in males.[55]

In line with previous observations, higher body fat percentage exacerbated the role of GRS-AD in increased cardiometabolic risk in females.[6] Nevertheless, we observed an association only for serum LDL cholesterol. Differences in sample characteristics, such as differences in the prevalence of overweight and obesity, and a longer follow-up period may explain these differences. Taken together, while overweight and obesity may exacerbate the influence of genetic risk factors on the cardiometabolic risk factors, overweight and obesity per se are probably more important determinants of cardiometabolic risk than genetic factors at a population level.

Although it is established that higher levels of physical activity and a healthier diet quality have significant impact on cardiometabolic risk factors since childhood,[56,57] previous studies on the associations of GRS-AD with cardiometabolic risk factors have not

considered these factors in their analyses.[13,14] We observed that the inverse association between GRS-AD and serum HDL cholesterol attenuated after controlling for lifestyle factors, specifically diet quality and physical activity. Therefore, a healthy lifestyle, including a healthy diet following the dietary recommendations and higher levels of physical activity, could partly overdrive the effects of AD-related genetic risk factors on cardiometabolic risk factors. Noteworthy, in this study most observed associations between GRS-AD and cardiometabolic risk factors were still independent of lifestyle. Furthermore, the Lancet Commission has suggested that even 45% of dementia could be prevented by improving modifiable risk factor profiles such as nutrition and physical activity.[58] Moreover, unhealthy diet and physical inactivity cause about 10% of non-communicable morbidities.[59,60] Therefore, diet, physical activity, and genetic factors could have different pathways influencing cardiometabolic and brain health.

We observed consistent associations between GRS-AD and lipid metabolism. Elevated serum LDL cholesterol and decreased HDL cholesterol may increase the risk of cardiovascular diseases and AD.[61,62] Due to their long aetiology, preventing degenerative brain diseases has been suggested to start in midlife. Because of fast brain development during childhood and adolescence, the prevention of unfavourable brain changes should begin early in childhood in order to increase cognitive and brain reserves, stagnating the deteriorating effects of AD.[63]

The strengths of the present study include a relatively large sample and an intensive 20-year follow-up. Additionally, in the STRIP study, cardiometabolic risk factors, diet, and physical activity quality have been comprehensively assessed during the whole follow-up period. Moreover, we calculated the GRS-AD using AD risk alleles identified by earlier GWAS meta-analyses among adults.[37,38] Because we aimed to replicate and extend the previous paediatric findings, we used a decade-old GWAS meta-analyses to identify risk alleles to calculate the GRS-AD, and the results may differ if the outcomes of more recent GWAS studies were used.[64,65] Moreover, we did not investigate cognitive functions or other indices of brain health in the present study, which precludes conclusions about the role of interactions of genetic and cardiometabolic factors in brain health. Therefore, our study does not provide specific information on whether cardiometabolic risk factors mediate the associations between genetic predisposition to brain health, i.e., vertical pleiotropy. Moreover, it has been suggested that several cardiometabolic factors associated with AD are not necessarily causal but rather symptoms of prodromal AD.[9] Therefore, further studies on the associations of GRS-AD with cardiometabolic risk factors, cognitive function, and the risk of AD since childhood are warranted. However, the cohorts spanning from early childhood to old age are scarce and the STRIP study has one of the longest and most comprehensive follow-ups since infancy.

In conclusion, a higher genetic predisposition to AD may associate with higher serum LDL and lower HDL cholesterol concentration over a 20-year follow-up from early childhood to young adulthood. Our results also suggest that the APOE variant largely explains these associations. Furthermore, although diet quality and physical activity have been inversely associated with cardiometabolic risk, they had a negligible role in the associations between genetic predisposition for AD and cardiometabolic risk factors. Further studies are warranted investigating the independent, combined, and additive associations of genetic and cardiometabolic risk factors with cognitive functions since childhood.

DATA AVAILABILITY

The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. World Health Organization. *Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines*. (World Health Organization, Geneva, 2019).
2. Abarca-Gómez, L. et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* **390**, 2627–2642 (2017).
3. Zhou, B. et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. *Lancet* **387**, 1513–1530 (2016).
4. Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K. & Brayne, C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol.* **13**, 788–794 (2014).
5. Hughes, T. M. et al. Hypertensive Aspects of Cardiometabolic Disorders Are Associated with Lower Brain Microstructure, Perfusion, and Cognition. *J. Alzheimer's. Dis.* **90**, 1589–1599 (2022).
6. Haapala, E. A., Paananen, J., Hiltunen, M. & Lakka, T. A. Associations of Genetic Susceptibility to Alzheimer's Disease with Adiposity and Cardiometabolic Risk Factors among Children in a 2-Year Follow-up Study. *J. Alzheimer's. Dis.* **64**, 587–595 (2018).
7. Kivimäki, M. et al. Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimer's. Dement.* **14**, 601–609 (2018).
8. Malik, R. et al. Midlife vascular risk factors and risk of incident dementia: Longitudinal cohort and Mendelian randomization analyses in the UK Biobank. *Alzheimer's. Dement.* **17**, 1422–1431 (2021).
9. Korologou-Linden, R. et al. The causes and consequences of Alzheimer's disease: phenome-wide evidence from Mendelian randomization. *Nat. Commun.* **13**, 4726 (2022).
10. Van Cauwenberghe, C., Van Broeckhoven, C. & Sleegers, K. The genetic landscape of Alzheimer disease: clinical implications and perspectives. *Genet Med* **18**, 421–430 (2016).
11. Elosua, R. et al. Obesity Modulates the Association among APOE Genotype, Insulin, and Glucose in Men. *Obes. Res.* **11**, 1502–1508 (2003).
12. Desikan, R. S. et al. Polygenic Overlap Between C-Reactive Protein, Plasma Lipids, and Alzheimer Disease. *Circulation* **131**, 2061–2069 (2015).
13. Sullivan, M., Deng, H.-W. & Greenbaum, J. Identification of genetic loci shared between Alzheimer's disease and hypertension. *Mol. Genet Genomics* **297**, 1661–1670 (2022).
14. Karlsson, I. K. et al. Genetic susceptibility to cardiovascular disease and risk of dementia. *Transl. Psychiatry* **7**, e1142–e1142 (2017).
15. Snaebjarnarson, A. S. et al. Complex effects of sequence variants on lipid levels and coronary artery disease. *Cell* **186**, 4085–4099.e15 (2023).
16. Dove, A. et al. Cardiometabolic multimorbidity and incident dementia: the Swedish twin registry. *Eur. Heart J.* **44**, 573–582 (2023).
17. Grace, C. et al. Lack of genetic support for shared aetiology of Coronary Artery Disease and Late-onset Alzheimer's disease. *Sci. Rep.* **8**, 7102 (2018).
18. Tai, X. Y. et al. Cardiometabolic multimorbidity, genetic risk, and dementia: a prospective cohort study. *Lancet Healthy Longev.* **3**, e428–e436 (2022).
19. Li, M., Zhao, J. V., Kwok, M. K. & Schooling, C. M. Age and sex specific effects of APOE genotypes on ischemic heart disease and its risk factors in the UK Biobank. *Sci. Rep.* **11**, 9229 (2021).
20. Shi, J. et al. Association between ApoE polymorphism and hypertension: A meta-analysis of 28 studies including 5898 cases and 7518 controls. *Gene* **675**, 197–207 (2018).
21. Khan, T. A. et al. Apolipoprotein E genotype, cardiovascular biomarkers and risk of stroke: Systematic review and meta-analysis of 14 015 stroke cases and pooled analysis of primary biomarker data from up to 60 883 individuals. *Int J. Epidemiol.* **42**, 475–492 (2013).
22. Bennet, A. M. et al. Association of Apolipoprotein E Genotypes With Lipid Levels and Coronary Risk. *JAMA* **298**, 1300–1311 (2007).
23. Eichner, J. et al. Apolipoprotein E Polymorphism and Cardiovascular Disease: A HuGE Review. *Am. J. Epidemiol.* **155**, 487–495 (2002).
24. Rovio, S. P. et al. Cardiovascular Risk Factors From Childhood and Midlife Cognitive Performance: The Young Finns Study. *J. Am. Coll. Cardiol.* **69**, 2279–2289 (2017).
25. Deckers, K. et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. *Int J. Geriatr. Psychiatry* **30**, 234–246 (2015).
26. Ye, Z. et al. Contrasting association pattern of plasma low-density lipoprotein with white matter integrity in *APOE4* carriers versus non-carriers. *Neurobiol. Aging* **143**, 41–52 (2024).
27. Tremblay, S. A. et al. Sex and APOE4-specific links between cardiometabolic risk factors and white matter alterations in individuals with a family history of Alzheimer's disease. *Neurobiol. Aging* **150**, 80–96 (2025).

28. Dias, I. H. K., Polidori, M. C. & Griffiths, H. R. Hypercholesterolaemia-induced oxidative stress at the blood–brain barrier. *Biochem Soc. Trans.* **42**, 1001–1005 (2014).
29. Alfaro, F. J. et al. White matter microstructure and cognitive decline in metabolic syndrome: a review of diffusion tensor imaging. *Metabolism* **78**, 52–68 (2018).
30. Borenstein, A. R. et al. Early-Life Risk Factors for Alzheimer Disease. *Alzheimer Dis. Assoc. Disord.* **20**, 63–72 (2006).
31. Alzheimer's Association Report. 2022 Alzheimer's disease facts and figures. *Alzheimer's Dementia* **18**, 700–789 (2022).
32. Walldius, G. et al. Long-term risk of a major cardiovascular event by apoB, apoA−1, and the apoB/apoA−1 ratio—Experience from the Swedish AMORIS cohort: A cohort study. *PLoS Med*. **18**, e1003853 (2021).
33. Hassen, C. B. et al. Change in lipids before onset of dementia, coronary heart disease, and mortality: A 28-year follow-up Whitehall II prospective cohort study. *Alzheimer's. Dement.* **19**, 5518–5530 (2023).
34. Niinikoski, H. et al. Effect of Repeated Dietary Counseling on Serum Lipoproteins From Infancy to Adulthood. *Pediatrics* **129**, e704–e713 (2012).
35. Simell, O. et al. Cohort Profile: The STRIP Study (Special Turku Coronary Risk Factor Intervention Project), an Infancy-onset Dietary and Life-style Intervention Trial. *Int J. Epidemiol.* **38**, 650–655 (2009).
36. Voight, B. F. et al. The Metabochip, a Custom Genotyping Array for Genetic Studies of Metabolic, Cardiovascular, and Anthropometric Traits. *PLOS Genet.* **8**, e1002793 (2012).
37. Lambert, J.-C. et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat. Gen.* **45**, 1452–1458 (2013).
38. Lambert, J.-C. et al. Genome-wide haplotype association study identifies the FRMD4A gene as a risk locus for Alzheimer's disease. *Mol. Psychiatry* **18**, 461–470 (2013).
39. Martiskainen, H. et al. Effects of Alzheimer's Disease-Associated Risk Loci on Cerebrospinal Fluid Biomarkers and Disease Progression: A Polygenic Risk Score Approach. *J. Alzheimer's Dis.* **43**, 565–573 (2015).
40. Jartti, L., Hakanen, M., Paakkunainen, U., Raittinen, P. & Rönnemaa, T. Comparison of hand-to-leg and leg-to-leg bioelectric impedance devices in the assessment of body adiposity in prepubertal children. The STRIP study. *Acta Paediatrica* **89**, 781–786 (2000).
41. Niinikoski, H. et al. Prospective Randomized Trial of Low-Saturated-Fat, Low-Cholesterol Diet During the First 3 Years of Life. *Circulation* **94**, 1386–1393 (1996).
42. Kostner, G. M. Letter: Enzymatic determination of cholesterol in high-density lipoprotein fractions prepared by polyanion precipitation. *Clin. Chem.* **22**, 695 (1976).
43. Matthews, D. R. et al. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **28**, 412–419 (1985).
44. Niinikoski, H. et al. Blood Pressure Is Lower in Children and Adolescents With a Low-Saturated-Fat Diet Since Infancy. *Hypertension* **53**, 918–924 (2009).
45. Rastas, M., Seppänen, R., Knuts, L., Hakala, P. & Karttila, V. *Nutrient Composition of Foods*. (The Social Insurance Institution, Helsinki, Finland, (1997).
46. Matthews, L. A. et al. Longitudinal effect of 20-year infancy-onset dietary intervention on food consumption and nutrient intake: the randomized controlled STRIP study. *Eur. J. Clin. Nutr.* **73**, 937–949 (2019).
47. Pahkala, K. et al. Association of Physical Activity With Vascular Endothelial Function and Intima-Media Thickness. *Circulation* **124**, 1956–1963 (2011).
48. Marshall, W. A. & Tanner, J. M. Variations in the Pattern of Pubertal Changes in Boys. *Arch. Dis. Child* **45**, 13–23 (1970).
49. Marshall, W. A. & Tanner, J. M. Variations in pattern of pubertal changes in girls. *Arch. Dis. Child* **44**, 291–303 (1969).
50. Lin, X. & Zhang, D. Inference in Generalized Additive Mixed Models by Using Smoothing Splines. *J. R. Stat. Soc. Ser. B: Statl. Methodol.* **61**, 381–400 (1999).
51. Soran, H., Dent, R. & Durrington, P. Evidence-based goals in LDL-C reduction. *Clin. Res Cardiol.* **106**, 237–248 (2017).
52. Baigent, C. et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur. Heart J.* **41**, 111–188 (2020).
53. Ying, H., Wang, J., Shen, Z., Wang, M. & Zhou, B. Impact of Lowering Low-Density Lipoprotein Cholesterol with Contemporary Lipid-Lowering Medicines on Cognitive Function: A Systematic Review and Meta-Analysis. *Cardiovasc Drugs Ther.* **35**, 153–166 (2021).
54. Carlsson, C. M. et al. Increased Atherogenic Lipoproteins are Associated With Cognitive Impairment: Effects of Statins and Subclinical Atherosclerosis. *Alzheimer Dis. Assoc. Dis.* **23**, 11 (2009).
55. Skinner, A. C., Perrin, E. M., Moss, L. A. & Skelton, J. A. Cardiometabolic Risks and Severity of Obesity in Children and Young Adults. *N. Engl. J. Med.* **373**, 1307–1317 (2015).
56. Poitras, V. J. et al. Systematic review of the relationships between objectively measured physical activity and health indicators in school-aged children and youth. *Appl. Physiol. Nutr. Metab.* **41**, S197–S239 (2016).
57. Eloranta, A.-M. et al. The effects of a 2-year physical activity and dietary intervention on plasma lipid concentrations in children: the PANIC Study. *Eur. J. Nutr.* **60**, 425–434 (2020).
58. Livingston, G. et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet* **404**, 572–628 (2024).
59. Lee, I.-M. et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* **380**, 219–229 (2012).
60. Rayner, M. & Scarborough, P. The burden of food related ill health in the UK. *J. Epidemiol. Comm. Health* **59**, 1054–1057 (2005).
61. Sedaghat, S. et al. Association of change in cardiovascular risk factors with incident dementia. *Alzheimer's. Dement.* **19**, 1821–1831 (2023).
62. Lisko, I. et al. How can dementia and disability be prevented in older adults: where are we today and where are we going? *J. Int Med.* **289**, 807–830 (2021).
63. Stern, Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol.* **11**, 1006–1012 (2012).
64. Bellenguez, C. et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat. Genet*. **54**, 412–436 (2022).
65. Wightman, D. P. et al. A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease. *Nat. Genet*. **53**, 1276–1282 (2021).

AUTHOR CONTRIBUTIONS

EAH, SH, KP, and SR contributed to conception and design, JM, HN, HL, PS, AJ, TR, JSAV, and OTR contributed to data acquisition, SH analysed the data, and all authors revised the manuscript critically for important intellectual content and gave final approval of the version to be published.

FUNDING

This work was supported by the Academy of Finland (grants 206374, 294834, 251360, 275595, 307996 and 322112), the Juho Vainio Foundation, the Finnish Foundation for Cardiovascular Research, the Finnish Ministry of Education and Culture, the Finnish Cultural Foundation, the Sigrid Jusélius Foundation, Special Governmental grants for Health Sciences Research (Turku University Hospital), the Yrjö Jahnsson Foundation, the Finnish Medical Foundation, and the Turku University Foundation. Funding sources had no role in the study design, the data collection, analysis, interpretation of the data, the writing of the report, or the decision to submit the manuscript for publication. Open access funding provided by University of Eastern Finland (including Kuopio University Hospital).

COMPETING INTERESTS

The authors declare no competing interests.

INFORMED CONSENT

Written informed consent was obtained from the parents in the beginning of the study and from the children at ages 15 and 18 years.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Eero A. Haapala.