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Associations of Genetic Susceptibility to Alzheimer's Disease with Adiposity and Cardiometabolic Risk Factors among Children in a 2-Year Follow-up Study

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Abstract. We investigated the associations of genetic risk score (GRS) for Alzheimer's disease and apolipoprotein E (*APOE*) ε variant with cardiometabolic risk factors during 2-year follow-up in children and whether body fat percentage (BF%) modify these associations. A population-based sample of 469 children (246 boys, 223 girls) at baseline and 398 children (201 boys, 197 girls) at 2-year follow-up participated in the study. Genotyping was performed using the the Illumina Custom Infinium CardioMetabo BeadChip and the Illumina Infinium HumanCoreExome BeadChip. The GRS was calculated using information on nine independent gene variants available in our genomic data. We assessed BF%, waist circumference, insulin, glucose, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and systolic and diastolic blood pressure. We computed a cardiometabolic risk score and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). In boys, the GRS was not associated with cardiometabolic risk factors. In girls, GRS was directly associated with LDL cholesterol (β = 0.133, 95% CI = 0.002 to 0.262) at baseline and with a higher cardiometabolic risk score (β = 0.154, 95% CI = 0.015 to 0.294), glucose (β = 0.143, 95% CI = 0.003 to 0.284), and HOMA-IR (β = 0.141, 95% CI = 0.004 to 0.278) at 2-year follow-up. GRS was directly associated with a cardiometabolic risk score at baseline and 2-year follow-up among girls in the highest third of BF% at baseline, but not in other girls ($p < 0.05$ for interaction). Children with the *APOE* ε3/3 genotype had higher LDL cholesterol at and 2-year follow-up than those with the *APOE* ε2/3 genotype. In conclusion, GRS was associated with increased cardiometabolic risk in girls and especially those with higher BF%.

Keywords: Alzheimer's disease, child, genetics, insulin resistance, metabolic syndrome

INTRODUCTION

Alzheimer's disease (AD) is one of the most debilitating neurodegenerative disease among older adults in Western countries [1]. Because of the aging populations in the Western countries, the prevalence of AD has been estimated to increase substantially [2]. The expenses related to AD will also rise markedly with increasing prevalence [2]. Therefore, the World Health Organization has recognized the prevention of AD and other dementias as a public health priority [3].

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A complicated gene-behavior interaction has been suggested to underlie the pathophysiology of AD. Cardiometabolic risk factors such as obesity, hyperlipidemia, metabolic syndrome, and type 2 diabetes mellitus in middle age have been associated with increased risk of AD [4–7]. The apolipoprotein E (*APOE*) ε4 allele remains the strongest genetic predictor of AD [8, 9] but increasing number of other gene variants associated with AD have also been identified from genome-wide association (GWAS) studies [10]. However, these single gene variants have only minor effects on the risk of AD [10]. Therefore genetic risk scores (GRSs) constructed by summing a large number of risk alleles for AD have been developed to produce more robust associations with the disease [11].

Children and adolescents with *APOE* ε4 allele have been reported to have a higher risk of increased plasma low-density lipoprotein (LDL) cholesterol concentration than those without *APOE* ε4 allele [12]. In adults, the *APOE* ε4 allele has also been linked to mitochondrial dysfunction [9, 13], high serum low-density lipoprotein (LDL) cholesterol concentration [9], type 2 diabetes mellitus [9], and coronary heart disease [9, 14]. Moreover, *APOE* ε4 allele has been observed to exacerbate the unfavorable effects of cardiometabolic risk factors on brain structures [15, 16]. In addition, those with the *APOE* ε3/3 or ε3/4 genotype have been found to have higher plasma LDL cholesterol concentrations than the *APOE* ε2 carriers in children and adolescents followed until adulthood [17–19]. Although a weak genetic overlap between AD and pediatric obesity has been reported [20], there are no studies on the associations of GRSs for AD with cardiometabolic risk factors and whether adiposity modify these associations in children.

We investigated the cross-sectional and longitudinal associations of a GRS for AD and *APOE* ε variant with adiposity and a number of other cardiometabolic risk factors among a general population of Finnish children in a 2-year follow-up study. We also examined a modifying effect of adiposity on the associations of GRS for AD with the cardiometabolic risk factors.

METHODS

Study design and study population

The present data are from the Physical Activity and Nutrition in Children (PANIC) Study, which is an ongoing physical activity and dietary intervention study in a population sample of children from the city of Kuopio, Finland. Altogether 736 children 6–8 years of age from primary schools of Kuopio were invited to participate in the baseline examination in 2007–2009. Altogether 512 children (70% of those invited) participated in the baseline examinations and were divided in the intervention group and the control group. The participants did not differ in sex distribution, age, or body mass index standard deviation score (BMI-SDS) from all children who started the first grade in 2007–2009 based on data from the standard school health examinations performed for all Finnish children before the first grade (data not shown). Altogether 440 children (86% of those participating in baseline examinations) also attended in the 2-year follow-up examinations. Complete data on variables used in this study were available for 469 children (246 boys, 223 girls) at baseline and for 398 children (201 boys, 197 girls) at 2-year follow-up. Complete data on variables used in the analyses on the associations of the GRS for AD with changes in cardiometabolic risk factors were available for 379 children (194 boys, 185 girls). The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo. Both children and their parents gave their written informed consent.

Assessment of cardiometabolic risk factors

Body weight was measured twice the children having fasted for 12 hours, having emptied the bladder, and standing in light underwear by a calibrated InBody® 720 bioelectrical impedance device (Biospace, Seoul, South Korea) to accuracy of 0.1 kg. The mean of these two values was used in the analyses. Body height was measured three times the children standing in the Frankfurt plane without shoes using a wall-mounted stadiometer to accuracy of 0.1 cm. The mean of the nearest two values was used in the analyses. Body mass index (BMI) was calculated by dividing body weight (kg) with body height (m) squared and BMI-standard deviation score (SDS) using the Finnish references [21]. The prevalence of normal weight and overweight was defined using the cut-off values provided by Cole et al. [22]. Waist circumference was measured at mid-distance between the bottom of the rib cage and the top of the iliac crest. Total fat mass, total body fat percentage (BF%), and lean mass were measured by the Lunar® dual-energy X-ray absorptiometry (GE Medical Systems, Madison, WI, USA) using standardized protocols [23].

A research nurse took blood samples in the morning after a 12-hour overnight fast. Plasma glucose was measured by a hexokinase method, serum insulin by an electrochemiluminescence immunoassay, plasma triglycerides by a colorimetric enzymatic assay and plasma high-density lipoprotein (HDL) cholesterol and plasma LDL cholesterol by homogeneous colorimetric enzymatic assays [24]. A research nurse measured systolic and diastolic blood pressure from the right arm using the Heine Gamma® G7 aneroid sphygmomanometer (Heine Optotechnik, Herrsching, Germany) to accuracy of 2 mmHg. The measurement protocol included a rest of 5 minutes and thereafter three measurements in the sitting position at 2-minute intervals. The mean of all three values was used as the systolic and diastolic blood pressure. We calculated Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) using the formula insulin (mU/L) × glucose (mmol/L)/22.5 [25]. We calculated the cardiometabolic risk score by computing population-specific and age-, sex-, and height-standardized z-scores for waist circumference, insulin, glucose, triglycerides, HDL cholesterol, and the average of systolic and diastolic blood pressure and using the formula waist circumference+insulin+glucose+triglycerides–HDL cholesterol+the average of systolic and diastolic blood pressure, a larger score indicating a higher cardiometabolic risk [26].

Assessment of Alzheimer's disease genetic risk score

Genotyping was performed using the the Illumina Custom Infinium CardioMetabo BeadChip and the Illumina Infinium HumanCoreExome BeadChip (Illumina, San Diego, CA, USA). The GRS for AD was calculated using information on nine independent gene variants available in our genomic data and originally selected from 22 AD risk alleles identified by earlier GWAS meta-analyses among adults [10, 27] as described previously [11]. The genes and their variants used to calculate the GRS for AD were *APOE* (ε2/3/4), *BIN1* (rs744373), *CLU* (rs11136000), *ABCA7* (rs3764650), *CR1* (rs3818361), *PICALM* (rs3851179), *MS4A6A* (rs610932), *CD33* (rs3865444), and *EPHA1* (rs11771145). Briefly, the GRS for AD was calculated by summing log-transformed odds ratios for AD associated with risk alleles reported in earlier GWAS meta-analyses [10, 27] weighted by the number of alternative alleles. Because *APOE* is the strongest genetic predictor of AD, we also calculated non-*APOE* GRS for AD excluding *APOE* from the score.

Statistical methods

We performed all data analyses using the SPSS Statistical software, Version 23.0 (IBM Corp., Armonk, NY, USA). We performed square root transformation for waist circumference, HOMA-IR, and triglycerides because of skewed distributions. Basic characteristics between boys and girls were compared using the Student's *t*-test, the Mann-Whitney U-test, or the Chi Square-test. We used linear regression analyses to study the cross-sectional associations of the GRS with cardiometabolic risk factors at baseline adjusted for age. We compared differences in cardiometabolic risk factors across *APOE* ε genotypes at baseline using general linear models (GLM) adjusted for age. Corresponding data on the associations of the GRS and the *APOE* ε variant with cardiometabolic risk factors at 2-year follow-up were additionally adjusted for the study group (intervention versus control). We also studied the relationships of the GRS to changes in cardiometabolic risk factors during 2-year follow-up using linear regression analyses adjusted for age, corresponding cardiometabolic risk factor at baseline, and the study group. Moreover, we compared differences in changes in cardiometabolic risk factors across the *APOE* ε genotypes using GLM adjusted for age, corresponding cardiometabolic risk factor at baseline, and the study group. We used GLM to examine the modifying effects of adiposity on the relationships between GRS and cardiometabolic risk factors. We carried out these analyses in boys and girls separately, because AD is known to be more prevalent in women than in men [28]. Sex also modified the association between the GRS and fasting plasma glucose concentration at 2-year follow-up ($p = 0.048$ for interaction).

RESULTS

Characteristics of children at baseline

At baseline, boys were taller and heavier, and had a lower BF% than girls (Table 1). Boys also had a longer waist circumference, lower fasting insulin, higher fasting glucose, lower HOMA-IR, higher HDL cholesterol, and lower LDL cholesterol than girls. There were no statistically significant differences in the GRS or the distribution of the *APOE* ε genotype

Table 1
Basic characteristics of children at baseline

	Boys	Girls	*p*
Age (y)	7.6 (0.4)	7.6 (0.4)	0.249
Height (cm)	129.6 (5.5)	127.7 (5.7)	**<0.001**
Weight (kg)	26.6 (5.7)	25.5 (5.9)	**0.032***
Body mass index-standard deviation score	–0.2 (1.1)	–0.2 (1.1)	0.754
Prevalence of overweight and obesity (%)	10.6	14.3	0.220
Body fat percentage (%)	14.9 (10.2)	20.6 (9.6)	**<0.001***
Cardiometabolic risk score	0.01 (3.7)	0.01 (3.5)	0.987
Waist circumference (cm)	56.2 (5.9)	54.8 (5.8)	**0.001***
Serum insulin (mU/L)	3.9 (3.1)	4.6 (2.8)	**0.001**
Plasma glucose (mmol/L)	4.9 (0.4)	4.8 (0.4)	**0.001**
Plasma triglycerides (mmol/L)	0.53 (0.24)	0.56 (0.28)	0.056*
Plasma HDL cholesterol (mmol/L)	1.64 (0.3)	1.56 (0.3)	**0.009**
Plasma LDL cholesterol (mmol/L)	2.3 (0.5)	2.4 (0.5)	**0.038**
Systolic blood pressure (mmHg)	100 (7.0)	100 (7.6)	0.599
Diastolic blood pressure (mmHg)	61.9 (6.6)	61.6 (6.8)	0.585
HOMA-IR	0.85 (0.72)	0.98 (0.65)	**0.010***
Genetic risk score for AD	0.2 (0.56)	0.26 (0.55)	0.300
APOE ε genotype (%)			0.636
APOE ε2/3	9.1	10.4	
APOE ε3/3	90.9	89.6	

Data are means (standard deviations) from the Student´s *t*-test for continuous variables with normal distributions and the Mann-Whitney U-test for continuous variables with skewed distributions* and from the Chi Square-test for categorical variables.

Table 2
Associations of GRS with cardiometabolic risk factors at baseline

	Boys (N = 246)			Girls (N = 223)		
	β	95% CI	*p*	β	95% CI	*p*
Body fat percentage (%)	0.039	–0.087 to 0.166	0.539	0.024	–0.106 to 0.154	0.716
Cardiometabolic risk score	0.035	–0.091 to 0.162	0.580	0.086	–0.047 to 0.218	0.203
Waist circumference (cm)	0.026	–0.099 to 0.152	0.679	0.035	–0.096 to 0.166	0.603
Serum insulin (mU/L)	0.069	–0.056 to 0.194	0.280	0.028	–0.105 to 0.161	0.676
Plasma glucose (mmol/L)	0.019	–0.107 to 0.145	0.764	0.105	–0.027 to 0.237	0.120
Plasma triglycerides (mmol/L)	0.005	–0.121 to 0.130	0.944	0.078	–0.054 to 0.210	0.243
Plasma HDL cholesterol (mmol/L)	–0.030	–0.157 to 0.096	0.636	–0.072	–0.204 to 0.060	0.282
Plasma LDL cholesterol (mmol/L)	0.040	–0.086 to 0.167	0.529	0.133	0.002 to 0.264	**0.047**
Systolic blood pressure (mmHg)	–0.082	–0.207 to 0.044	0.200	0.001	–0.132 to 0.134	0.988
Diastolic blood pressure (mmHg)	0.019	–0.108 to 0.145	0.722	–0.016	–0.148 to 0.116	0.811
HOMA-IR	0.062	–0.063 to 0.187	0.330	0.037	–0.096 to 0.170	0.581

Data are standardized regression coefficients (β) and their 95 % confidence intervals (CI) from linear regression models adjusted for age.

between boys and girls. None of the children had *APOE* ε4 genotype.

Cross-sectional associations of GRS and APOE ε variant with cardiometabolic risk factors at baseline

In boys, the GRS was not associated with cardiometabolic risk factors at baseline (Table 2). However, children with the *APOE* ε3/3 genotype had higher LDL cholesterol than children with the *APOE* ε2/3 genotype (2.34 versus 1.88 mmol/L; mean difference 0.46, 95% CI for the difference 0.21 to 0.68, $p < 0.001$). In boys, BF% did not modify the associations between GRS and cardiometabolic risk factors.

In girls, a higher GRS was associated with a higher LDL-cholesterol at baseline after adjustment for age (Table 2). Non-*APOE* GRS was not statistically significantly associated with LDL-cholesterol (β = –0.060, 95% CI = –0.072 to 0.193, $p = 0.897$). We also observed a tendency for a positive associations of GRS with BF% and insulin. Moreover, girls with the *APOE* ε3/3 genotype had a higher cardiometabolic risk score (0.11 versus –1.52; mean difference 1.63, 95% CI for the difference 0.11 to 3.14, $p = 0.036$), insulin (4.91 versus 77 mU/l, mean difference 1.13, 95% CI for difference 0.14 to 2.13, $p = 0.026$), LDL-cholesterol (2.55 versus 1.95 mmol/l, mean difference 0.51, 95% CI for difference 0.28 to 0.74 to, $p < 0.001$), and HOMA-IR

Table 3
Associations of GRS with cardiometabolic risk factors at 2-yr follow-up

	Boys (N = 201)			Girls (N = 197)		
	β	95% CI	*p*	β	95% CI	*p*
Body fat percentage (%)	0.059	–0.081 to 0.199	0.405	0.125	–0.010 to 0.260	0.069
Cardiometabolic risk score	–0.003	–0.143 to 0.138	0.968	0.154	0.015 to 0.294	**0.030**
Waist circumference (cm)	0.027	–0.113 to 0.166	0.707	0.101	–0.036 to 0.238	0.146
Serum insulin (mU/L)	0.027	–0.111 to 0.165	0.698	0.131	–0.006 to 0.268	0.061
Plasma glucose (mmol/L)	–0.004	–0.144 to 0.137	0.958	0.143	0.003 to 0.284	**0.046**
Plasma triglycerides (mmol/L)	–0.083	–0.233 to 0.057	0.244	0.047	–0.095 to 0.189	0.511
Plasma HDL cholesterol (mmol/L)	–0.044	–0.184 to 0.097	0.540	–0.047	–0.189 to 0.095	0.514
Plasma LDL cholesterol (mmol/L)	0.086	–0.054 to 0.226	0.229	0.012	–0.128 to 0.151	0.164
Systolic blood pressure (mmHg)	–0.025	–0.162 to 0.113	0.725	0.060	–0.081 to 0.201	0.402
Diastolic blood pressure (mmHg)	0.023	–0.115 to 0.161	0.747	0.035	–0.107 to 0.177	0.627
HOMA-IR	0.027	–0.111 to 0.165	0.703	0.141	0.004 to 0.278	**0.043**

Data are standardized regression coefficients (β) and their 95% confidence intervals (CI) from linear regression models adjusted for age and the study group.

(1.00 versus 0.85; mean difference 0.15, 95% CI for the difference 0.03 to 0.27, $p = 0.012$) than girls with the *APOE* ε2/3 genotype after adjustment for age.

GRS was directly associated with the cardiometabolic risk score among girls in the highest third of BF% (β = 0.272, 95% CI = 0.049 to 0.495, $p = 0.018$) but not among other girls (lowest third, β = –0.042, 95% CI = –0.275 to 0.191, $p = 0.720$; middle third, β = –0.019, 95% CI = –0.254 to 0.216, $p = 0.872$; $p = 0.043$ for interaction). GRS was directly associated with waist circumference among girls in the highest third of BF% (β = 0.243, 95% CI = 0.014 to 0.472, $p = 0.038$) but not among girls in other thirds (lowest third, β = –0.100, 95% CI = –0.338 to 0.137, $p = 0.360$; middle third, β = –0.187, 95% CI = –0.411 to 0.036, $p = 0.099$; $p = 0.015$ for interaction). These direct associations of GRS with the cardiometabolic risk score (β = 0.205, 95% CI = –0.022 to 0.432, $p = 0.077$) and waist circumference (β = 0.227, 95% CI = –0.003 to 0.457, $p = 0.053$) in girls with higher BF% were slightly attenuated when non-*APOE* GRS was used in the analyses.

Cross-sectional associations of GRS with cardiometabolic risk factors at 2-year follow-up

In boys, the GRS was not associated with cardiometabolic risk factors at 2-year follow-up after adjustment for age and the study group (Table 3). However, boys with the *APOE* ε3/3 genotype had a higher LDL cholesterol than boys with *APOE* ε2/3 genotype at 2-year follow-up after adjustment for age and the study group (2.34 versus 1.90 mmol/L; mean difference 0.44, 95% CI for the difference 0.163 to 0.720, $p = 0.002$). In boys, BF% did not modify the associations between GRS and cardiometabolic risk factors.

In girls, a higher GRS was associated with a higher cardiometabolic risk score, glucose, and HOMA-IR after adjustment for age and the study group (Table 3). Non-*APOE* GRS was also directly related to cardiometabolic risk score (β = 0.150, 95% CI = 0.011 to 0.290, $p = 0.035$) and glucose (β = 0.144, 95% CI = 0.003 to 0.284, $p = 0.045$) but the association with HOMA-IR was not statistically significant (β = 0.130, 95% CI = –0.010 to 0.270, $p = 0.068$). Moreover, girls with the *APOE* ε3/3 genotype had higher LDL cholesterol than girls with the *APOE* ε2/3 genotype (2.37 versus 2.00 mmol/L; mean difference 0·36, 95% CI for the difference 0.10 to 0.63 to, $p = 0.007$).

GRS was directly associated with cardiometabolic risk score in girls with the highest BF% at baseline (β = 0.290, 95% CI = 0.051 to 0.528, $p = 0.018$) but not girls with lower BF% at baseline (lowest third, β = 0.067, 95% CI = –0.181 to 0.314, $p = 0.592$; middle third, β = –0.027, 95% CI = –0.263 to 0.526, $p = 0.979$; $p = 0.093$ for interaction). The direct association of GRS with the cardiometabolic risk score in girls in the highest third of BF% remained similar when non-*APOE* GRS was used in the analyses (β = 0.286, 95% CI = 0.033 to 0.538, $p = 0.028$).

Associations of GRS with changes in cardiometabolic risk factors during 2-year follow-up

In boys, the GRS was not associated with the changes in cardiometabolic risk factors during 2-year follow-up. There were no differences in the changes

in cardiometabolic risk factors during 2-year follow-up between boys with the *APOE* ε2/3 genotype and boys with the *APOE* ε3/3 genotype, either.

In girls, a higher GRS (β = –0.192, 95% CI = –0.328 to –0.055, $p = 0.006$) and non-*APOE* GRS used (β = –0.188, 95% CI = –0.323 to –0.053, $p = 0.007$) were associated with a smaller change in LDL cholesterol after adjustment of age, the study group, and LDL cholesterol at baseline. Moreover, there were tendency for statistically significant associations of a higher GRS with larger changes in insulin (β = 0.125, 95% CI = –0.010 to –0.260, $p = 0.070$) and HOMA-IR (β = 0.124, 95% CI = –0.004 to 0.252, $p = 0.057$) during 2-year follow-up after adjustment for age, the study group, and corresponding cardiometabolic risk factors at baseline. Nevertheless, a higher non-*APOE* GRS was associated with a larger changes in insulin (β = 0.151, 95% CI = 0.008 to 0.294, $p = 0.039$) and HOMA-IR (β = 0.164, 95% CI = 0.022 to 0.307, $p = 0.024$) over 2-year follow-up. There were no differences in the changes in cardiometabolic risk factors during 2-year follow-up between girls with the *APOE* ε2/3 genotype and girls with the *APOE* ε3/3 genotype, either.

We observed no modifying effect of BF% on the associations between GRS and changes in cardiometabolic risk factors.

DISCUSSION

To the best of our knowledge this is the first longitudinal study on the associations of the GRS for AD with cardiometabolic risk factors in children. In girls, a higher GRS was linked to a higher LDL cholesterol concentration at baseline and a higher cardiometabolic risk score, fasting plasma glucose concentration, and HOMA-IR at 2-year follow-up. We also observed that a higher GRS was associated with unfavorable cardiometabolic risk profile particularly in girls with higher body fat percentage. Most of these associations remained similar when non-APOE GRS was used in the analyses. Furthermore, we found that a higher non-*APOE* GRS was related to larger increase in insulin and HOMA-IR over 2-year follow-up. The GRS was not related to cardiometabolic risk factors in boys. Finally, our results confirm previous findings that children with the *APOE* ε genotype 3/3 have higher LDL cholesterol concentration than children with *APOE* ε2/3 genotype.

The magnitude of the associations of the GRS with cardiometabolic risk factors in the present study were modest and were observed only in girls. The reason for these sexually dimorphic associations is currently unknown. However, our results in children suggest that genetic susceptibility to AD is linked to cardiometabolic risk factors associated with increased risk of AD in adults [6].

There are no previous studies on the associations of the GRS for AD with cardiometabolic risk factors in children However, overweight, insulin resistance, and particularly their combination have been linked to increased serum concentrations of AD pathophysiology-related amyloid β_{42}-protein and presenilin 1 in adolescents [29]. Nevertheless, that specific study did not address the question whether genetic predisposition to AD modifies the associations of overweight and insulin resistance with serum amyloid β_{42} and presenilin 1 concentrations. Our observation that GRS was directly associated with cardiometabolic risk particularly among girls with higher levels of adiposity suggest that increased adiposity may exacerbate the effects genetic susceptibility for AD on pathophysiological process of the disease. The results of one previous study among older adults suggest that lower body mass index attenuate the negative effects of a higher GRS with cerebrospinal fluid biomarkers of AD, such as phosphorylated tau/amyloid β_{42}-protein ratio [30]. These results together indicate that preventing overweight and obesity may prevent negative effects of genetic susceptibility to AD on pathophysiological biomarkers of AD already from childhood. Nevertheless, there are no studies on the relationships of the GRS to brain structures or functions and cognition and whether cardiometabolic risk factors modify these associations in children. However, a higher GRS has been associated with a smaller hippocampal volumes among young adults [31] and overweight and insulin resistance have been related to smaller hippocampal and cortical volumes, and the existence of white matter lesions, and poorer cognitive functions already in children and adolescents [32, 33].

Our results are in line with previous observations that children and adolescents with *APOE* ε3/3 or 3/4 genotype have higher LDL cholesterol concentrations than those with *APOE* ε2/3 genotype [12, 19]. Our findings also support previous findings that the *APOE* ε variant is related to tracking of a plasma LDL cholesterol concentration [18]. In the present study, children with *APOE* ε3/3 genotype had higher LDL cholesterol concentration than those with *APOE*

ε2/3 genotype during 2-year follow-up. However, the results of our study along with previous findings suggest that the *APOE* ε variant is not associated with the changes in LDL cholesterol concentration during childhood and adolescence [18]. Furthermore, we observed that girls with the *APOE* ε3/3 genotype had also higher cardiometabolic risk score, fasting insulin, and HOMA-IR than girls with the *APOE* ε2/3 genotype at baseline but not 2-year follow-up. Previous studies in adults have found higher risk of dyslipidemia and metabolic syndrome among the *APOE* ε4 carriers than the *APOE* ε2 carriers [9, 34]. In our population sample of children, however, there were no *APOE* ε4 carriers. Moreover, we found no association between the *APOE* ε variant and cardiometabolic risk factors other than LDL cholesterol at 2-year follow-up.

Genetic predisposition for AD and poor cardiometabolic risk profile have been found to expose middle-aged adults to a higher risk of AD later in life [4–9]. Although little is known about their reciprocal confounded effects on brain structure, brain function, and cognition in youth, our results along with the results of some previous studies suggest that GRS for AD, obesity, insulin resistance, and metabolic syndrome, brain health and function, and cognition may be interrelated [32, 35]. We observed that the associations of GRS with cardiometabolic risk factors were modified by BF% and that the direct association between GRS and cardiometabolic risk factors were stronger among girls with higher BF% than in other girls. The evidence on the modifying effects of lifestyle modifications, such as increased physical activity and improved diet quality, on the associations between GRS, cardiometabolic risk, and cognition is sparse. However, higher levels of physical activity and a better diet quality have been associated with better cardiometabolic risk profile in children and adolescents [36, 37]. Emerging evidence also suggest that physical activity and diet quality are positively associated with brain functioning, cognition, and academic achievement in youth [38–40]. These studies together suggest the prevention of AD should begin as early as possible before any signs of mild cognitive impairment [2], maybe even in childhood. Therefore, increasing physical activity and diet quality particularly in overweight and obese youth may support normal brain and cognitive development. Improving physical activity and diet quality during childhood may thereby delay the onset of cognitive impairments later in life regardless of the genetic predisposition for these diseases.

The strengths of the present study include a relatively large population sample of children followed for two years. We also had comprehensive and valid assessments of cardiometabolic risk factors. We were not able to use all alleles proposed by GWAS meta-analyses among adults in the GRS for AD, which tends to decrease overall variance in the GRS score and accentuate the role of the *APOE* ε variant in the GRS. In contrast to some previous observations suggesting a relatively high prevalence of *APOE* ε4 allele in Finnish youth [41], our population sample of children did not include *APOE* ε4 carriers which may weaken the relationships of the *APOE* ε variant and the GRS for AD with cardiometabolic risk factors in children. Finally, the large number of analyses may increase the risk of type I errors and therefore some of observed associations might have been found by chance

In conclusion, our results provide the first evidence that genetic predisposition to AD was associated with increased cardiometabolic risk in children and especially in girls. A higher GRS for AD was associated with a higher plasma LDL cholesterol concentration at baseline and a higher cardiometabolic risk score, fasting plasma glucose concentration, and HOMA-IR at 2-year follow-up in girls. In addition, a higher non-*APOE* GRS was related to unfavorable changes in insulin and HOMA-IR over 2-year follow-up. We also observed that adiposity modified the association of GRS with cardiometabolic risk factors in girls. Furthermore, those with the *APOE* ε3/3 genotype had a higher LDL cholesterol concentration than those with the *APOE* ε2/3 genotype in boys and girls. Longer follow-up studies are warranted to investigate whether the GRS for AD, the *APOE* ε variant, and other gene variants associated with AD predict changes in cardiometabolic risk factors since childhood and whether genetic susceptibility for AD intensify the influence of adiposity on the risk of developing metabolic syndrome and type 2 diabetes in adulthood. Finally, more studies on the associations of genetic predisposition for AD and the modifying effect of lifestyle factors with biomarkers for AD, brain health, and cognition from childhood to adulthood are warranted.

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