

This is a self-archived version of an original article. This version may differ from the original in pagination and typographic details.

Author(s): Haapala, Eero; Paananen, Jussi; Hiltunen, Mikko; Lakka, Timo A.

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

Year: 2018

Version: Accepted version (Final draft)

Copyright: © 2018 IOS Press

Rights: In Copyright

Rights url: <http://rightsstatements.org/page/InC/1.0/?language=en>

Please cite the original version:

Haapala, E., Paananen, J., Hiltunen, M., & Lakka, T. A. (2018). Associations of Genetic Susceptibility to Alzheimer's Disease with Adiposity and Cardiometabolic Risk Factors among Children in a 2-Year Follow-up Study. *Journal of Alzheimer's Disease*, 64(2), 587-595.
<https://doi.org/10.3233/JAD-180216>

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

Eero A. Haapala^{a,b,*}, Jussi Paananen^b, Mikko Hiltunen^b and Timo A. Lakka^{b,c,d}

^a*Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland*

^b*Institute of Biomedicine, University of Eastern Finland, Kuopio Campus, Finland*

^c*Kuopio Research Institute of Exercise Medicine, Kuopio, Finland*

^d*Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland*

Handling Associate Editor: Patricia Manzine

Accepted 1 May 2018

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 ($\beta = 0.133$, 95% CI = 0.002 to 0.262) at baseline and with a higher cardiometabolic risk score ($\beta = 0.154$, 95% CI = 0.015 to 0.294), glucose ($\beta = 0.143$, 95% CI = 0.003 to 0.284), and HOMA-IR ($\beta = 0.141$, 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* $\epsilon 3/3$ genotype had higher LDL cholesterol at and 2-year follow-up than those with the *APOE* $\epsilon 2/3$ 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].

*Correspondence to: Eero A. Haapala, PhD, Sports and Exercise Medicine, Faculty of Sport and Health Sciences, University of Jyväskylä, PO Box 35, FI-40014 Jyväskylä, Finland. Tel.: +358 408054210; E-mail: eero.a.haapala@jyu.fi.

37 A complicated gene-behavior interaction has been
38 suggested to underlie the pathophysiology of AD.
39 Cardiometabolic risk factors such as obesity, hyper-
40 lipidemia, metabolic syndrome, and type 2 diabetes
41 mellitus in middle age have been associated with
42 increased risk of AD [4–7]. The apolipoprotein E
43 (*APOE*) $\epsilon 4$ allele remains the strongest genetic pre-
44 dictor of AD [8, 9] but increasing number of other
45 gene variants associated with AD have also been
46 identified from genome-wide association (GWAS)
47 studies [10]. However, these single gene variants have
48 only minor effects on the risk of AD [10]. Therefore
49 genetic risk scores (GRSs) constructed by summing a
50 large number of risk alleles for AD have been devel-
51 oped to produce more robust associations with the
52 disease [11].

53 Children and adolescents with *APOE* $\epsilon 4$ allele
54 have been reported to have a higher risk of increased
55 plasma low-density lipoprotein (LDL) cholesterol
56 concentration than those without *APOE* $\epsilon 4$ allele
57 [12]. In adults, the *APOE* $\epsilon 4$ allele has also been
58 linked to mitochondrial dysfunction [9, 13], high
59 serum low-density lipoprotein (LDL) cholesterol
60 concentration [9], type 2 diabetes mellitus [9], and
61 coronary heart disease [9, 14]. Moreover, *APOE* $\epsilon 4$
62 allele has been observed to exacerbate the unfavor-
63 able effects of cardiometabolic risk factors on brain
64 structures [15, 16]. In addition, those with the *APOE*
65 $\epsilon 3/3$ or $\epsilon 3/4$ genotype have been found to have
66 higher plasma LDL cholesterol concentrations than
67 the *APOE* $\epsilon 2$ carriers in children and adolescents
68 followed until adulthood [17–19]. Although a weak
69 genetic overlap between AD and pediatric obesity has
70 been reported [20], there are no studies on the asso-
71 ciations of GRSs for AD with cardiometabolic risk
72 factors and whether adiposity modify these associa-
73 tions in children.

74 We investigated the cross-sectional and longitu-
75 dinal associations of a GRS for AD and *APOE* ϵ
76 variant with adiposity and a number of other car-
77 diometabolic risk factors among a general population
78 of Finnish children in a 2-year follow-up study. We
79 also examined a modifying effect of adiposity on the
80 associations of GRS for AD with the cardiometabolic
81 risk factors.

82 METHODS

83 *Study design and study population*

84 The present data are from the Physical Activity
85 and Nutrition in Children (PANIC) Study, which is

86 an ongoing physical activity and dietary intervention
87 study in a population sample of children from the
88 city of Kuopio, Finland. Altogether 736 children 6–8
89 years of age from primary schools of Kuopio were
90 invited to participate in the baseline examination in
91 2007–2009. Altogether 512 children (70% of those
92 invited) participated in the baseline examinations and
93 were divided in the intervention group and the control
94 group. The participants did not differ in sex distribu-
95 tion, age, or body mass index standard deviation score
96 (BMI-SDS) from all children who started the first
97 grade in 2007–2009 based on data from the standard
98 school health examinations performed for all Finnish
99 children before the first grade (data not shown). Alto-
100 gether 440 children (86% of those participating in
101 baseline examinations) also attended in the 2-year
102 follow-up examinations. Complete data on variables
103 used in this study were available for 469 children (246
104 boys, 223 girls) at baseline and for 398 children (201
105 boys, 197 girls) at 2-year follow-up. Complete data
106 on variables used in the analyses on the associations
107 of the GRS for AD with changes in cardiometabolic
108 risk factors were available for 379 children (194 boys,
109 185 girls). The study protocol was approved by the
110 Research Ethics Committee of the Hospital District of
111 Northern Savo. Both children and their parents gave
112 their written informed consent.

113 *Assessment of cardiometabolic risk factors*

114 Body weight was measured twice the children
115 having fasted for 12 hours, having emptied the
116 bladder, and standing in light underwear by a cali-
117 brated InBody[®] 720 bioelectrical impedance device
118 (Biospace, Seoul, South Korea) to accuracy of 0.1 kg.
119 The mean of these two values was used in the anal-
120 yses. Body height was measured three times the
121 children standing in the Frankfurt plane without shoes
122 using a wall-mounted stadiometer to accuracy of
123 0.1 cm. The mean of the nearest two values was used
124 in the analyses. Body mass index (BMI) was calcu-
125 lated by dividing body weight (kg) with body height
126 (m) squared and BMI-standard deviation score (SDS)
127 using the Finnish references [21]. The prevalence of
128 normal weight and overweight was defined using the
129 cut-off values provided by Cole et al. [22]. Waist cir-
130 cumference was measured at mid-distance between
131 the bottom of the rib cage and the top of the iliac crest.
132 Total fat mass, total body fat percentage (BF%), and
133 lean mass were measured by the Lunar[®] dual-energy
134 X-ray absorptiometry (GE Medical Systems, Madi-
135 son, 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 $\text{insulin (mU/L)} \times \text{glucose (mmol/L)} / 22.5$ [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 $\text{waist circumference} + \text{insulin} + \text{glucose} + \text{triglycerides} - \text{HDL cholesterol} + \text{the average of systolic and diastolic blood pressure}$, 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* ($\epsilon 2/3/4$), *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	<i>p</i>
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
<i>APOE</i> ϵ genotype (%)			0.636
<i>APOE</i> ϵ 2/3	9.1	10.4	
<i>APOE</i> ϵ 3/3	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	<i>p</i>	β	95% CI	<i>p</i>
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* ϵ 4 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* ϵ 3/3 genotype had higher LDL cholesterol than children with the *APOE* ϵ 2/3 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 ($\beta = -0.060$, 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* ϵ 3/3 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	<i>p</i>	β	95% CI	<i>p</i>
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* $\epsilon 2/3$ genotype after adjustment for age.

GRS was directly associated with the cardiometabolic risk score among girls in the highest third of BF% ($\beta=0.272$, 95% CI=0.049 to 0.495, $p=0.018$) but not among other girls (lowest third, $\beta=-0.042$, 95% CI=-0.275 to 0.191, $p=0.720$; middle third, $\beta=-0.019$, 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% ($\beta=0.243$, 95% CI=0.014 to 0.472, $p=0.038$) but not among girls in other thirds (lowest third, $\beta=-0.100$, 95% CI=-0.338 to 0.137, $p=0.360$; middle third, $\beta=-0.187$, 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 ($\beta=0.205$, 95% CI=-0.022 to 0.432, $p=0.077$) and waist circumference ($\beta=0.227$, 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* $\epsilon 3/3$ genotype had a higher LDL cholesterol than boys with *APOE* $\epsilon 2/3$ 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 ($\beta=0.150$, 95% CI=0.011 to 0.290, $p=0.035$) and glucose ($\beta=0.144$, 95% CI=0.003 to 0.284, $p=0.045$) but the association with HOMA-IR was not statistically significant ($\beta=0.130$, 95% CI=-0.010 to 0.270, $p=0.068$). Moreover, girls with the *APOE* $\epsilon 3/3$ genotype had higher LDL cholesterol than girls with the *APOE* $\epsilon 2/3$ 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 ($\beta=0.290$, 95% CI=0.051 to 0.528, $p=0.018$) but not girls with lower BF% at baseline (lowest third, $\beta=0.067$, 95% CI=-0.181 to 0.314, $p=0.592$; middle third, $\beta=-0.027$, 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 ($\beta=0.286$, 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

329 in cardiometabolic risk factors during 2-year follow- 377
330 up between boys with the *APOE* ϵ 2/3 genotype and 378
331 boys with the *APOE* ϵ 3/3 genotype, either. 379

332 In girls, a higher GRS ($\beta = -0.192$, 95% 380
333 CI = -0.328 to -0.055 , $p = 0.006$) and non-*APOE* 381
334 GRS used ($\beta = -0.188$, 95% CI = -0.323 to -0.053 , 382
335 $p = 0.007$) were associated with a smaller change 383
336 in LDL cholesterol after adjustment of age, the 384
337 study group, and LDL cholesterol at baseline. 385
338 Moreover, there were tendency for statistically sig- 386
339 nificant associations of a higher GRS with larger 387
340 changes in insulin ($\beta = 0.125$, 95% CI = -0.010 to 388
341 -0.260 , $p = 0.070$) and HOMA-IR ($\beta = 0.124$, 95% 389
342 CI = -0.004 to 0.252 , $p = 0.057$) during 2-year follow- 390
343 up after adjustment for age, the study group, and 391
344 corresponding cardiometabolic risk factors at base- 392
345 line. Nevertheless, a higher non-*APOE* GRS was 393
346 associated with a larger changes in insulin ($\beta = 0.151$, 394
347 95% CI = 0.008 to 0.294 , $p = 0.039$) and HOMA-IR 395
348 ($\beta = 0.164$, 95% CI = 0.022 to 0.307 , $p = 0.024$) over 396
349 2-year follow-up. There were no differences in the 397
350 changes in cardiometabolic risk factors during 2-year 398
351 follow-up between girls with the *APOE* ϵ 2/3 geno- 399
352 type and girls with the *APOE* ϵ 3/3 genotype, either. 400

353 We observed no modifying effect of BF% on 401
354 the associations between GRS and changes in car- 402
355 diometabolic risk factors. 403

356 DISCUSSION

357 To the best of our knowledge this is the first lon- 404
358 gitudinal study on the associations of the GRS for 405
359 AD with cardiometabolic risk factors in children. 406
360 In girls, a higher GRS was linked to a higher LDL 407
361 cholesterol concentration at baseline and a higher 408
362 cardiometabolic risk score, fasting plasma glucose 409
363 concentration, and HOMA-IR at 2-year follow-up. 410
364 We also observed that a higher GRS was associated 411
365 with unfavorable cardiometabolic risk profile par- 412
366 ticularly in girls with higher body fat percentage. 413
367 Most of these associations remained similar when 414
368 non-*APOE* GRS was used in the analyses. Further- 415
369 more, we found that a higher non-*APOE* GRS was 416
370 related to larger increase in insulin and HOMA-IR 417
371 over 2-year follow-up. The GRS was not related 418
372 to cardiometabolic risk factors in boys. Finally, our 419
373 results confirm previous findings that children with 420
374 the *APOE* ϵ genotype 3/3 have higher LDL cholest- 421
375 terol concentration than children with *APOE* ϵ 2/3 422
376 genotype. 423
424
425
426
427
428

377 The magnitude of the associations of the GRS with 378
379 cardiometabolic risk factors in the present study were 379
380 modest and were observed only in girls. The reason 380
381 for these sexually dimorphic associations is currently 381
382 unknown. However, our results in children suggest 382
383 that genetic susceptibility to AD is linked to car- 383
384 diometabolic risk factors associated with increased 384
385 risk of AD in adults [6]. 385

386 There are no previous studies on the associa- 386
387 tions of the GRS for AD with cardiometabolic risk 387
388 factors in children. However, overweight, insulin 388
389 resistance, and particularly their combination have 389
390 been linked to increased serum concentrations of AD 390
391 pathophysiology-related amyloid β ₄₂-protein and 391
392 presenilin 1 in adolescents [29]. Nevertheless, that 392
393 specific study did not address the question whether 393
394 genetic predisposition to AD modifies the associa- 394
395 tions of overweight and insulin resistance with serum 395
396 amyloid β ₄₂ and presenilin 1 concentrations. Our 396
397 observation that GRS was directly associated with 397
398 cardiometabolic risk particularly among girls with 398
399 higher levels of adiposity suggest that increased 399
400 adiposity may exacerbate the effects genetic suscep- 400
401 tibility for AD on pathophysiological process of the 401
402 disease. The results of one previous study among 402
403 older adults suggest that lower body mass index 403
404 attenuate the negative effects of a higher GRS with 404
405 cerebrospinal fluid biomarkers of AD, such as phos- 405
406 phorylated tau/amyloid β ₄₂-protein ratio [30]. These 406
407 results together indicate that preventing overweight 407
408 and obesity may prevent negative effects of genetic 408
409 susceptibility to AD on pathophysiological biomark- 409
410 ers of AD already from childhood. Nevertheless, 410
411 there are no studies on the relationships of the GRS 411
412 to brain structures or functions and cognition and 412
413 whether cardiometabolic risk factors modify these 413
414 associations in children. However, a higher GRS has 414
415 been associated with a smaller hippocampal volumes 415
416 among young adults [31] and overweight and insulin 416
417 resistance have been related to smaller hippocampal 417
418 and cortical volumes, and the existence of white mat- 418
419 ter lesions, and poorer cognitive functions already in 419
420 children and adolescents [32, 33]. 420

421 Our results are in line with previous observations 421
422 that children and adolescents with *APOE* ϵ 3/3 or 422
423 3/4 genotype have higher LDL cholesterol concen- 423
424 trations than those with *APOE* ϵ 2/3 genotype [12, 424
425 19]. Our findings also support previous findings that 425
426 the *APOE* ϵ variant is related to tracking of a plasma 426
427 LDL cholesterol concentration [18]. In the present 427
428 study, children with *APOE* ϵ 3/3 genotype had higher 428
429 LDL cholesterol concentration than those with *APOE*

429 $\epsilon 2/3$ genotype during 2-year follow-up. However, 481
430 the results of our study along with previous findings 482
431 suggest that the *APOE* ϵ variant is not associated 483
432 with the changes in LDL cholesterol concentration 484
433 during childhood and adolescence [18]. Furthermore, 485
434 we observed that girls with the *APOE* $\epsilon 3/3$ genotype 486
435 had also higher cardiometabolic risk score, fasting 487
436 insulin, and HOMA-IR than girls with the *APOE* 488
437 $\epsilon 2/3$ genotype at baseline but not 2-year follow-up. 489
438 Previous studies in adults have found higher risk 490
439 of dyslipidemia and metabolic syndrome among the 491
440 *APOE* $\epsilon 4$ carriers than the *APOE* $\epsilon 2$ carriers [9, 34]. 492
441 In our population sample of children, however, there 493
442 were no *APOE* $\epsilon 4$ carriers. Moreover, we found no 494
443 association between the *APOE* ϵ variant and car- 495
444 diometabolic risk factors other than LDL cholesterol 496
445 at 2-year follow-up. 497

446 Genetic predisposition for AD and poor car- 498
447 diometabolic risk profile have been found to expose 499
448 middle-aged adults to a higher risk of AD later in life 500
449 [4–9]. Although little is known about their reciprocal 501
450 confounded effects on brain structure, brain function, 502
451 and cognition in youth, our results along with the 503
452 results of some previous studies suggest that GRS for 504
453 AD, obesity, insulin resistance, and metabolic syn- 505
454 drome, brain health and function, and cognition may 506
455 be interrelated [32, 35]. We observed that the asso- 507
456 ciations of GRS with cardiometabolic risk factors 508
457 were modified by BF% and that the direct associa- 509
458 tion between GRS and cardiometabolic risk factors 510
459 were stronger among girls with higher BF% than in 511
460 other girls. The evidence on the modifying effects 512
461 of lifestyle modifications, such as increased physical 513
462 activity and improved diet quality, on the associations 514
463 between GRS, cardiometabolic risk, and cognition is 515
464 sparse. However, higher levels of physical activity 516
465 and a better diet quality have been associated with 517
466 better cardiometabolic risk profile in children and 518
467 adolescents [36, 37]. Emerging evidence also suggest 519
468 that physical activity and diet quality are positively 520
469 associated with brain functioning, cognition, and aca- 521
470 demic achievement in youth [38–40]. These studies 522
471 together suggest the prevention of AD should begin 523
472 as early as possible before any signs of mild cognitive 524
473 impairment [2], maybe even in childhood. Therefore, 525
474 increasing physical activity and diet quality partic-
475 ularly in overweight and obese youth may support
476 normal brain and cognitive development. Improving
477 physical activity and diet quality during childhood
478 may thereby delay the onset of cognitive impairments
479 later in life regardless of the genetic predisposition for
480 these diseases.

481 The strengths of the present study include a rela-
482 tively large population sample of children followed
483 for two years. We also had comprehensive and valid
484 assessments of cardiometabolic risk factors. We were
485 not able to use all alleles proposed by GWAS meta-
486 analyses among adults in the GRS for AD, which
487 tends to decrease overall variance in the GRS score
488 and accentuate the role of the *APOE* ϵ variant in the
489 GRS. In contrast to some previous observations sug-
490 gesting a relatively high prevalence of *APOE* $\epsilon 4$ allele
491 in Finnish youth [41], our population sample of chil-
492 dren did not include *APOE* $\epsilon 4$ carriers which may
493 weaken the relationships of the *APOE* ϵ variant and
494 the GRS for AD with cardiometabolic risk factors in
495 children. Finally, the large number of analyses may
496 increase the risk of type I errors and therefore some
497 of observed associations might have been found by
498 chance

499 In conclusion, our results provide the first evidence
500 that genetic predisposition to AD was associated with
501 increased cardiometabolic risk in children and espe-
502 cially in girls. A higher GRS for AD was associated
503 with a higher plasma LDL cholesterol concentration
504 at baseline and a higher cardiometabolic risk score,
505 fasting plasma glucose concentration, and HOMA-
506 IR at 2-year follow-up in girls. In addition, a higher
507 non-*APOE* GRS was related to unfavorable changes
508 in insulin and HOMA-IR over 2-year follow-up. We
509 also observed that adiposity modified the associa-
510 tion of GRS with cardiometabolic risk factors in
511 girls. Furthermore, those with the *APOE* $\epsilon 3/3$ geno-
512 type had a higher LDL cholesterol concentration
513 than those with the *APOE* $\epsilon 2/3$ genotype in boys
514 and girls. Longer follow-up studies are warranted
515 to investigate whether the GRS for AD, the *APOE*
516 ϵ variant, and other gene variants associated with
517 AD predict changes in cardiometabolic risk factors
518 since childhood and whether genetic susceptibility
519 for AD intensify the influence of adiposity on the
520 risk of developing metabolic syndrome and type 2
521 diabetes in adulthood. Finally, more studies on the
522 associations of genetic predisposition for AD and the
523 modifying effect of lifestyle factors with biomarkers
524 for AD, brain health, and cognition from childhood
525 to adulthood are warranted.

526 ACKNOWLEDGMENTS

527 The PANIC Study has financially been supported
528 by Ministry of Education and Culture of Fin-
529 land, Research Committee of the Kuopio University

Hospital Catchment Area (State Research Funding), Finnish Innovation Fund Sitra, Social Insurance Institution of Finland, Finnish Cultural Foundation, Foundation for Paediatric Research, Diabetes Research Foundation in Finland, Finnish Foundation for Cardiovascular Research, Juho Vainio Foundation, Paavo Nurmi Foundation, Yrjö Jahnsson Foundation, and the city of Kuopio. Moreover, the PhD students and postdoctoral researchers of the PANIC Study have been supported by Program for Clinical Research and Program for Health Sciences of Doctoral School of University of Eastern Finland, Finnish Doctoral Programs in Public Health, Päivikki and Sakari Sohlberg Foundation, Paulo Foundation, Jalmari and Rauha Ahokas Foundation, Aarne and Aili Turunen Foundation, Finnish Medical Foundation, Jenny and Antti Wihuri Foundation, Kuopio Naturalists' Society, Olvi Foundation, and the city of Kuopio. The work of Dr. Haapala was part of the University of Jyväskylä profiling area of multi-disciplinary brain research funded by Academy of Finland. The sponsors had no role in designing the study, the collection, analysis, or interpretation of the data, the writing of the report, or the decision to submit the manuscript for publication.

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/18-0216r1>).

REFERENCES

- [1] Alzheimer's Association (2013) 2013 Alzheimer's disease facts and figures. *Alzheimers Dement* **9**, 208-245.
- [2] Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, Cedazo-Minguez A, Dubois B, Edvardsson D, Feldman H, Fratiglioni L, Frisoni GB, Gauthier S, Georges J, Graff C, Iqbal K, Jessen F, Johansson G, Jönsson L, Kivipelto M, Knapp M, Mangialasche F, Melis R, Nordberg A, Rikkert MO, Qiu C, Sakmar TP, Scheltens P, Schneider LS, Sperling R, Tjernberg LO, Waldemar G, Wimo A, Zetterberg H (2016) Defeating Alzheimer's disease and other dementias: A priority for European science and society. *Lancet Neurol* **15**, 455-532.
- [3] World Health Organization (2012) *Dementia: A public health priority*.
- [4] Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B, Helkala E-L, Tuomilehto J, Soininen H, Nissinen A (2005) Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol* **62**, 1556-1560.
- [5] Vuorinen M, Solomon A, Rovio S, Nieminen L, Kåreholt I, Tuomilehto J, Soininen H, Kivipelto M (2011) Changes in vascular risk factors from midlife to late life and white matter lesions: A 20-year follow-up study. *Dement Geriatr Cogn Disord* **31**, 119-125.
- [6] Frisardi V, Solfrizzi V, Seripa D, Capurso C, Santamato A, Sancarlo D, Vendemiale G, Pilotto A, Panza F (2010) Metabolic-cognitive syndrome: A cross-talk between metabolic syndrome and Alzheimer's disease. *Ageing Res Rev* **9**, 399-417.
- [7] Altman R, Rutledge JC (2010) The vascular contribution to Alzheimer's disease. *Clin Sci (Lond)* **119**, 407-421.
- [8] Mayeux R, Saunders A, Shea S, Mirra S, Evans D, Roses A, Hyman B, Crain B, Tang M, Phelps C (1998) Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. Alzheimer's Disease Centers Consortium on Apolipoprotein E and Alzheimer's Disease. *N Engl J Med* **338**, 506-511.
- [9] Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC (2002) Apolipoprotein E polymorphism and cardiovascular disease: A HuGE review. *Am J Epidemiol* **155**, 487-495.
- [10] Lambert J-C (2014) Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet* **45**, 1452-1458.
- [11] Martiskainen H, Helisalmi S, Viswanathan J, Kurki M, Hall A, Herukka S-K, Sarajärvi T, Natunen T, Kurkinen KM a, Huovinen J, Mäkinen P, Laitinen M, Koivisto AM, Mattila KM, Lehtimäki T, Remes AM, Leinonen V, Haapasalo A, Soininen H, Hiltunen M (2014) Effects of Alzheimer's disease-associated risk loci on cerebrospinal fluid biomarkers and disease progression: A polygenic risk score approach. *J Alzheimers Dis* **43**, 565-573.
- [12] Ruottinen S, Rönnemaa T, Niinikoski H, Lagström H, Saarienen M, Pakkala K, Kaitosaari T, Viikari J, Simell O (2009) Carbohydrate intake, serum lipids and apolipoprotein e phenotype show association in children. *Acta Paediatr* **98**, 1667-1673.
- [13] Liu C-C, Kanekiyo T, Xu H, Bu G (2013) Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. *Nat Rev Neurol* **9**, 106-118.
- [14] Song Y, Stampfer MJ, Liu S (2004) Meta-analysis: Apolipoprotein E genotypes and risk for coronary heart disease. *Ann Intern Med* **141**, 137-147.
- [15] Wang R, Fratiglioni L, Laukka EJ, Lövdén M, Keller L, Graff C (2015) Effects of vascular risk factors and APOE e4 on white matter integrity and cognitive decline. *Neurology* **84**, 1128-1135.
- [16] Solomon A, Kivipelto M, Soininen H (2012) Prevention of Alzheimer's disease: Moving backward through the lifespan. *Adv Alzheimers Dis* **3**, 465-469.
- [17] Grönroos P, Raitakari O, Kähönen M, Hutri-Kähönen N, Marniemi J, Viikari J, Lehtimäki T (2007) Influence of apolipoprotein E polymorphism on serum lipid and lipoprotein changes: A 21-year follow-up study from childhood to adulthood. The Cardiovascular Risk in Young Finns Study. *Clin Chem Lab Med* **45**, 592-598.
- [18] Srinivasan SR, Ehnholm C, Eklaabany A, Berenson G (1999) Influence of apolipoprotein E polymorphism on serum lipid and lipoprotein changes from childhood to adulthood: The Bogalusa Heart Study. *Atherosclerosis* **143**, 435-443.
- [19] Fulton JE, Dai S, Grunbaum JA, Boerwinkle E, Labarthe DR (2009) Effects of apolipoprotein E genotype on blood cholesterol in adolescent girls. *Am J Prev Med* **37**, S78-S85.
- [20] Bulik-sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh P, ReprGenConsortium, Psychiatric Genomics Consortium, Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium 3, Duncan L, Perry JRB, Patterson N, Robinson EB, Daly MJ, Price AL, Neale BM (2015) An atlas of genetic correlations across human diseases and traits. *Nat Genet* **47**, 1236-1241.

- 649 [21] Saari A, Sankilampi U, Hannila M-L, Kiviniemi V, Kesseli K, Dunkel L (2011) New Finnish growth refer- 706
650 ences for children and adolescents aged 0 to 20 years: 707
651 Length/height-for-age, weight-for-length/height, and body 708
652 mass index-for-age. *Ann Med* **43**, 235-248. 709
- 653 [22] Cole T, Bellizzi M, Flegal K, Dietz W (2000) Establish- 710
654 ing a standard definition for child overweight and obesity 711
655 worldwide: International survey. *Br Med J* **320**, 1240-1243. 712
- 656 [23] Tompuri TT, Lakka TA, Hakulinen M, Lindi V, Laaksonen 713
657 DE, Kilpeläinen TO, Jääskeläinen J, Lakka H-M, Laitinen 714
658 T (2015) Assessment of body composition by dual-energy 715
659 X-ray absorptiometry, bioimpedance analysis and anthropo- 716
660 metrics in children: The Physical Activity and Nutrition 717
661 in Children study. *Clin Physiol Funct Imaging* **35**, 21-33. 718
- 662 [24] Viitasalo A, Laaksonen DE, Lindi V, Eloranta A-M, 719
663 Jääskeläinen J, Tompuri T, Väisänen S, Lakka H-M, Lakka 720
664 TA (2012) Clustering of metabolic risk factors is associ- 721
665 ated with high-normal levels of liver enzymes among 6- to 722
666 8-year-old children: The PANIC study. *Metab Syndr Relat 723*
667 *Disord* **10**, 337-343. 724
- 668 [25] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, 725
669 Treacher DF, Turner RC (1985) Homeostasis model assess- 726
670 ment: Insulin resistance and beta-cell function from fasting 727
671 plasma glucose and insulin concentrations in man. *Diab- 728*
672 *etologia* **28**, 412-419. 729
- 673 [26] Viitasalo A, Lakka TA, Laaksonen DE, Savonen K, Lakka 730
674 H-M, Hassinen M, Komulainen P, Tompuri T, Kurl S, 731
675 Laukkanen JA, Rauramaa R (2014) Validation of metabolic 732
676 syndrome score by confirmatory factor analysis in children 733
677 and adults and prediction of cardiometabolic outcomes in 734
678 adults. *Diabetologia* **57**, 940-949. 735
- 679 [27] Lambert J-C, Grenier-Boley B, Harold D, Zelenika D, 736
680 Chouraki V, Kamatani Y, Sleegers K, Ikram MA, Hiltunen 737
681 M, Reitz C, Mateo I, Feulner T, Bullido M, Galimberti 738
682 D, Concarì L, Alvarez V, Sims R, Gerrish A, Chapman J, 739
683 Deniz-Naranjo C, Solfrizzi V, Sorbi S, Arosio B, Spalletta 740
684 G, Siciliano G, Epelbaum J, Hannequin D, Dartigues J-F, 741
685 Tzourio C, Berr C, Schrijvers EMC, Rogers R, Tosto G, 742
686 Pasquier F, Bettens K, Van Cauwenbergh C, Fratiglioni 743
687 L, Graff C, Delepine M, Ferri R, Reynolds CA, Lannfelt 744
688 L, Ingelsson M, Prince JA, Chillotti C, Pilotto A, Seripa 745
689 D, Boland A, Mancuso M, Bossù P, Annoni G, Nacmias B, 746
690 Bosco P, Panza F, Sanchez-Garcia F, Del Zompo M, Coto E, 747
691 Owen M, O'Donovan M, Valdivieso F, Caffara P, Scarpini 748
692 E, Combarros O, Bué L, Campion D, Soyninen H, Breteler 749
693 M, Riemenschneider M, Van Broeckhoven C, Alperovitch 750
694 A, Lathrop M, Trégouët D-A, Williams J, Amouyel P (2013) 751
695 Genome-wide haplotype association study identifies the 752
696 FRMD4A gene as a risk locus for Alzheimer's disease. *Mol 753*
697 *Psychiatry* **18**, 461-470. 754
- 698 [28] Mazure CM, Swendsen J (2016) Sex differences in 755
699 Alzheimer's disease and other dementias. *Lancet Neurol* **15**, 756
700 451-452. 757
- 701 [29] Luciano R, Barraco GM, Muraca M, Ottino S, Spreghini 758
702 MR, Sforza RW, Rustico C, Morino GS, Manco M (2015) 759
703 Biomarkers of Alzheimer disease, insulin resistance, and 760
704 obesity in childhood. *Pediatrics* **135**, 1074-1081. 761
- [30] Schultz SA, Boots EA, Darst BF, Zetterberg H, Blennow 706
707 K, Edwards DF, Kosciak RL, Carlsson CM, Gallagher CL, 708
709 Bendlin BB, Asthana S, Sager MA, Hogan KJ, Hermann 709
710 BP, Cook DB, Johnson SC, Engelman CD, Okonkwo OC 710
711 (2017) Cardiorespiratory fitness alters the influence of a 711
712 polygenic risk score on biomarkers of AD. *Neurology* **88**, 712
1650-1658.
- [31] Foley SF, Tansey KE, Caseras X, Lancaster T, Bracht T, 713
714 Parker G, Hall J, Williams J, Linden DEJ (2017) Multimodal 714
715 brain imaging reveals structural differences in Alzheimer's 715
716 disease polygenic risk carriers: A study in healthy young 716
717 adults. *Biol Psychiatry* **81**, 154-161. 717
- [32] Yau PL, Javier DC, Ryan CM, Tsui WH, Ardekani BA., Ten 718
719 S, Convit A. (2010) Preliminary evidence for brain compli- 718
720 cations in obese adolescents with type 2 diabetes mellitus. 719
721 *Diabetologia* **53**, 2298-2306. 720
- [33] Yau PL, Kang EH, Javier DC, Convit A (2014) Preliminary 722
723 evidence of cognitive and brain abnormalities in uncompli- 722
724 cated adolescent obesity. *Obesity* **22**, 1865-1871. 723
- [34] Sun Y, Wei R, Yan D, Xu F, Zhang X, Zhang B, Yimiti D, Li 724
725 H, Sun H, Hu C, Luo L, Yao H (2016) Association between 724
726 APOE polymorphism and metabolic syndrome in Uyghur 725
727 ethnic men. *BMJ Open* **6**, e010049. 726
- [35] Yau PL, Castro MG, Tagani A, Tsui WH, Convit A (2012) 727
728 Obesity and metabolic syndrome and functional and struc- 727
729 tural brain impairments in adolescence. *Pediatrics* **130**, 728
730 e856-64. 729
- [36] Poitras VJ, Gray CE, Borghese MM, Carson V, Chaput J, 731
732 Janssen I, Katzmarzyk PT, Pate RR, Gorber SC, Kho ME, 731
733 Sampson M, Tremblay MS (2016) Systematic review of the 732
734 relationships between objectively measured physical activi- 732
735 ty and health indicators in school-aged children and youth. 733
736 *Appl Physiol Nutr Metab* **41**, 197-239. 734
- [37] Eloranta AM, Schwab U, Venäläinen T, Kiiskinen S, Lakka 735
736 HM (2016) Dietary quality indices in relation to cardi- 735
737 ometabolic risk among Finnish children aged 6-8 years - 736
738 The PANIC study. *Nutr Metab Cardiovasc Dis* **26**, 737
739 833-841. 738
- [38] Donnelly JE, Hillman CH, Castelli D, Etnier JL, Lee S, Tom- 740
741 porowski P, Lambourne K, Szabo-Reed AN (2016) Physical 740
742 activity, fitness, cognitive function, and academic achieve- 741
743 ment in children: A systematic review. *Med Sci Sport Exerc* 742
744 **48**, 1197-1222. 743
- [39] Nyaradi A, Li J, Hickling S, Foster J, Oddy WH (2013) The 744
745 role of nutrition in children's neurocognitive development, 744
746 from pregnancy through childhood. *Front Hum Neurosci* **7**, 745
747 97. 746
- [40] Haapala EA, Eloranta A-M, Venäläinen T, Schwab U, Lindi 747
748 V, Lakka T (2015) Associations of diet quality with cogni- 747
749 tion in children - The Physical Activity and Nutrition in 748
750 Children Study. *Br J Nutr* **114**, 1080-1087. 749
- [41] Lehtimäki T, Moilanen T, Viikari J, Akerblom HK, Ehnholm 750
751 C, Rönnemaa T, Marniemi J, Dahlen G, Nikkari T (1990) 750
752 Apolipoprotein E phenotypes in Finnish youths: A cross- 751
753 sectional and 6-year follow-up study. *J Lipid Res* **31**, 487- 752
754 495. 753