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Abdominal adiposity and cardiometabolic risk factors in children and adolescents; a Mendelian randomization analysis

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Short running head: Abdominal adiposity and metabolic risk in children

Abbreviations: GRS= genetic risk score; WHR= waist-hip ratio; WHR_{adjBMI}= waist-hip ratio adjusted BMI

Abstract

Background: Mendelian randomization studies in adults suggest that abdominal adiposity is causally associated with increased risk of type 2 diabetes and coronary heart disease in adults, but its causal effect on cardiometabolic risk in children remains unclear.

Objective: To study the causal relationship of abdominal adiposity with cardiometabolic risk factors in children by applying Mendelian randomization.

Design: We constructed a genetic risk score using variants previously associated with waist-hip ratio adjusted for BMI (WHR_{adjBMI}) and examined its associations with cardiometabolic factors by linear regression and Mendelian Randomization in a meta-analysis of six cohorts, including 9,895 European children and adolescents aged 3-17 years.

Results: WHR_{adjBMI} genetic risk score was associated with higher WHR_{adjBMI} (beta=0.021 SD/allele, CI95% 0.016, 0.026, $P=3\times10^{-15}$) and with unfavorable concentrations of blood lipids (higher LDL cholesterol: beta=0.006 SD/allele, 95% 0.001, 0.011, P=0.025; lower HDL cholesterol: beta=-0.007 SD/allele, CI95% -0.012, -0.002, P=0.009; higher triglycerides: beta=0.007 SD/allele, CI95% 0.002, 0.012, P=0.006). No differences were detected between pre-pubertal and pubertal/post-pubertal children. The WHR_{adjBMI} genetic risk score had a stronger association with fasting insulin in children and adolescents with overweight/obesity (beta=0.016 SD/allele, CI95% 0.001, 0.032, P=0.037) than in those with normal weight (beta=-0.002 SD/allele, CI95% -0.010, 0.006, P=0.605) (P for difference=0.034). In a two-stage least-squares regression analysis, each genetically instrumented one SD increase in WHR_{adjBMI} increased circulating triglycerides by 0.17 mmol/l (0.35 SD, P=0.040), suggesting that the relationship between abdominal adiposity and circulating triglycerides may be causal.

Conclusions: Abdominal adiposity may have a causal, unfavorable effect on plasma triglycerides and potentially other cardiometabolic risk factors starting in childhood. The results highlight the importance of early weight management through healthy dietary habits and physically active lifestyle among children with tendency for abdominal adiposity.

Introduction

Childhood obesity has increased worldwide during the last four decades (1) and is associated with cardiometabolic impairments, including insulin resistance, dyslipidemia, and hypertension in young age (2). Obesity during childhood often tracks into adulthood where it is associated with an increased risk and earlier onset of type 2 diabetes and cardiovascular disease (3). It is crucial to fully understand the factors that contribute to increased cardiometabolic risk starting in childhood, in order to develop early interventions and treatment strategies to risk groups.

Observational studies in adults suggest that obesity is a heterogeneous condition and that for any given amount of body fat, its regional distribution, particularly when located within the abdominal cavity, is an independent risk factor of cardiometabolic disease (4). In this regard, waist circumference has been shown to add to BMI in risk assessment. A study implementing a Mendelian randomization approach suggested that the link between abdominal adiposity and cardiometabolic risk may be causal (5). Mendelian randomization utilizes the random assortment of genetic variants at conception to reduce and limit confounding and reverse causality (6). When using a genetic risk score (GRS) comprising 48 known variants for waist-hip ratio (WHR) adjusted for BMI (WHR_{adjBMI}) (7), a genetically instrumented increase in WHR_{adjBMI} was associated with higher levels of triglycerides, 2-hour glucose, and systolic blood pressure, as well as an increased risk of type 2 diabetes and coronary heart disease, suggesting that the relationship between abdominal adiposity and cardiometabolic risk may be causal in adults (5). Similar to adults, increased WHR indicates abdominal adiposity in childhood (8), and gene variants increasing WHR_{adjBMI} have been associated with a higher ratio of visceral to subcutaneous fat in children and adolescents (9). However, it remains unclear whether abdominal adiposity is causally linked to increased levels of blood lipids, insulin resistance, and blood pressure among children and adolescents (10-13).

In the present study, we aimed to examine the causal relationships of abdominal adiposity with cardiometabolic risk factors by applying Mendelian randomization in a meta-analysis of 9,895 children and adolescents from the United Kingdom, Finland, and Denmark.

Methods

Study populations

The present study includes i) 5,474 children 8-11 years of age from the Avon Longitudinal Study of Parents and Children (ALSPAC) (14, 15); ii) 2,099 Finnish children and adolescents 3-18 years of age from the Cardiovascular risk in Young Finns Study (YFS) (16); iii) 705 Danish children and adolescents 3-18 years of age with overweight or obesity as well as a population-based control sample consisting of 361 Danish children and adolescents 6-17 years of age from The Danish Childhood Obesity Biobank (17); hereafter named TDCOB cases and controls, respectively; iv) 470 Finnish adolescents 14-15 years of age from the Special Turku Coronary Risk Factor Intervention Project (STRIP) (18); v) 460 Finnish children 6-9 years of age from the Physical Activity and Nutrition in Children (PANIC) study (19) and vi) 326 Danish children 3 years of age from the Småbørns Kost Og Trivsel (SKOT) I and II studies (20). (**Supplemental Figure 1**). Details on the recruitment, inclusion criteria and ethical approvals of the participating studies are presented in **Supplemental Methods.**

Children with a history of type 1 or type 2 diabetes, mental or developmental disorders, or monogenic obesity; children with medication for hypercholesterolemia or hypertension; children of non-European genetic ancestry based on genome-wide principal component analysis (YFS, TDCOB, STRIP and SKOT) or self-reported ethnicity (ALSPAC, PANIC), were excluded. For twin-pairs, one twin was excluded. The categories of self-reported ethnicity in the ALSPAC cohort were “black”, “yellow”, and “white”. The categories of self-reported ethnicity in the PANIC cohort were “Caucasian” and “non-Caucasian”. We excluded all ALSPAC participants whose self-reported ethnicity was “black” or “yellow”, and PANIC participants whose self-reported ethnicity was “non-

Caucasian", due to these ethnicities being considered to represent non-European genetic ancestry for whom the genetic architecture (allele frequencies, effect sizes) differ from European genetic ancestry. The analytic codes for the exclusion of participants in the ALSPAC and PANIC cohorts based on self-reported ethnicity are provided in the **Supplemental Methods.**

Measurements of body size and composition, cardiometabolic risk factors, and pubertal status

Body height and body weight were measured in all studies, and BMI was calculated as body weight (kg) divided by height squared (m^2). BMI-SDS was calculated according to UK (ALSPAC) (21), Finnish (PANIC, STRIP and YFS) (22) and Danish (SKOT, TDCOB cases and TDCOB controls) (23) national reference values. Waist circumference was measured at mid-distance between the bottom of the rib cage and the top of the iliac crest. Hip circumference was measured at the level of the greater trochanters. Body fat mass, body lean mass, and body fat percentage were measured using bioimpedance analysis (STRIP, SKOT) or dual-energy X-ray absorptiometry (PANIC, ALSPAC, TDCOB). Blood pressure was measured manually using calibrated sphygmomanometers (PANIC, YFS) or an oscillometric device (ALSPAC, TDCOB, STRIP, SKOT). Blood samples were taken after an overnight fast in ALSPAC, YFS, TDCOB, STRIP and PANIC studies and after >2h fasting in SKOT. Plasma glucose was measured using the hexokinase method, and serum insulin was analyzed by immunoassays. Triglycerides, total, LDL, and HDL cholesterol were measured enzymatically. Overweight and obesity were defined using the age- and sex-specific BMI cut-offs of the International Obesity Task Force (IOTF) (24). In YFS, TDCOB cases, STRIP, and PANIC studies, the research physician or the study nurse assessed pubertal status using the 5-stage criteria described by Tanner (25, 26). Boys were defined as having entered clinical puberty if their testicular volume assessed by an orchidometer was ≥4 ml (Tanner Stage ≥2). Girls were defined as having entered clinical puberty if their breast development had started (Tanner Stage ≥2). Among TDCOB controls, pubertal staging was obtained via a questionnaire with picture pattern recognition of the five different Tanner stages

accompanied by a text describing each category. To divide children and adolescents into pre-puberty-onset and onset/ post-onset groups, children with Tanner Stage 1 were considered pre-onset, and all others were considered onset/post-onset. Children in the SKOT study (aged 3 years) were all considered pre-onset. Children 8-11 years of age in the ALSPAC were excluded from analyses using puberty stratification due to insufficient information on puberty. These assessments have been previously described in detail for each study population (18, 27-31).

Genotyping, imputation and genetic risk score construction

Children in YFS, TDCOB, and SKOT were genotyped using the Illumina Infinium HumanCoreExome BeadChip (Illumina, San Diego, CA, USA) (32). Children in STRIP were genotyped using the Illumina Cardio-MetaboChip (33). Children in PANIC were genotyped using the Illumina HumanCoreExome Beadchip and the Illumina Cardio-MetaboChip, and the genotypes from the two arrays were combined. Children in ALSPAC were genotyped using the Illumina HumanHap550 Quad chip. In all studies, genotype imputation was performed using the 1000 Genomes reference panel (34).

To construct the WHR_{adjBMI} GRS, we used 49 single nucleotide polymorphisms (SNPs) known to associate with WHR_{adjBMI} in the largest available genome-wide association study (GWAS) published at the time of the present analyses, including up to 224,459 adults from the Genetic Investigation of Anthropometric Traits (GIANT) consortium (7) **(Supplemental Table 1)**. One of the SNPs, rs7759742, was not available in all six studies of the present meta-analysis and was therefore excluded from the final GRS. The established WHR_{adjBMI} variants were extracted either as alleles from the genotyped datasets or dosages from the imputed datasets of each cohort. The GRS was then calculated as the sum of the number of WHR_{adjBMI} - increasing number of alleles or dosages: WHR_{adjBMI} genetic risk score = $SNP_1 + SNP_2 + SNP_3 + \ldots SNP_n$; where SNP is the number of alleles or dosage of the WHR_{adjBMI}-raising allele (i.e. ranging from 0-2 WHR_{adjBMI}-raising alleles per locus).

Statistical methods

All statistical analyses and construction of GRS were performed using R software, version 3.3.1. Linear regression models for inverse normally transformed residuals, adjusted for age, sex, puberty (YFS, TDCOB, STRIP, PANIC), and study group, if needed (SKOT, STRIP), and first three genome-wide principal components were used to examine the associations of WHR_{adjBMI} GRS with cardiometabolic risk factors. For WHR, we additionally adjusted the residuals for BMI. For systolic and diastolic blood pressure, we additionally adjusted the residuals for height. Variables were rank inverse normally transformed to approximate normal distribution with a mean of 0 and a standard deviation (SD) of 1. Thus, the effect sizes are reported in SD units of the inverse normally transformed traits. We also studied the associations of WHR_{adjBMI} GRS with cardiometabolic risk factors stratified by puberty (pre-onset vs. onset/post-onset). The results from the different studies were pooled by fixed effect meta-analyses using the 'meta' package of the R software, version 4.6.0 (35). Independent samples t-test was used to compare differences in the effects of the GRS for cardiometabolic risk factors between groups. The associations of the WHR_{adjBMI} GRS with potential confounding lifestyle factors were examined by linear regression adjusted for age and sex in ALSPAC. We estimated the causal effects of WHR_{adjBMI} on cardiometabolic risk factors using two-staged least-squares regression analyses, implemented in the 'AER' R-package (v1.2-6) including all studies from which information on WHR was available (ALSPAC, TDCOB, STRIP, PANIC). We tested for differences between the estimates from linear regression and instrumental variable analyses using the Durbin-Wu-Hausman test and assessed the strength of the genetic instrument by calculating the F-statistic (36). We tested for potential directional pleiotropy in the genetic instrument using the intercept from Egger regression implemented in the 'MendelianRandomization' R-package (v0.3.0). Hereby, deviation of the Egger intercept from zero provides evidence for pleiotropy (37). Using the same package we performed additional sensitivity analyses to confirm that the direction of effect that we observed in least squares

regression analysis was consistent with effect estimates based on multiple genetic variants derived from Egger regression and weighted median methods.

Results

Characteristics

Of the 9,895 children and adolescents, 50% were girls and 22% exhibited overweight or obesity **(Table 1).** The mean age was 10.0 years (range 2.7-18.0 years). Altogether, 54% of the children and adolescents were defined as pre-pubertal after excluding participants of the ALSPAC study due to lack of information on their pubertal status.

Association of the WHR_{adjBMI} GRS with cardiometabolic risk factors in children and adolescents

A key assumption of the Mendelian randomization approach is that genetic variants used as an instrument are associated with the exposure variable. In a meta-analysis of all 9,895 children and adolescents from the six studies, we found that the WHR_{adjBMI} GRS, calculated as the unweighted sum of the number of WHR_{adjBMI}-raising alleles (7), was robustly associated with higher WHR_{adjBMI} (beta=0.021 SD/allele, CI95% 0.016, 0.026, $P=3\times10^{-15}$) (**Supplemental Table 2**).

The primary outcome variables of the present analyses were circulating LDL cholesterol, HDL cholesterol and triglycerides, fasting glucose, fasting insulin, systolic blood pressure, and diastolic blood pressure. We found that the WHR_{adjBMI}-increasing GRS was associated with unfavorable concentrations of blood lipids (higher LDL cholesterol: beta=0.006 SD/allele, CI 95% 0.001, 0.011, P=0.025; lower HDL cholesterol: beta=-0.007 SD/allele, CI95% -0.012, -0.002, P=0.009; higher triglycerides: beta=0.007 SD/allele, CI95% 0.002, 0.012, P=0.006). There were no associations between the WHR_{adjBMI} GRS and fasting glucose, fasting insulin, systolic blood pressure or diastolic blood pressure (P>0.05) (**Figure 1, Supplemental Table 2, Supplemental Figure 2**).

In the original GWAS for WHR_{adjBMI} in adults, 20 of the 49 WHR_{adjBMI} loci showed sexual dimorphism, 19 of which displayed a stronger effect in women (7). In sex-stratified analyses, we found that the WHR_{adjBMI} GRS had a comparable effect on WHR_{adjBMI} in boys and girls but the effect on waist circumference was found only in girls (beta=0.013 SD/allele, CI95% 0.005, 0.020, P=0.001) and not in boys (beta=-0.002 SD/allele, CI 95% -0.009, 0.005, P=0.599) (P for difference=0.006). The WHR_{adjBMI} GRS was also associated with decreased BMI-SDS in boys (beta=-0.008 SD/allele, CI95% -0.015, -0.002, P=0.016) but had no effect on BMI-SDS in girls (beta=0.002 SD/allele, CI95% -0.004, 0.009, P=0.450) (P for difference=0.022). Finally, we also found a difference between sexes (P for difference=3×10^{-4}) in the effect of the WHR_{adjBMI} GRS on diastolic blood pressure; the WHR_{adjBMI} GRS had a blood pressure-increasing effect in girls (beta=0.0109 SD/allele, CI95% 0.005, 0.017, P=0.001) but not in boys (beta=-0.006, 95% CI -0.013, 0.001, P=0.072). No differences were found in other cardiometabolic risk factors between girls and boys (p>0.05).

A previous mendelian randomization study in adults (5) found a significant inverse association between the WHR_{adjBMI} GRS and BMI and thus performed sensitivity analyses using a WHR_{adjBMI} GRS where all variants associated with BMI (P<0.05) were excluded. We only found a significant inverse association between the WHR_{adjBMI} GRS and BMI in boys, and thus performed boys-specific sensitivity analyses using a GRS constructed of only those 19 WHR_{adjBMI} SNPs that have not been associated with BMI in the largest GWAS thus far published in adults (P>0.05) (38). Comparing the results between the 19 SNP GRS and the full 48 SNP GRS in boys **(Supplemental Table 3)**, we found very similar effect sizes in the associations of the two scores with cardiometabolic risk traits, except for the expected differences in BMI and related adiposity measures. The results were similar when comparing effect sizes between the 19 SNP GRS and the 48 SNP GRS in all children **(Supplemental Table 4).**

Puberty has a major effect on body fat distribution (39). We performed additional analyses stratified by puberty status to test whether the relationship between WHR_{adjBMI} GRS and cardiometabolic risk factors is established before puberty, but no differences were found (P>0.05).

A previous study in the TDCOB cohort suggested that there may be differences in genetic influences on body fat distribution between children who are overweight/obese and those who are normal-weight (40). We performed analyses stratified by weight status to test whether the effect of the WHR_{adjBMI} GRS on body fat distribution and cardiometabolic risk is modified by overweight/obesity. The WHR_{adjBMI} GRS was associated with fasting insulin in children and adolescents with overweight/obesity (beta=0.016 SD/allele, CI95% 0.001, 0.032, P=0.037) but not in those with normal weight (beta=-0.002 SD/allele, CI95% -0.010, 0.006, P=0.564) (P for difference=0.034). Furthermore, the WHR_{adjBMI} GRS was also associated with HDL cholesterol in children with overweight and obesity (beta=-0.018 SD/allele, CI95% -0.030, -0.006, P=0.036) but not in children with normal body weight (beta=-0.004 SD/allele CI95% -0.010, 0.001, P=0.121) (P for difference=0.036). No differences were found in other cardiometabolic risk factors between children with overweight/obesity and those with normal body weight (p>0.05).

Instrumental variable analyses

We estimated the causal effects of WHR_{adjBMI} on the three traits that the WHR_{adjBMI} GRS was significantly associated with (triglycerides, HDL cholesterol, and LDL cholesterol) (**Supplemental Table 2**) using two-staged least-squares regression analyses. The observational associations of WHR_{adjBMI} with cardiometabolic risk factors are shown in **Supplemental Table 5**. In two-stage least-squares regression analysis, each genetically instrumented one SD increase in WHR_{adjBMI} increased circulating triglycerides by 0.17 mmol/l (0.35 SD per allele, P=0.040, **Figure 2, Supplemental Figure 3**) indicating a causal relationship. No difference was found between the observational results and genetically instrumented results in the Durbin-Wu Hausman test (P_{ALSPAC}>0.05). There was no evidence of pleiotropy in the genetic instrument using the Egger intercept test (Estimate= -0.001,

CI95% -0.011, 0.009, $P_{intercept}$ for triglycerides=0.841). The estimates from Egger regression and weighted median regression were directionally consistent with those derived from the two-stage least squares method. The two-stage least-squares regression analyses did not suggest that a genetically instrumented increase in WHR_{adjBMI} has a causal effect on HDL cholesterol (0.24 SD per allele, P=0.138) or LDL cholesterol (0.19 SD per allele, P=0.259) (**Figure 2**).

To conduct a valid Mendelian randomization analysis, the instrumental variable must not be associated with possible confounders that could bias the relationship between the exposure and the outcome, and it must relate to the outcome phenotype only through its association with the exposure and not through pleiotropy (6). Some lifestyle and environmental factors, for example physical activity and dietary habits, have been associated with body fat distribution (4) and cardiometabolic risk, and could therefore confound the association between WHR_{adjBMI} and cardiometabolic risk factors. However, we did not find an association between the WHR_{adjBMI} GRS and any of the potential confounders we tested in the ALSPAC cohort, including objectively measured physical activity (p=0.508) sedentary time (p=0.580), family socioeconomic status (p=0.676), total energy intake (p=0.744), and dietary intakes (E%) of protein (p=0.661), total fat (p=0.193), saturated fat (p=0.413), monounsaturated fat (p=0.168), polyunsaturated fat (p=0.306), carbohydrates (p=0.467), and added sugar (p=0.201). We acknowledge that unobserved confounders could still be present that we were not able to control for.

Discussion

In the present study, genetic predisposition to higher WHR_{adjBMI} was associated with higher triglycerides, lower HDL cholesterol, and higher LDL cholesterol in children and adolescents. The associations of the WHR_{adjBMI} GRS with lipids were similar between prepubertal and pubertal/post-pubertal children and adolescents, indicating that this relationship is established already before

puberty. Instrumental variable analyses indicated that higher WHR_{adjBMI} may be causally associated with higher triglycerides.

Sex and age have major effects on WHR_{adjBMI} (39). Sexual dimorphism in body composition emerges primarily during pubertal development and is driven by the action of sex steroids (41). Women typically have overall higher body fat content, whereas men have a more central body fat distribution. The WHR_{adjBMI} GRS, constructed of the 49 loci, also shows a stronger effect on WHR_{adjBMI} in women than in men (7). In contrast to adults, we observed that the WHR_{adjBMI} GRS had a comparable effect on WHR_{adjBMI} in children regardless of sex. However, the effect on waist circumference was higher in girls than in boys. Previous studies have shown that sexual dimorphism in body fat distribution is distinct already in the first six years of age, characterized by an average smaller waist and larger hip circumference in girls (42). However, unlike in adulthood, the difference in this age is more pronounced for waist circumference than for hip circumference (42), which could partly explain why the genetic influences on waist circumference seem more pronounced in girls than in boys during childhood but not in adulthood.

The effects of the WHR_{adjBMI} GRS on fasting insulin and HDL cholesterol were more pronounced among children and adolescents with overweight/obesity than among those with normal body weight, indicating that higher overall adiposity may enhance the harmful effect of genetic predisposition to abdominal adiposity on insulin resistance and dyslipidemia. Although the biological mechanisms for this enhancement are uncertain, we speculate that higher overall adiposity may lead to a suppressed capacity of subcutaneous fat tissue to store additional fat and a higher deposition of fat in visceral and other ectopic storage sites. The metabolically active visceral fat releases a number of inflammatory cytokines as well as a flux of free fatty acids into portal circulation. This may, in turn, impair hepatic metabolism, thereby leading to reduced hepatic insulin clearance, increased production of triglyceride-rich lipoproteins, and increased hepatic glucose production (43, 44). Thus, increased visceral fat has a central role in the development of insulin resistance. Higher overall

adiposity also results in greater storage of abdominal subcutaneous fat which has a high lipolytic activity and increases the flux of free fatty acids, contributing to insulin resistance and cardiovascular risk (45). This impact may be particularly relevant in children who have a relatively large volume of abdominal subcutaneous fat compared to visceral fat (12, 13).

Previous studies in adults support the role for gradually increasing visceral fat as a determinant of unfavorable changes in plasma lipid concentrations with advancing age (46). Although the effect sizes of the GRS for WHR_{adjBMI} on WHR_{adjBMI} and cardiometabolic risk factors in children and adolescents in the present study were generally weaker than in adults (7), it remains unclear how age plays into the observed causal relationships as partly different variants may associate with WHR_{adjBMI} in different ages.

The strength of the present study is the comprehensive data on anthropometry, cardiometabolic risk factors, and genetic variation from several European child cohorts. To our knowledge, this is the first study investigating the causal associations of abdominal adiposity on cardiometabolic risk factors by Mendelian Randomization in children. Limitations of the study are the use of adult GWAS-based variants for WHR_{adjBMI}, which may not all be associated with abdominal adiposity in children. Furthermore, we did not address the possibility of bi-directional relationships between WHR_{adjBMI} and cardiometabolic risk factors in children. Despite the large sample size, our study may have been underpowered to detect a difference for the studied outcome traits. In the present analysis, we did not correct for multiple testing due to many of the outcome traits being correlated, and we acknowledge that adjustment of the significance threshold could reduce the statistical power further. Finally, as our study only included children of European genetic ancestry, the results cannot be generalized to other ethnic groups.

Conclusions

Our results suggest that there may be a causal, unfavorable effect of abdominal adiposity on plasma triglycerides in childhood, providing new insights into the relationship between body fat distribution and cardiometabolic risk in young age. The results underscore the importance of early weight management through healthy dietary habits and physically active lifestyle among children with tendency for abdominal fat accumulation.

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Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

A.V. and T.M.S researched data, A.V. wrote paper. T.O.K. designed research, Other co-authors conducted research and/or provided essential materials. A.V had primary responsibility for the final content. All authors read and approved the final manuscript.

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Table 1. Characteristics of children and adolescents in the studies included in the present meta-analyses.

	ALSPAC	YFS	TDCOB cases	TDCOB controls	STRIP	PANIC	SKOT
N (total)	5474	2099	705	361	470	460	326
Girls (%)	2754 (50%)	1139 (54%)	415 (59%)	238 (66%)	227 (48%)	219 (48%)	154 (47%)
Prepubertal (%)[1]	NA	1244 (51%)	314 (45%)	73 (22%)	0 (0%)	448 (97%)	326 (100%)
Overweight/obese[2]	1088 (20%)	161 (8%)	699 (99%)	46 (13%)	54 (12%)	56 (12%)	34 (10%)
Age (years)	9.9 (0.32)	9.8 (4.0)	11.5 (2.9)	13.0 (3.1)	15.0 (0.0)	7.6 (0.4)	3.0 (0.1)
Body height (cm)	139.6 (6.3)	137 (25)	152 (16)	157 (16)	170 (8)	129 (6)	96.2 (3.6)
Body weight (kg)	34.7 (7.3)	35.1 (16.5)	64.9 (23.9)	48.4 (15.3)	61.3 (6.9)	26.7 (4.8)	14.9 (1.7)
BMI (kg/cm^2)	17.7 (2.8)	17.4 (2.8)	27.0 (5.3)	19.1 (3.2)	20.5 (3.3)	16.1 (2.0)	16.1 (1.2)
BMI-SDS	0.29 (1.11)	-0.29 (1.00)	2.90 (0.66)	0.31 (1.05)	-0.08 (0.97)	-0.20 (1.1)	0.43 (0.92)
Waist circumference (cm)	62.9 (7.7)	NA	93 (15)	70 (9)	73 (8)	57 (5)	47 (4)
Waist-hip-ratio	0.85 (0.0)	NA	0.97 (0.07)	0.82 (0.1)	0.80 (0.05)	0.85 (0.0)	NA
Total body lean mass (kg)	24.6 (3.2)	NA	NA	NA	45 (9)	21 (2)	NA
Total body fat mass (kg)	8.5 (5.0)	NA	28.0 (12.2)	NA	12.7 (7.5)	5.6 (3.3)	2.6 (0.8)
Body fat percentage (%)	23.2 (9.0)	NA	43.6 (5.2)	NA	20.9 (9.3)	20 (8)	17.4 (4.3)
Insulin (mU/l)	NA	9.2 (5.8)	6.9 (7.2)	4.5 (2.2)	8.3 (3.5)	4.5 (2.5)	3.2 (3.5)
Glucose (mmol/l)	NA	NA	5.2 (0.6)	5.4 (1.1)	4.9 (0.3)	4.8 (0.4)	4.8 (0.6)
LDL cholesterol (mmol/l)	2.3 (0.6)	3.5 (0.8)	2.5 (0.8)	2.2 (0.5)	2.4 (0.7)	2.3 (0.5)	2.5 (0.6)
HDL cholesterol (mmol/l)	1.4 (0.3)	1.6 (0.3)	1.2 (0.3)	1.5 (0.3)	1.2 (0.2)	1.6 (0.3)	1.2 (0.2)
Triglycerides (mmol/l)	1.1 (0.6)	0.65 (0.29)	1.1 (0.6)	0.7 (0.3)	0.85 (0.42)	0.60 (0.25)	1.1 (0.6)
Systolic blood pressure (mmHg)	103 (9)	111 (12)	114 (12)	114 (10)	117 /12)	100 (7)	96 (8)
Diastolic blood pressure (mmHg)	57 (6)	68 (9)	65 (8)	62 (7)	61 (9)	61 (7)	61 (7)
GRS$_{WHRadjBMI}$, 48 SNPs (number of WHR$_{adjBMI}$ increasing risk alleles)	46.1 (4.3)	47.8 (4.4)	46.4 (4.3)	46.2 (4.3)	46.6 (4.8)	48.2 (4.2)	46.5 (4.4)

Values are mean (SD) or *n* (%). BMI-SDS= body mass index standard deviation score; GRS= genetic rik score, WHRa$_{djBMI}$= waist hip ratio adjusted BMI

[1] Children with Tanner Stage 1 were considered pre-onset and all others were considered onset/post-onset (25, 26).

[2] Overweight and obesity were defined using the age and sex-specific BMI cut-offs of the International Obesity Task Force (IOTF) (24).

Figure 1.

Linear regression analysis to test the association of the WHR_{adjBMI}-increasing genetic score with cardiometabolic variables in all children and adolescents (n=9,895). The results are expressed as beta values (confidence intervals) of the inverse-normally transformed traits and are aligned according to the WHR_{adjBM}-increasing allele of the genetic score. All analyses are adjusted for age, puberty, and first three genome-wide principal components. The effects were pooled using fixed effects models meta-analyses. *P-values <0.05. [beta in SD/allele = effect on the inverse-normally transformed trait per allele increase]. The numerical values for betas, standard errors, P-values, and sample sizes are presented in **Supplemental Table 2**.

Figure 2. Mendelian randomization analysis to test the causal effect of childhood abdominal adiposity on LDL cholesterol, HDL cholesterol and triglycerides. The figure shows associations of the WHR_{adjBMI} genetic risk score with LDL cholesterol, HDL cholesterol, triglycerides and observational WHR_{adjBMI}, as well as the associations of the observational WHR_{adjBMI} with LDL cholesterol, HDL cholesterol and triglycerides. The results of instrumental analysis are obtained from two-staged least-squares regression analyses. Beta values are expressed as units of standard deviation (SD) of the inverse-normally transformed traits. [beta in SD/allele = effect on the inverse-normally transformed trait per allele increase]. P-values <0.05 are shown in bold.

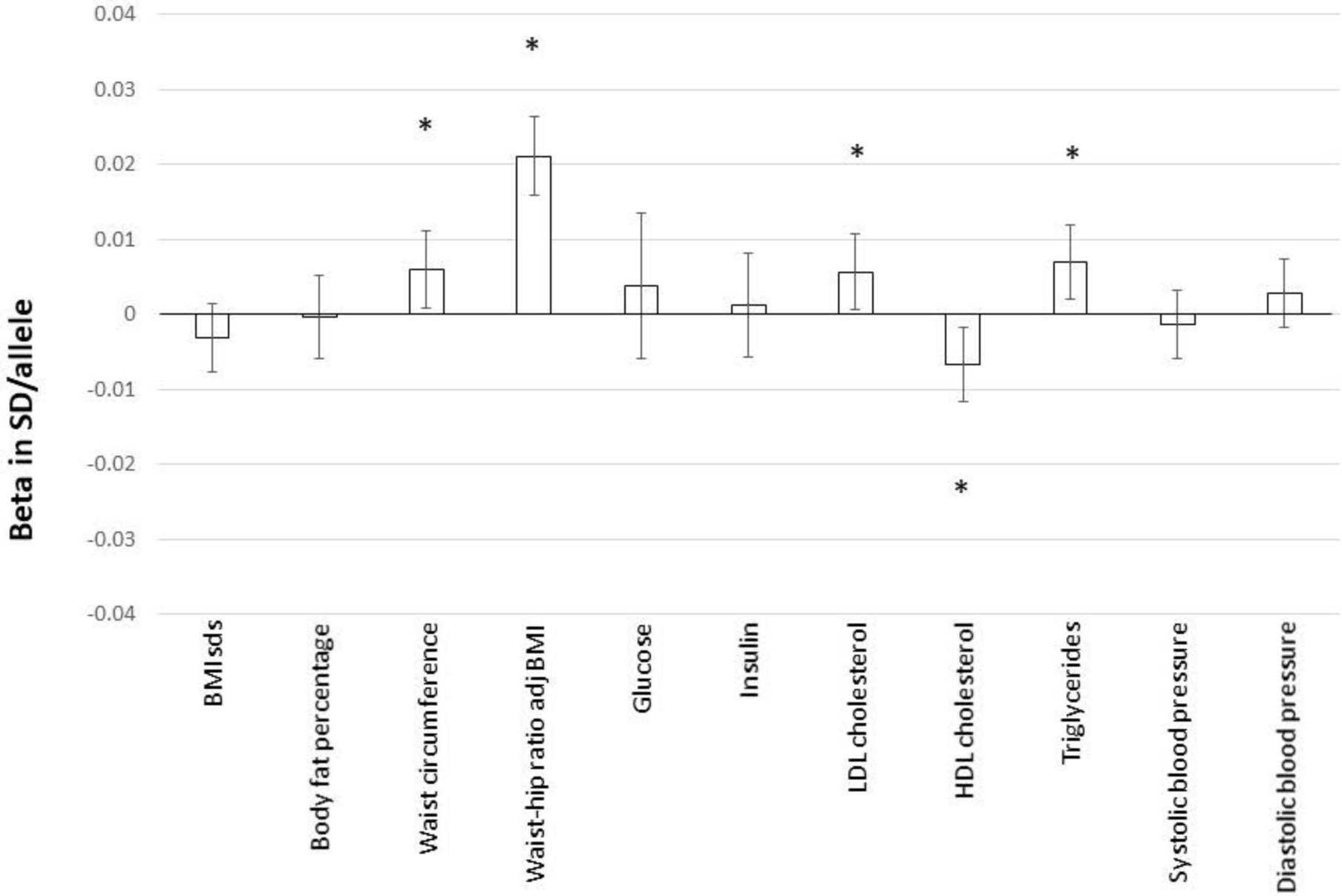
Beta in SD/allele
0.04
0.03
0.02
0.01
0
-0.01
-0.02
-0.03
-0.04
*
*
*
*
*
BMI sds
Body fat percentage
Waist circumference
Waist-hip ratio adj BMI
Glucose
Insulin
LDL cholesterol
HDL cholesterol
Triglycerides
Systolic blood pressure
Diastolic blood pressure

Figure 1.

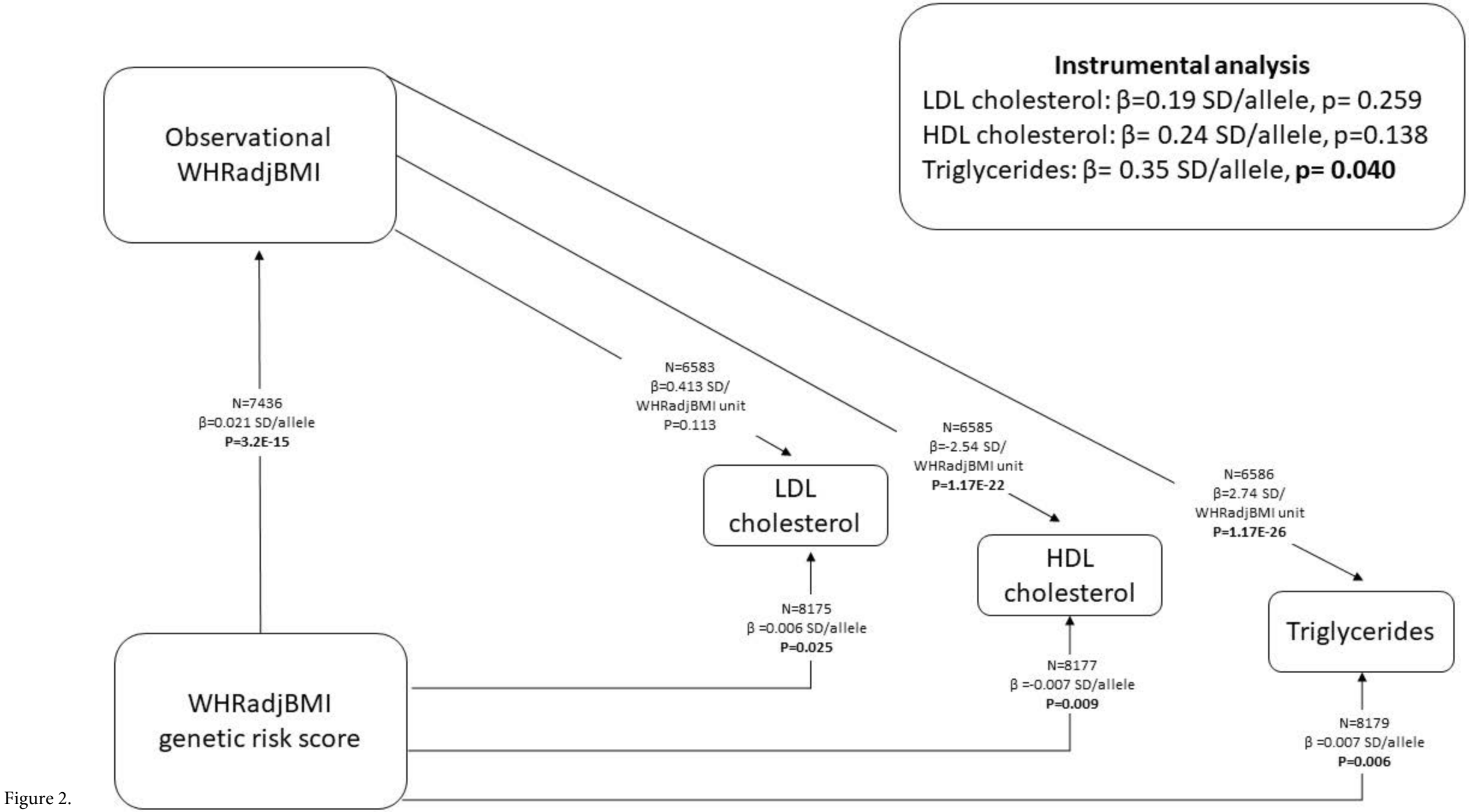
Instrumental analysis
LDL cholesterol: β=0.19 SD/allele, p= 0.259
HDL cholesterol: β= 0.24 SD/allele, p=0.138
Triglycerides: β= 0.35 SD/allele, p= 0.040
Observational WHRadjBMI
N=7436
β=0.021 SD/allele
P=3.2E-15
N=6583
β=0.413 SD/ WHRadjBMI unit
P=0.113
N=6585
β=-2.54 SD/ WHRadjBMI unit
P=1.17E-22
N=6586
β=2.74 SD/ WHRadjBMI unit
P=1.17E-26
LDL cholesterol
HDL cholesterol
Triglycerides
N=8175
β =0.006 SD/allele
P=0.025
N=8177
β =-0.007 SD/allele
P=0.009
N=8179
β =0.007 SD/allele
P=0.006
WHRadjBMI genetic risk score

Figure 2.