Genetic Susceptibility to Obesity and Related Traits in Childhood and Adolescence

Influence of Loci Identified by Genome-Wide Association Studies

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OBJECTIVE—Large-scale genome-wide association (GWA) studies have thus far identified 16 loci incontrovertibly associated with obesity-related traits in adults. We examined associations of variants in these loci with anthropometric traits in children and adolescents.

RESEARCH DESIGN AND METHODS—Seventeen variants representing 16 obesity susceptibility loci were genotyped in 1,252 children (mean ± SD age 9.7 ± 0.4 years) and 790 adolescents (15.5 ± 0.5 years) from the European Youth Heart Study (EYHS). We tested for association of individual variants and a genetic predisposition score (GPS-17), calculated by summing the number of effect alleles, with anthropometric traits. For 13 variants, summary statistics for associations with BMI were meta-analyzed with previously reported data (N_{total} = 13,071 children and adolescents).

RESULTS—In EYHS, 15 variants showed associations or trends with anthropometric traits that were directionally consistent with earlier reports in adults. The meta-analysis showed directionally consistent associations with BMI for all 13 variants, of which 9 were significant (0.033–0.098 SD/allele; $P < 0.05$). The near-*TMEM18* variant had the strongest effect (0.098 SD/allele $P = 8.5 \times 10^{-11}$). Effect sizes for BMI tended to be more pronounced in children and adolescents than reported earlier in adults for variants in or near *SEC16B*, *TMEM18*, and *KCTD15*, (0.028–0.035 SD/allele higher) and less pronounced for rs925946 in *BDNF* (0.028 SD/allele lower). Each additional effect allele in the GPS-17 was associated with an increase of 0.034 SD in BMI ($P = 3.6 \times 10^{-5}$), 0.039 SD, in sum of skinfolds ($P = 1.7 \times 10^{-7}$), and 0.022 SD in waist circumference ($P = 1.7 \times 10^{-4}$), which is comparable with reported results in adults (0.039 SD/allele for BMI and 0.033 SD/allele for waist circumference).

CONCLUSIONS—Most obesity susceptibility loci identified by GWA studies in adults are already associated with anthropometric traits in children/adolescents. Whereas the association of some variants may differ with age, the cumulative effect size is similar. ***Diabetes*** **59:2980–2988, 2010**

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Received 16 March 2010 and accepted 6 August 2010. Published ahead of print at http://diabetes.diabetesjournals.org on 19 August 2010. DOI: 10.2337/db10-0370.

Over the past three decades, the prevalence of obesity has reached epidemic proportions not only in adults, but in children and adolescents alike (1,2). A high BMI during childhood and adolescence often persists into adulthood (3–5) and has been independently associated with cardiovascular risk factors, coronary heart disease events, and all-cause mortality (2,6–9). Family and twin studies have estimated that 40–70% of the variance in obesity-related traits is due to genetic factors (10,11). Longitudinal twin studies have shown that the genetic contribution to BMI increases from childhood to adolescence (12–14), and cross-sectional twin studies suggest that the heritability of BMI is higher in adolescence than during adulthood (15,16).

Six genome-wide association (GWA) studies in adults of white European descent have thus far identified 16 obesity susceptibility loci; 12 loci were consistently associated with BMI (17–22), and 4 loci were identified in GWA studies for waist circumference. Only variants in the *FTO* and near-*MC4R* loci have as of yet convincingly been associated with obesity-related traits in children and adolescents (12,18,20,23–27). Two studies have examined the effect of variants in GWA-derived loci other than *FTO* and *MC4R* in children and adolescents (20,28). However, both studies focused only on BMI and neither study examined the association of all 16 obesity susceptibility loci or their cumulative effect. Examining the association of these obesity susceptibility loci with measures of adiposity in childhood and adolescence may provide insight into their impact on obesity risk early in life. Furthermore, it has been suggested that physical activity modifies the association of genetic variation with general adiposity in adults (29–31). Thus far, this has not been demonstrated in children.

In this study, we examined whether obesity susceptibility loci identified by GWA studies in adults are associated with anthropometric traits and risk of obesity in children and adolescents from the European Youth Heart Study (EYHS). To increase statistical power and to compare effect sizes in children/adolescents and adults, we additionally meta-analyzed our findings with those reported by others (20,28). Furthermore, we examined the cumulative effect of variants in the 16 loci on anthropometric traits in EYHS and tested whether the association between genetic predisposition and anthropometric traits is modified by physical activity.

TABLE 1
Descriptive characteristics of children and adolescents of the EYHS stratified by sex

	Children (n = 1,252)		Adolescents (n = 790)	
	Male (n = 593)	Female (n = 659)	Male (n = 351)	Female (n = 439)
Age (years)	9.7 ± 0.4	9.6 ± 0.4	15.5 ± 0.5	15.5 ± 0.5
Tanner stage (1–5)	1.03 ± 0.17	1.29 ± 0.50	4.30 ± 0.89	4.35 ± 0.68
BMI (kg/m^2)	17.1 ± 2.2	17.1 ± 2.6	20.5 ± 2.5	20.5 ± 2.7
Weight (kg)	33.3 ± 6.1	33.1 ± 6.9	62.5 ± 10.1	56.2 ± 8.3
Height (cm)	139.1 ± 6.6	138.7 ± 6.7	174.3 ± 7.6	165.3 ± 6.0
Sum of skinfolds (mm)	29.5 ± 14.4	37.0 ± 18.1	32.1 ± 15.3	47.8 ± 17.0
Waist circumference (cm)	59.4 ± 5.5	58.4 ± 6.6	71.3 ± 5.9	66.8 ± 5.8
Physical activity (cpm)	740.2 ± 235.7	613.2 ± 188.3	558.8 ± 238.5	455.0 ± 166.4
Moderate/vigorous physical activity (% registered time)	11.1 ± 5.2	7.9 ± 3.8	8.0 ± 4.9	6.2 ± 3.5
% normal weight	80.8	85.7	86.0	88.2
% overweight, nonobese	12.1	9.1	8.8	9.3
% obese	7.1	5.2	5.1	2.5

Data are means ± SD. Obese, BMI ≥95th percentile; overweight but nonobese, BMI ≥ 85th percentile and <95th percentile; normal weight, BMI <85th percentile. For moderate and vigorous intensity physical activity, data were available for 408 and 462 children (male and female, respectively) and 166 and 247 adolescents.

RESEARCH DESIGN AND METHODS

Study population and anthropometry. The EYHS is a school-based, mixed longitudinal study of pre- and early pubertal children and adolescents aged 9.7 ± 0.4 and 15.5 ± 0.5 years, respectively (32). Participants were randomly selected via application of a two-stage sampling strategy in four countries (Denmark, Estonia, Norway, and Portugal). The present study includes 1,252 children and 790 adolescents from Denmark and Estonia (944 boys and 1,098 girls) for whom data on anthropometric traits were available at baseline (Table 1). DNA was not available for the other two EYHS centers.

Body mass and height were measured using standard procedures, with participants dressed in light clothing and barefoot (33). The BMI was standardized according to BMI reference charts derived by Cole's LMS method (34). Thickness of skinfolds was measured at four locations (triceps brachi, biceps brachi, sub-scapula and supra-iliaca in millimeters) (35) and was combined to obtain the sum of skinfolds. Waist circumference was measured using a metal anthropometric tape midway between the lower rib margin and the iliac crest at the end of a gentle expiration. Sexual maturity was assessed using the five-stage Tanner scale for breast development in girls and pubic hair in boys (Table 1) (36).

Overall physical activity and the fraction of time spent on moderate and vigorous intensity physical activity (>2,000 cpm [ref. 37]) were measured in daily life during 2 weekdays and 2 weekend days with a validated MTI Actigraph accelerometer (Manufacturing Technology, Fort Walton Beach, FL) (38). For the present study, physical activity data were available for 870 children and 413 adolescents (Table 1).

The study was approved by the local scientific committees and was performed in accordance with the Declaration of Helsinki. All parents gave written informed consent for their child to participate, and all children and adolescents gave verbal consent.

Genotyping. Seventeen SNPs in the 16 obesity susceptibility loci (17–22) identified by recent GWA studies were genotyped: rs2815752, rs10913469, rs2605100, rs6548238, rs7647305, rs10938397, rs987237, rs545854, rs1488830, rs925946, rs10838738, rs7138803, rs10146997, rs8055138, rs1121980, rs17782313, and rs11084753 (*NEGR*, *SEC16B*, *LYPLAL1*, *TMEM18*, *ETV5*, *GNPDA2*, *TFAP2B*, *MSRA*, *BDNF*, *MTCH2*, *BCDIN3D*, *NRXN3*, *SH2B1*, *FTO*, *MC4R*, and *KCTD15* loci, respectively) (supplementary Table 1, available in the online appendix [http://diabetes.diabetesjournals.org/cgi/content/full/db10-0370/DC1]). Two variants in the *BDNF* locus were included (rs1488830 [*BDNF* SNP 1]) and rs925946 [*BDNF* SNP 2]; linkage disequilibrium $r^2 = 0.10$) because these variants were previously independently associated with BMI (19).

Markers rs7647305, rs10938397, and rs1121980 were genotyped using Custom TaqMan SNP Genotyping assays according to the manufacturer's protocol (Applied Biosystems, Warrington, U.K.). The remaining markers were genotyped using a Sequenom iPLEX platform (Sequenom, San Diego, CA) as previously described (39).

All variants passed quality-control criteria with a call rate >95% and a blind duplicate concordance rate of 100%. The distributions of all variants were in Hardy-Weinberg equilibrium, as determined by a χ^2 test with 1 d.f. (supplementary Table 1).

Statistical analyses. Before testing for associations, all traits were transformed to normal distributions, with a mean of zero and an SD of 1 in all participants combined using inverse normal transformation. Effect sizes can be interpreted as changes in Z scores, which allows comparison across traits and with effect sizes previously reported in adults.

The association of each SNP with BMI, sum of skinfolds, and waist circumference was tested using linear regression assuming an additive effect. Associations with height were examined to evaluate whether SNPs were specifically associated with adiposity or with body size in general. The effect alleles were those that increased BMI in adults in the original GWA studies (17–22). Logistic regression was used to test the association of each SNP with the risk of obesity and overweight versus not overweight. Assessing the risk by comparing with nonobese instead of not overweight did not change the results. Obesity (N = 105) and overweight (N = 309) were defined using age- and sex-specific thresholds of BMI (≥95th and ≥85th percentiles, respectively [ref. 34]).

A genetic predisposition score (GPS) was calculated by summing the number of effect alleles carried by each individual (GPS-17). The GPS-17 was normally distributed, with the majority of individuals (73.8%) carrying 13–18 of the 34 possible effect alleles. Only 2.9% of the individuals carried 10 or fewer effect alleles, and 3.2% carried ≥21 (Fig. 1). We did not weight the effect alleles by their effect size, which has been suggested to have only a limited effect (40), to allow comparison with the nonweighted score reported for adults of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study. The latter represents the largest population-based study (N = 20,431) thus far in which the association of variants in all 12 loci identified in GWA studies for BMI have been examined in a consistent manner and the only study that has additionally reported their cumulative association with BMI and waist circumference (39). Given its large sample size, effect sizes are likely stable and representative. An alternative GPS (GPS-12) was calculated in EYHS, which contained 12 variants representing the 12 loci discovered in GWA studies for BMI (Fig. 3) (39). Associations of GPS-17 and GPS-12 with continuous anthropometric traits and the risk of obesity and overweight were examined using general linear model and logistic regression analyses, respectively. Differences in effect size of the GPS-12 between children/adolescents and adults were examined by estimating the amount of heterogeneity between the two groups.

All analyses were adjusted for sex, age, age-group, country, and maturity, including BMI, which was still significantly associated with age and sex after application of the LMS method. Associations with sum of skinfolds and waist circumference were additionally adjusted for height. For the GPS-17, interactions with sex, age-group, country, habitual physical activity, and the time spent on moderate and vigorous intensity physical activity were tested via inclusion of product terms in the model.

To increase the statistical power to detect an association, a meta-analysis using inverse variance weighted–fixed-effect models was performed for single-SNP associations with BMI. Summary statistics from the current study were meta-analyzed with those from two recently reported studies examining a cohort of children of the Children's Hospital of Philadelphia (CHP) (N = 6,078) (28) and the Avon Longitudinal Study of Parents and Children

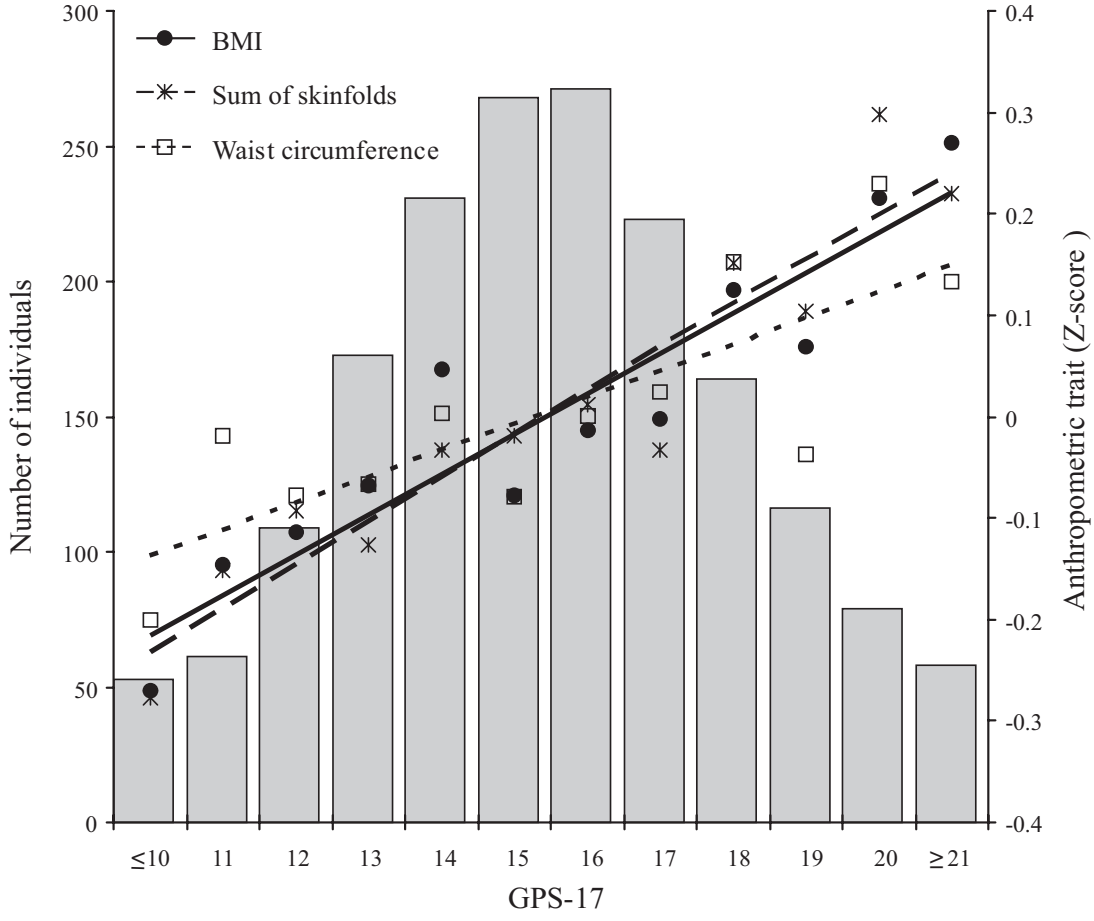

FIG. 1. Distribution of the GPS-17 and cumulative effects of the effect alleles from the 17 obesity susceptibility variants on inverse normally transformed BMI, sum of skinfolds, and waist circumference.

(ALSPAC) (N = 4,951) (20) for SNPs in loci identified in GWA studies for BMI. The meta-analysis included a maximum sample of 13,071 children and adolescents for variants in or near *NEGR1*, *TMEM18*, *GNPDA2*, *MTCH2*, *SH2B1*, *FTO*, *MC4R*, and *KCTD15*, for which data were available from EYHS, ALSPAC, and CHP, and 8,120 children and adolescents for variants in or near *SEC16B*, *ETV5*, *BDNF* and *BCIN3D*, for which data were available from EYHS and CHP only. Five SNPs were identical to those studied in the EYHS. For eight SNPs, the CHP and/or ALSPAC studies had reported results on proxy SNPs that were either in complete linkage disequilibrium (r^2 = 1; three SNPs) or high linkage disequilibrium (r^2 = 0.8–1.0; four SNPs). For the *KCTD15* locus, the CHP study reported on a variant of which linkage disequilibrium with the variant chosen in EYHS and ALSPAC was somewhat lower but still acceptable (r^2 = 0.64) (supplementary Table 2). Effect sizes observed in the meta-analysis in children and adolescents were compared with those reported recently in adults from the EPIC-Norfolk study, a large population-based sample (N = 20,431) in which the associations of variants in the 12 obesity susceptibility loci identified in GWA studies for BMI with BMI and waist circumference were recently reported (39).

Statistical analyses were performed using SAS, version 9.1, for Windows (SAS Institute, Cary, NC). STATA software was used for the meta-analysis and to compare effect sizes of children/adolescents and adults (metan), as well as to determine the power to detect such a difference in effect size (sampsi) (version 10; StataCorp, College Station, TX). A two-sided P value ≤0.05 was considered statistically significant.

Quanto, v1.1.1 (http//hydra.usc.edu/gxe), was used to estimate the smallest effect size detectable with a power of 80% and an α-level of 5% (supplementary Fig. 1*A*), as well as to estimate the power to detect association as a function of the frequency of the effect allele—both assuming an additive model (supplementary Fig. 1*B*).

RESULTS

The association of 15 of the 17 obesity susceptibility SNPs with BMI, sum of skinfolds, and waist circumference was directionally consistent with results reported in the original GWA studies, 7 of which reached statistical significance (Table 2). Variants in/near *TMEM18* and *SEC16B* showed the largest effect size for all three continuous traits (Table 2 and supplementary Fig. 2). For both loci, effect sizes were twofold larger for associations with BMI and sum of skinfolds than for waist circumference. For rs2605100 near *LYPLAL1*, effect sizes were fivefold larger for associations with sum of skinfolds and waist circumference than for association with BMI (Table 2 and supplementary Fig. 2). Associations with sum of skinfolds and waist circumference remained significant after additionally adjusting for BMI (effect size 0.047 and 0.050 SD/allele; P value = 0.0035 and 0.0095, respectively). Associations with obesity risk were most pronounced for variants near *TMEM18* and *ETV5* (supplementary Table 3 and supplementary Fig. 3). Variants in/near *TMEM18* and *BCIN3D* were significantly associated with greater height (Table 2).

Based on effect allele frequencies (supplementary Table 1) and effect sizes for BMI reported earlier in children/adolescents (Fig. 2), the power to detect single SNP associations with anthropometric traits in EYHS alone ranged from <10% for variants in/near *ETV5*, *BDNF* (SNP 2), *MTCH2*, and *SH2B1* to 80% for the SNP in *FTO* (supplementary Fig. 1). This may explain why few associations reached statistical significance. The meta-analysis in up to 13,071 children and adolescents, however, showed significant associations with BMI for 9 of 13 variants (Fig. 2). There was little heterogeneity in effect size across the

three studies except for the near-*NEGR1*, *SEC16B*, *FTO*, and near-*MC4R* variants ($P_{\text{heterogeneity}}$ = 0.13, 0.045, 0.006, and 0.069, respectively). The most pronounced effect on BMI was observed for the near-*TMEM18* variant (0.098 SD/allele [95% CI 0.07–0.13]), followed by variants in or near *FTO* (0.076 [0.05–0.10]), *SEC16B* (0.068 [0.03–0.10]), and *MC4R* (0.067 [0.04–0.09]) (Fig. 2). Variants in/near *ETV5*, *BDNF* (SNP 2), *MTCH2*, and *SH2B1* were not significantly associated with BMI in the meta-analysis.

The power to detect a difference in effect size between children/adolescents and adults was low (5–47%), and differences in effect size ranging from 0.045 to 0.069 SD/allele between age-groups could be detected with 80% power (supplementary Table 1). Whereas no differences reached statistical significance (Fig. 3), the associations tended to be more pronounced in children/adolescents than in adults for variants near *KCTD15*, *SEC16B*, and *TMEM18* ($P_{\text{heterogeneity}}$ = 0.086, 0.11, and 0.16, respectively). The effect size of the *BDNF* variant (rs925946), on the other hand, was twice as large in children and adolescents as that in adults ($P_{\text{heterogeneity}}$ = 0.14) (Fig. 3).

The GPS-17, which examines the cumulative effects of the 17 SNPs in EYHS, was significantly associated with BMI (effect size 0.034 SD/allele [95% CI 0.018–0.050]; $P = 3.6 \times 10^{-5}$), sum of skinfolds (0.039 [0.024 - 0.053]; $P = 1.7 \times 10^{-7}$), and waist circumference (0.022 [0.011–0.034]; $P = 1.7 \times 10^{-4}$) (Table 2), explaining 0.8, 1.1, and 0.4% of their variance, respectively. The 3.2% (N = 58) of individuals who carried 21 or more effect alleles had a BMI that was 0.51 SD, a sum of skinfolds that was 0.28 SD, and a waist circumference that was 0.35 SD larger than the 2.9% (N = 53) of individuals who carried 10 or fewer effect alleles (Fig. 1). The associations of the GPS-12, which includes only the 12 variants of the GPS used in the EPIC-Norfolk study for adults (N = 20,431), were slightly more pronounced; 0.044 SD/allele for BMI (95% CI 0.025–0.063), 0.043 for sum of skinfolds (0.026–0.061), and 0.025 for waist circumference (0.011–0.039). These effect sizes were similar to those reported for adults of the EPIC-Norfolk study (i.e., 0.039 SD/allele for BMI [95% CI 0.031–0.047] and 0.033 for waist circumference [0.025–0.041]) (39).

The GPS-17 did not show a significant association with height (effect size 0.012 SD/allele [95% CI −0.004 to 0.029]; P = 0.15), whereas the GPS-12 did (0.023 [0.003–0.043]; P = 0.024) (Table 2). The latter association was substantially attenuated after removing the near-*TMEM18* and *BCIN3D* variants from the score (effect size 0.015 SD/allele; P value 0.19), suggesting that the association was largely driven by these variants.The association of the GPS-17 and the risk of obesity and overweight showed that each additional effect allele was associated with a 1.12-fold increased odds of obesity (95% CI 1.04–1.22) and a 1.09-fold increased odds of overweight (1.04–1.15) (supplementary Table 3). Consistent with the observation for continuous traits, the GPS-12 showed somewhat more pronounced effects than the GPS-17, with 1.18-fold (1.08–1.30) and 1.13-fold (1.06–1.20) increased odds for obesity and overweight per additional effect allele, respectively. These effects were similar to those reported for adults, i.e., 1.11 (1.08–1.14) and 1.06 (1.04–1.07) for obesity and overweight, respectively (39).

We found no evidence for sex-, age-group–, or country-specific effects of the GPS-17 on BMI, sum of skinfolds, or waist circumference or on the risk of obesity or overweight ($P > 0.4$ for product terms). Furthermore, no

TABLE 2
Associations of the individual obesity susceptibility SNPs and the GPS-12 and GPS-17 with anthropometric traits in children and adolescents of the EYHS (n = 2,042)

		BMI			Sum of skinfolds			Waist circumference			Height		
SNP	nearest gene	Effect size (SD/allele)	SE	P	Effect size (SD/allele)	SE	P	Effect size (SD/allele)	SE	P	Effect size (SD/allele)	SE	P
rs2815752	*NEGR1*	0.081	0.03	8.9×10^{-3}	0.052	0.03	0.06	0.062	0.02	4.8×10^{-3}	0.031	0.03	0.32
rs10913469	*SEC16B*	0.136	0.04	4.2×10^{-4}	0.126	0.03	2.5×10^{-4}	0.075	0.03	6.8×10^{-3}	−0.009	0.04	0.82
rs260100*	*LYPLAL1*	0.012	0.03	0.73	0.060	0.03	3.9×10^{-2}	0.060	0.02	1.0×10^{-2}	−0.027	0.03	0.42
rs6548238	*TMEM18*	0.148	0.04	1.9×10^{-4}	0.150	0.04	2.5×10^{-5}	0.068	0.03	1.6×10^{-2}	0.085	0.04	3.8×10^{-2}
rs7647305	*ETV5*	0.048	0.04	0.21	0.028	0.03	0.42	0.030	0.03	0.27	0.034	0.04	0.39
rs10938397	*GNPDA2*	0.051	0.03	0.08	0.061	0.03	2.5×10^{-2}	0.041	0.02	0.06	−0.004	0.03	0.89
rs987237*	*TFAP2B*	0.069	0.04	0.06	0.042	0.03	0.21	0.056	0.03	3.5×10^{-2}	−0.025	0.04	0.50
rs545854*	*MSRA*	−0.080	0.04	0.07	0.001	0.04	0.99	−0.050	0.03	0.10	−0.033	0.04	0.47
rs1488830	*BDNF*	0.037	0.04	0.35	0.028	0.03	0.41	0.003	0.03	0.91	0.026	0.04	0.52
rs925946	*BDNF*	0.057	0.03	0.08	0.065	0.03	2.7×10^{-2}	0.034	0.02	0.14	0.052	0.03	0.12
rs10838738	*MTCH2*	−0.017	0.03	0.61	−0.012	0.03	0.67	0.001	0.02	0.97	−0.042	0.03	0.21
rs7138803	*BCDIN3D*	0.045	0.03	0.13	0.029	0.03	0.28	0.023	0.02	0.29	0.078	0.03	1.3×10^{-2}
rs10146997*	*NRXN3*	0.022	0.04	0.56	0.029	0.03	0.38	0.018	0.03	0.51	0.039	0.04	0.31
rs805138	*SH2B1*	0.012	0.03	0.68	0.031	0.03	0.26	0.004	0.02	0.87	0.004	0.03	0.91
rs1121980	*FTO*	0.020	0.03	0.47	0.033	0.03	0.22	0.004	0.02	0.85	0.009	0.03	0.77
rs17782313	*MC4R*	0.013	0.04	0.72	0.015	0.03	0.65	−0.006	0.03	0.83	0.004	0.04	0.93
rs11084753	*KCTD15*	0.020	0.03	0.54	0.023	0.03	0.41	0.009	0.02	0.69	0.039	0.03	0.24
GPS-12		0.044	0.01	7.1×10^{-6}	0.043	0.01	7.2×10^{-7}	0.025	0.01	3.4×10^{-4}	0.023	0.01	2.4×10^{-2}
GPS-17		0.034	0.01	3.6×10^{-5}	0.039	0.01	1.7×10^{-7}	0.022	0.01	1.7×10^{-4}	0.012	0.01	0.15

Results were obtained using multiple linear regression analysis assuming an additive effect while adjusting for sex, age, age-group, country, and maturity. The sum of skinfolds and waist circumference were additionally adjusted for height. *Located in or near loci identified in GWA studies for waist circumference; all other SNPs were identified in GWA studies for BMI.

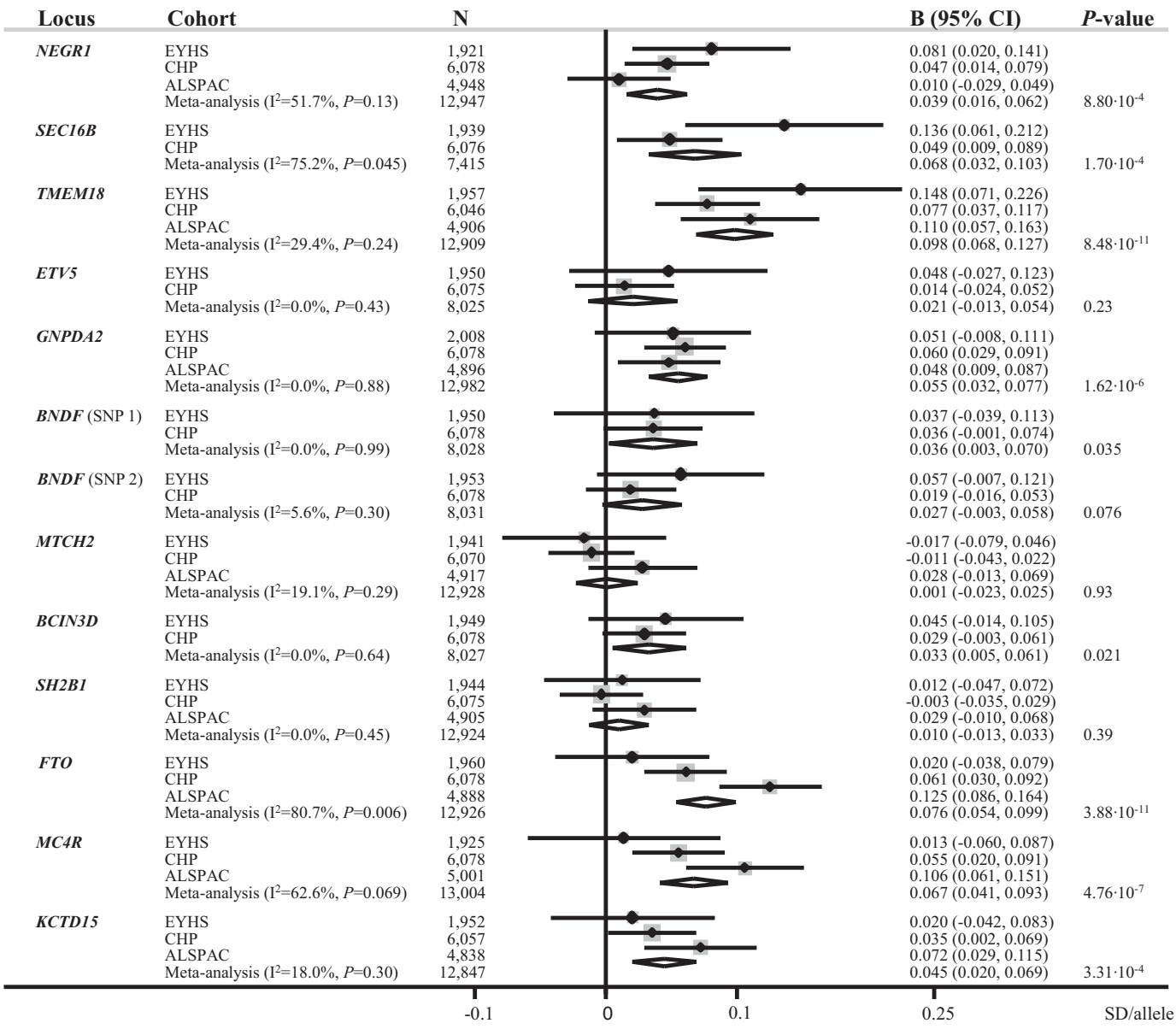

FIG. 2. Meta-analysis for summary statistics of the association between variants in the obesity susceptibility loci with BMI in the EYHS, CHP (28), and ALSPAC (20). I^2 and P values for heterogeneity between cohorts are provided. For associations within cohorts, effect sizes (B) and 95% CIs are shown; for the meta-analysis, P values for effect sizes are additionally provided.

significant interactions were observed between either overall physical activity or the fraction of time spent on moderate and vigorous intensity physical activity and the GPS-17 for any of these anthropometric traits ($P > 0.15$ for product terms).

DISCUSSION

Nine of 13 variants in the obesity susceptibility loci identified by GWA studies in adults also showed significant associations with BMI in a meta-analysis of up to 13,071 children and adolescents. In the EYHS, for which we had data on 16 obesity susceptibility loci, BMI, skinfolds, and waist circumference, effect sizes were similar across traits for most variants. Each additional effect allele in the GPS-17, which combined the data of 17 variants in 16 obesity susceptibility loci, increased BMI by 0.034 SD, sum of skinfolds by 0.039 SD, and waist circumference by 0.022 SD.

Four of the 13 variants included in the meta-analysis for BMI showed a moderate to high heterogeneity in effect size between studies ($I^2 > 50\%$), which is more than would be expected based on chance. The near-*NEGR1* and *SEC16B* variants were more strongly associated with BMI in EYHS than reported earlier in children and adolescents (20,28), whereas the variants in/near *FTO* and *MC4R* were strongly and significantly associated with BMI in ALSPAC (20) and CHP (28) but not in EYHS.

Overall, the effect size for BMI was largest for the near-*TMEM18* variant (0.098 SD/allele), followed by the *FTO*, *SEC16B*, and near-*MC4R* variants (0.076, 0.068, and 0.067 SD/allele, respectively), and ranged from 0.033 to 0.055 SD/allele for the five remaining variants that reached significance. In adults, the *FTO* locus has the largest effect of all currently established obesity susceptibility loci (19,20). Our study was not sufficiently powered to examine whether differences in effect size between the near-

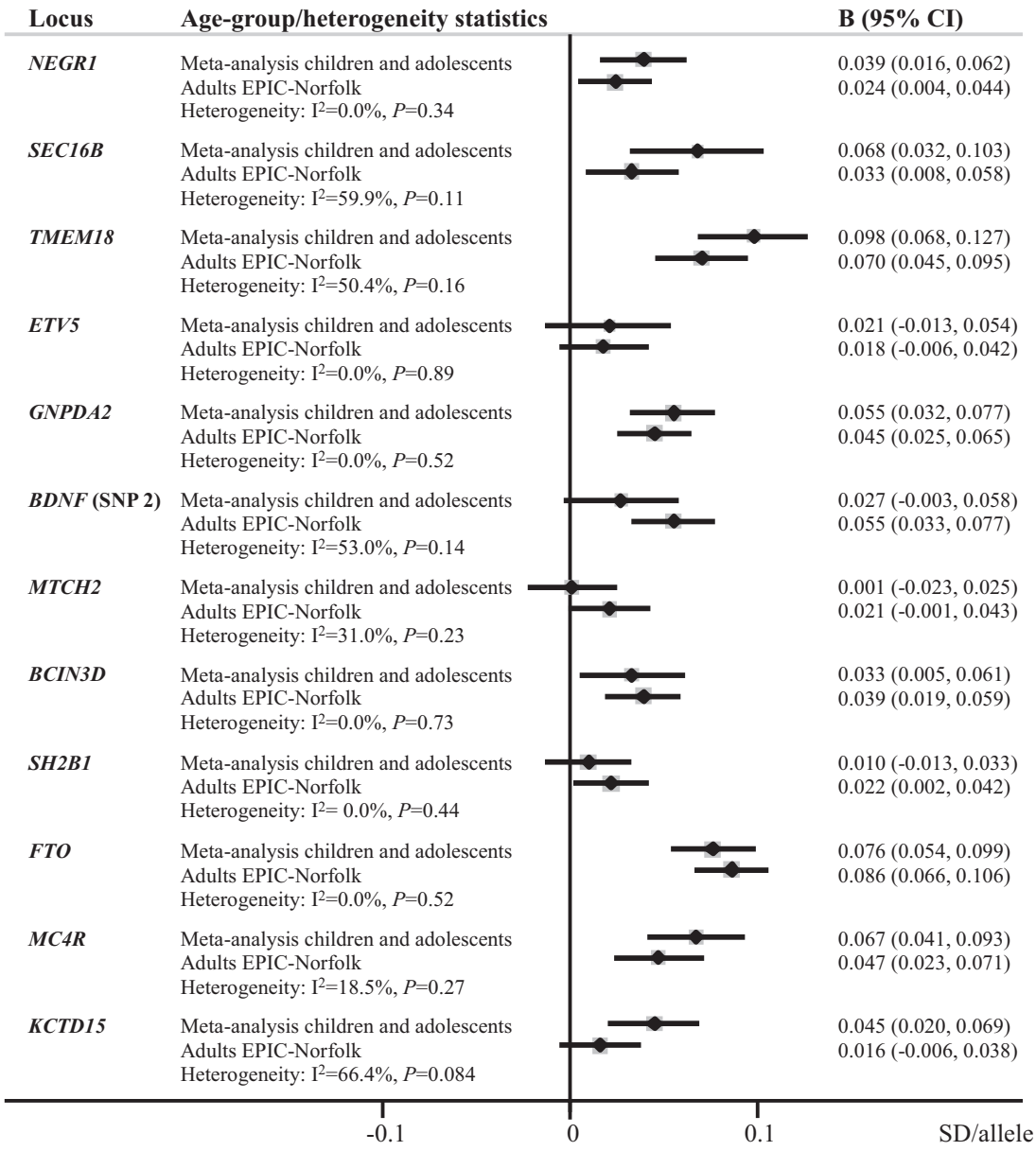

FIG. 3. Association of variants in the obesity susceptibility loci with BMI after meta-analysis in a maximal sample of 13,071 (*NEGR1*, *TMEM18*, *GNPDA2*, *MTCH2*, *SH2B1*, *FTO*, *MC4R*, and *KCTD15*) or 8,120 (*SEC16B*, *ETV5*, *BDNF*, and *BCIN3D*) children and adolescents compared with 20,431 adults from the EPIC-Norfolk cohort. Effect sizes (*B*) and 95% CIs are shown; I^2 and *P* values for heterogeneity between age-groups are additionally provided.

TMEM18 and *FTO* variants were statistically significant. Larger studies, as well as longitudinal studies, are needed to identify changes in effect sizes during the life course. A recent longitudinal study on the life course effects of the *FTO* and near-*MC4R* loci suggests that, at least for these loci, effects strengthen during childhood and adolescence, peak at age 20 years, and weaken during adulthood (24).

Of the four variants that were not significantly associated with BMI, the association of rs925946 in *BDNF* (P = 0.076) was directionally consistent with that observed in adults (19,39,41), whereas for the near-*MTCH2* variant the association was completely absent. For variants near *ETV5* and *SH2B1*, results remain inconclusive; associations were not significant in the meta-analysis but were directionally consistent with those reported earlier in adults (19,20,39,41). Studies of larger samples may be required to confirm an association of these variants with anthropometric traits in children.

In EYHS, rs2605100 was associated with sum of skinfolds and waist circumference but not with BMI. This SNP, which is located ~259 kb upstream of *LYPLAL1*, was also associated with waist circumference but not with BMI in adult women (22). The present study extends these results, strongly suggesting that the locus represents a pure abdominal obesity hit that is already seen in children. This is an important finding because waist circumference is independently associated with the risk of death in adults (42) and is already associated with elevated concentrations of lipids and insulin in children (43). Contrary to the original study in adults, no evidence was observed for a sex-specific effect of the near-*LYPLAL1* variant on waist circumference ($P_{\text{interaction term}}$ = 0.50) in children and adolescents. The *LYPLAL1* gene encodes a lysophospholipase-like 1 protein that may act as a triglyceride lipase and is upregulated in subcutaneous adipose tissue of obese individuals (44).

No significant differences in effect size were observed for BMI between children/adolescents and adults of the EPIC-Norfolk study (39). However, effect sizes tended to be 1.4- to 2.8-fold higher in children/adolescents than in adults for variants in/near *SEC16B*, *TMEM18*, and *KCTD15* and twofold lower for rs925946 in *BDNF*. This discrepancy may reflect a truly different association with adiposity between age-groups but may also result from a lack of comparability of the phenotype. The GPS-12 showed that the cumulative or average effect of 12 obesity-susceptibility loci on BMI and waist circumference was very similar in children/adolescents and adults (39).

As was reported earlier in adults of the EPIC-Norfolk study, the GPS-12 and GPS-17 tended to be more strongly associated with BMI than with waist circumference. The GPS-17 and GPS-12 both explained ~1% of the inter-individual variation in BMI and sum of skinfolds and ~0.4% of the variation in waist circumference. This suggests that the predictive value for risk of obesity based on these variants is likely very low in children and adolescents, consistent with observations in adults (39). In the EYHS, effect sizes were larger for the GPS-12 than the GPS-17 for all anthropometric traits. Apparently, SNPs identified in GWA studies for BMI are on average more strongly associated with (abdominal) obesity than SNPs identified in GWA studies for waist circumference in children/adolescents.

In contrast with previous results in adults, the GPS-12 was additionally associated with height. However, this association was largely attenuated after removal of the near-*TMEM18* and *BCIN3D* variants from the score. Moreover, the effect size of the GPS-12 for BMI was almost twice that of height, indicating a larger effect on body mass than on height. Objectively measured habitual physical activity did not modify the association of the GPS-17 with anthropometric traits in EYHS. This may result from a relatively high level of physical activity in children and adolescents compared with adults. Physical activity measured by Actigraph in EYHS was comparable with earlier reports in children from the ALSPAC and SPEEDY cohorts (45,46) but higher than reported in adults (47,48). Alternatively, the lack of interaction may result from the relatively small sample in which objective data on physical activity were available.

At this stage, little is known about the mechanisms responsible for the association of these loci with anthropometric traits. Given that *NEGR1*, *TMEM18*, *GNPDA2*, *FTO*, *MC4R* and *KCTD15* are all expressed at high levels in the hypothalamus (20,49,50), the associations may result from a neuronal effect on energy balance. However, many of these loci are located near multiple genes, and before a neuronal influence on energy balance can be confirmed, the causal variants will have to be identified.

In conclusion, common variants in obesity susceptibility loci identified by GWA studies in adults have, on average, similar effect sizes on anthropometric traits and risk of obesity in children and adolescents, with variants in the *TMEM18* locus showing the largest effect. Although the association of some variants may not be constant throughout life, this discrepancy levels off when their cumulative effect is evaluated.

ACKNOWLEDGMENTS

This study received funding from the following sources: the Danish Heart Foundation; the Danish Medical Research Council Health Foundation; the Danish Council for Sports Research; the Foundation in Memory of Asta Florida Bolding Renée Andersen; the Faculty of Health Sciences, University of Southern Denmark; and the Estonian Science Foundation and the Medical Research Council, U.K.

No potential conflicts of interest relevant to this article were reported.

M.d.H. designed the study, outlined the analysis plan, analyzed the data, interpreted the results, wrote the manuscript, and contributed to the discussion. U.E. contributed to the discussion and reviewed and edited the manuscript. S.B. contributed to the discussion and reviewed and edited the manuscript. A.G. contributed to the discussion and reviewed and edited the manuscript. J.H.Z. contributed to the discussion and reviewed and edited the manuscript. S.J.S. contributed to the discussion and reviewed and edited the manuscript. K.K.O. contributed to the discussion and reviewed and edited the manuscript. N.J.W. contributed to the discussion and reviewed and edited the manuscript. R.J.F.L. designed the study, outlined the analysis plan, contributed to the discussion, and reviewed and edited the manuscript.

We thank the volunteers in the EYHS, who gave their time to take part in this study. We also acknowledge the EYHS study teams who collected the data used in these analyses.

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