Genetic and environmental effects on body mass index from infancy to the onset of adulthood: an individual-based pooled analysis of 45 twin cohorts participating in the CODATwins study

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Running head: Heritability of BMI in childhood and adolescence

Abbreviations

-2LL= -2 log-likelihood

Δ=change

95% CI= 95 percent confidence interval

A=additive genetic variance component

a^2=the proportion of total variance explained by additive genetic factors, heritability

BMI=body mass index

C=shared environmental variance component

c^2=the proportion of total variance explained by shared environmental factors

d.f.=degrees of freedom

DZ=dizygotic twin

E=unique environmental variance component

e^2=the proportion of total variance explained by unique environmental factors

logBMI= natural logarithm of body mass index

MZ=monozygotic twin

SD=standard deviation

Not a clinical trial

Abstract

Background: Both genetic and environmental factors are known to affect body mass index (BMI), but detailed understanding of how their effects differ during childhood and adolescence is lacking.

Objective: We analyzed the genetic and environmental contributions to BMI variation from infancy to early adulthood and how they differ by sex and geographic regions representing high (North-America and Australia), moderate (Europe) and low levels (East-Asia) of obesogenic environments.

Design: Data were available for 87,782 complete twin pairs from 0.5 to 19.5 years of age from 45 cohorts. Analyses were based on 383,092 BMI measures. BMI variation was decomposed into genetic and environmental components through genetic structural equation modeling.

Results: The variance of BMI increased from 5 years of age along with increasing mean BMI. The proportion of BMI variation explained by additive genetic factors was lowest at 4 years of age in boys (a^2=0.42) and girls (a^2=0.41) and then generally increased to be 0.75 both in boys and girls at 18 years of age. This was because of a stronger influence of environmental factors shared by co-twins at these ages. After 15 years of age, the effect of shared environment was not observed. The sex-specific expression of genetic factors occurred already in infancy, but was prominent at 13 years and later ages. The variance of BMI was highest in North-America and Australia and lowest in East-Asia, but still the relative proportion of genetic variation to total variation was roughly similar across different regions.

Conclusions: Environmental factors shared by co-twins affect BMI in childhood and during puberty, but little evidence for their contribution was found in late adolescence. Our results suggest that genetic

25 factors play a major role in the variation of BMI in adolescence in populations of different ethnicities
26 and exposed to different environmental factors predisposing to obesity.
27
28 Key words: BMI, children, genetics, twins, international comparisons
29

Introduction

Childhood obesity is a major public health problem throughout the world. In the USA, more than 30% of children and adolescents were classified as overweight or obese in 2011-2012 (1), and childhood obesity is also a growing problem in many developing countries (2). Previous twin and family studies have shown that both genetic and environmental factors contribute to obesity. As early as in 1923, the tendency toward obesity was found to vary between families, suggesting a role of genetic factors (3), and a recent meta-analysis of 31 twin studies showed that for adults the heritability estimates of body mass index (BMI), i.e. total BMI variation explained by genetic variation, ranged from 47% to 80% (4). However, much less is known about the variation of the genetic architecture of BMI during childhood and adolescence. A meta-analysis of nine twin studies found that the environmental factors shared by co-twins contributed to BMI in infancy and early childhood, but were not evident after mid-childhood when genetic factors become more important (5). An individual-based analysis of four twin cohorts found shared environmental contributions to BMI from 3 to 8 years of age, which disappeared at 9 to 19 years of age (6). Somewhat different results were found in a Finnish longitudinal study, which found that shared environment affected BMI at 11-12 and 14 years of age but was no longer evident at 17 years of age (7). Thus, previous twin studies suggest that the effect of shared environmental factors influencing BMI disappears in late adolescence when genetic factors explain around 80% of the variation of BMI.

However, little is known about the universality of these results considering that the two previous multinational analyses were primarily based on Western populations, with the exception of one Korean twin cohort. A multinational study pooling eight cohorts of adolescent twins found that the heritability estimates of BMI were approximately similar in Western and East-Asian populations even when the

mean BMI and total variation of BMI were higher in Western populations (8). However, it is still unknown whether the genetic architecture is similar at earlier ages. Furthermore, because of a lack of data in the previous multinational analyses (5,6), it is still unclear how genetic influences on BMI differ between boys and girls over infancy and childhood.

To answer these questions on differences in the genetic architecture of BMI during childhood and adolescence, we conducted an individual-based analysis pooling twin cohorts from different countries. Our very large sample size allowed us to estimate the proportions of BMI variation explained by genetic and environmental factors using 1-year age groups in boys and girls separately. We aimed (i) to estimate how the genetic architecture of BMI changes from infancy to the onset of adulthood, (ii) to study age and sex-differences in the contributions of genetic and environmental factors, and (iii) to analyze whether these estimates are similar in different geographic-cultural regions representing different levels of obesogenic environment.

Subjects and methods

The data were derived from the CODATwins (COllaborative project of Development of Anthropometrical measures in Twins) database described elsewhere (9). Briefly, the CODATwins project was intended to collect height and weight measurements from all twin cohorts in the world having information both on monozygotic (MZ) and dizygotic (DZ) twins. For the present analysis, we selected 46 twin cohorts from 20 countries having at least 50 twin individuals having height and weight measures available from 0.5 to 19.5 years of age. We divided these cohorts into three geographic-cultural regions: Europe, North-America and Australia, and East-Asia. The prevalence of obesity and overweight is lowest in East-Asia, thus representing a lesser obesogenic environment, and highest in

North-America and Australia thus representing a more obesogenic environment (10). We had 20 cohorts from Europe, 15 cohorts from North-America and Australia and eight cohorts from East-Asia. Furthermore, we had one cohort from Africa and two from the Middle-East. However, during the course of the study, we found that in a large Chinese National Twin Cohort Study, the heritability estimates of BMI were substantially lower than in other East-Asian cohorts as also reported previously (11). Give this heterogeneity, we presented the East-Asian results both without (main results) and with (supplemental results) this cohort.

The names of the cohorts included in the main analyses are given in the footnotes of **Supplemental table 1**, and more information on these cohorts is available elsewhere (9). We eliminated impossible values and outliers in each age and sex group based on visual inspection allowing the BMI distribution to be positively skewed. We removed 1151 measurements as outliers representing 0.3% of the measurements. Further we selected only one observation per twin individual for each 1-year age group. The construction of the study cohort is presented as flow diagram in Supplemental figure 1. After these exclusions, we had 383,092 BMI values from 180,390 twin individuals (46% females). Thus, on average, we had two BMI measures per individual, but the number of longitudinal measures varied between cohorts as described elsewhere (9). For 87,782 twin pairs, we had information for both co-twins (36% MZ twins, 37% same-sex DZ and 27% opposite-sex DZ twins) and for 4826 twin pairs, information only for another twin. These incomplete twin pairs were removed from all genetic analyses. To test the effect of having multiple measures for the same individual, we repeated the genetic analyses after randomly selected only one observation for each twin pair.

The number of complete twin pairs by age, zygosity and region is presented in Supplemental table 1. The number of BMI measures varied from 6,174 at six years of age to 31,708 at one year of age. The

largest number of measures was available from Europe (N=278,479), followed by North-America and Australia (N=66,204), and finally East-Asia (N=36,528). In the additional analyses including the Chinese National Twin Cohort Study, the number of BMI measures in East-Asia was 55,756. From all BMI measures, 57% were done in the year 2000 or later and 88% in the year 1990 or later. The majority of the BMI measures were based on self-report (66%) or parental report (20%) and only minority were clinically measured (14%). Because the collaborators were asked to send height and weight measures, no missing cases existed for BMI.

The data were analyzed using classical genetic twin modeling based on linear structural equations (12). Genetic twin modeling is based on the fact that MZ twins share virtually the same DNA sequence whereas DZ twins share, on average, 50% of their genes identical-by-descent. DZ within-pair correlations of BMI were more than half of the MZ correlations suggesting the presence of environmental effects shared by co-twins (Supplemental table 1). Thus we decomposed the trait variation into (i) an additive genetic component (A), which is the sum of the effects of all alleles affecting the trait, (ii) a common environmental component (C) including all environmental factors shared by co-twins and (iii) an unique environmental component (E) reflecting the effects of all environmental factors that make co-twins dissimilar including measurement error. The additive genetic correlation is 1 between MZ co-twins and 0.5 between DZ co-twins, whereas the correlation between the shared environmental factors is 1 and that between unique environmental factors 0 both in MZ and DZ co-twins. All genetic models were fitted with the OpenMx package, version 2.0.1, which is part of the R statistical platform (13). All parameter estimates and corresponding 95% confidence intervals (95% CI) were estimated by raw-data maximum likelihood method. Heritability is defined as the proportion of total variation accounted for by additive genetic variation.

126 BMI showed increasing right skewness from 1 to 18 years of age, and thus we used a log-
127 transformation to normalize the BMI distribution at all ages when calculating the relative proportions
128 of genetic and environmental variation. Further, we adjusted BMI for age and study cohort differences
129 within each 1-year age and sex group by calculating regression residuals. Cohort differences, i.e.
130 differences in mean BMI between cohorts, were adjusted for by including a group of dummy variables
131 in the regression models. We tested the technical assumptions of twin modeling by comparing the ACE
132 model to the saturated model, which specifies an unconstrained model for trait means, variances and
133 co-variances between co-twins. The fit of nested models was compared by calculating differences in -2
134 log-likelihood values (Δ-2LL), which follows the χ^2-distribution with a difference in degrees of
135 freedom (Δd.f.) that corresponds to the difference in the number of free parameters estimated. As
136 reported previously, DZ twins had slightly higher mean BMI as well as higher standard deviation (SD)
137 compared to MZ twins at some ages over childhood and adolescence (14). We therefore allowed
138 different means for MZ and DZ twins, but in the genetic models constrained variance components to be
139 the same in all zygosity groups within sex.
140
141 The model fit results are presented in **Supplemental table 2**. At most of the ages, the fit of the full
142 ACE model was significantly poorer than the fit of the saturated model, because of the higher SD of
143 BMI in DZ twins. Even when the differences were small, they were statistically significant because of
144 our very large sample size. Moreover, we tested possible sex differences by constraining the A, C and
145 E parameter estimates to be equal in boys and girls. We found that at most ages, the fit of this model
146 was poor suggesting that these variance components differed between sexes. We also tested whether
147 this difference was because of different variances of logBMI in boys and girls by fitting a scaled model
148 allowing different sizes of variance components but fixing the relative size of these components to be

equal. This model also showed significant differences compared to the full ACE model. Accordingly, we presented results separately for boys and girls. Finally, we tested whether a partly different set of genes affects BMI in boys and girls by fitting a sex-limitation model. This model tests whether the genetic correlation of opposite-sex DZ twins is lower than 0.5. We found evidence of a sex-specific genetic effect at some ages seen also as lower opposite-sex DZ correlations (Supplemental table 1 and 2). Therefore, sex-specific genetic effects were allowed at all ages.

The pooled analysis was approved by the ethical board of the Department of Public Health, University of Helsinki. The data collection procedures of participating twin cohorts were approved by local ethical boards following the regulations in each country. Only anonymized data were delivered to the data management center at University of Helsinki (9).

Results

Mean BMI decreased from infancy, reaching a nadir at 5 years of age in boys and girls before increasing until 19 years of age in the pooled data (**Table 1**). Along with the increasing mean BMI, the variance of BMI also started to increase after 5 years of age. The increase in mean BMI started in Europe after 5 years of age, but slightly later in East-Asia (6 years) and in North-America and Australia (7 years). Boys had higher BMI than girls from 1 to 4 years of age and again from 17 to 19 years of age, but at other ages sex differences were small. In Europe and North-America and Australia, BMI variances were higher in girls than in boys, especially in adolescence and early adulthood. North-American and Australian boys and girls had the highest mean BMI at all ages, and this difference increased after 7 years of age. European boys and girls had also slightly higher BMI than East-Asians

at most ages. Similar differences were also seen in the BMI variation, and at all ages variances were highest in North-America and Australia.

Figure 1 presents the relative proportions of logBMI variation explained by additive genetic, shared environmental and unique environmental factors in the pooled data. The heritability estimates of logBMI was lowest in boys (a^2=0.42 95%CI 0.37-0.47) and girls (a^2=0.41 95%CI 0.35-0.46) at 4 years of age. They started to increase after 8 years of age, and in 19 years of age they were 0.75 both in boys (95% CI 0.67-0.80) and girls (95% CI 0.67-0.82); the heritability was highest in boys at 10 (a^2=0.85 95% CI 0.78-0.88) and in girls at 16 years of age (a^2=0.84 95% CI 0.78-0.85), but these estimates did not differ statistically significantly from the heritability at 19 years of age. The differences in the heritability estimates were explained by changes in the relative proportions of shared environmental variation (panels C and D). The proportion of logBMI variation accounted for unique environmental factors varied between 0.10 and 0.20. Some of these differences were statistically significant, but unique environmental variation did not show any clear age pattern. The age pattern was generally similar in boys and girls in spite of the significant sex differences in the relative variance components at most ages (Supplemental table 2). In the sensitivity analyses where we selected randomly only one observation per individual, the variation in the heritability estimates between ages increased. However also in these analyses, the heritability estimates were statistically significantly lower in mid-childhood than in late adolescence and onset of adulthood (Supplemental table 4).

Genetic correlations within opposite-sex DZ pairs were generally lower than 0.5, suggesting sex-specific genetic effects, especially in adolescence (**Figure 2**). Wide upper 95% CIs were seen at ages 10, 12 and 14. This was because of difference in shared environmental variation between boys and girls at these ages; if this difference increases it can compensate the effect of increasing additive genetic

196 correlation for opposite-sex pairs in the statistical model. However, higher additive genetic correlation
197 in opposite-sex than in same-sex DZ pairs is not biologically plausible.
198
199 We then fitted similar univariate models for logBMI by region. Only the estimates of additive genetic
200 factors are presented in **Figure 3**, but all estimates with 95% CIs are available in **Supplemental table**
201 **3**. In Europe and North-America and Australia, the age-related differences in the heritability estimates
202 were largely similar to those in the pooled data. In Europe the lowest heritability was found at 4 years
203 of age in boys (a^2=0.41 95% CI 0.35-0.47) and in girls (a^2=0.42 95% CI 0.35-0.49) whereas in North-
204 America and Australia the heritability was lowest at 2 years of age in boys (a^2=0.35 95% CI 0.16-0.57)
205 and 4 years of age in girls (a^2=0.27 95% CI 0.18-0.37). After childhood, the heritability estimates
206 generally increased and at 19 years of age were 0.78 (95% CI 0.73-0.80) in boys and 0.75 (95% CI
207 0.66-0.82) in girls in Europe and 0.65 (95% CI 0.55-0.77) and 0.82 (95% CI 0.67-0.85), respectively,
208 in North-America and Australia; the heritability estimates were even higher at some other ages in
209 adolescence, but they did not differ statistically significantly from the estimates at 19 years of age. In
210 East-Asia, the pattern was not as clear due to the smaller sample size but showed some increase in the
211 heritability estimates. However especially after 12 years of age, the number of twin pairs was small in
212 this region leading to wide 95% CIs. In spite of the roughly similar age patterns, the proportions of
213 logBMI variation explained by genetic and environmental factors were significantly different between
214 the regions at all ages (Supplemental table 2). When the Chinese National Twin Cohort Study was
215 included in the East-Asia region, the proportion of genetic factors decreased and shared environmental
216 factors increased dramatically; the change was from 0.1 to 0.4 unit depending on the age group
217 (Supplemental table 5).
218
219 **Discussion**

In this very large study of nearly 400,000 BMI measures in nearly 88,000 complete twin pairs from 20 countries, we demonstrated increasing heritability in BMI from mid-childhood to the onset of adulthood, such as suggested previously by two international studies (5,6). The increasing role of genetic factors are consistent with previous molecular genetic studies which have found that the variants of FTO gene, which account for the largest fraction of variance in BMI among the known candidate genes for BMI (15), and other obesity related candidate genes have increasing effects on BMI after 6 years of age (16-19). Evidence of increasing heritability of BMI from 4 to 10 years of age has also been reported in genome-wide complex trait analysis (20).

However, this increasing role of genetic factors in BMI with age does not negate the importance of health behaviors associated with childhood obesity, as genetic factors can affect BMI by modifying food intake and other behavioral factors. For example, the variants of FTO gene, which act on the actual functional gene IRX3 (21), were found to be associated with food-intake self-regulation and eating styles in childhood which are further associated with weight gain (22). Although not yet conclusive, there is evidence that common genetic risk variants of BMI are active in the hypothalamus, pituitary gland, hippocampus and limbic system, i.e., areas of brain having an important role in appetite regulation, learning, cognition, emotion and memory (23). It has also been found that shared environmental factors have effects on nutritional intake in childhood (24), but they disappear in adulthood when genetic factors become more important (25,26). The increasing proportion of genetic variation in BMI may thus reflect the increasing independence of children from their parents in eating and other behavioral factors associated with the variation of BMI. However, the associations between energy intake and obesity are complex and still an object of debate (27). Differences in DNA methylation have also been found between lean and obese children (28), and epigenetic processes by

244 themselves are in part genetically regulated (29). Therefore, it is possible that part of the genetic
245 variation may be mediated by epigenetic effects.
246
247 We found some evidence for sex-specific genetic contributions to BMI. The lowest genetic correlation
248 within opposite-sex DZ pairs was found at 13 years of age probably coinciding with the onset of
249 puberty. However, a sex-specific genetic contribution was also clear after puberty, which probably
250 reflects the increasing differences in body composition between boys and girls with age (30). This is
251 consistent with the sex-specific genetic contribution in adult BMI found in a study of twin cohorts with
252 opposite-sex twins from 7 countries (31). However, it is noteworthy that lower genetic correlations for
253 opposite-sex pairs were found even in infancy, indicating that a partly different set of genes regulates
254 BMI prior to the major hormonal changes that occur during puberty. This suggests some caution when
255 interpreting results from genetic studies that have relied upon BMI pooling of boys and girls, even
256 while focusing on pre-pubertal children. Otherwise, there were relatively minor differences in the
257 genetic architecture of BMI between boys and girls, and the general age patterns were largely similar.
258
259 When comparing regions, North-American and Australian children and adolescents presented greater
260 means and larger total variation of BMI than their European and East-Asian peers. The relative
261 proportions of genetic and environmental sources of variations were, however, roughly similar in these
262 three regions. These results are consistent with those of previous international twin studies showing
263 larger mean and variance of BMI, yet similar heritability estimates in Caucasian and in East-Asian
264 populations in adolescence (8). Thus, increasing BMI was associated with increasing variation in BMI
265 whereas the proportion of genetic variation was largely similar between the regions. This suggests that
266 genetic factors have an important role in individual differences in BMI in various populations differing
267 in ethnicity, environmental exposures, as well as in their possible interactions. These results are

consistent with studies in Denmark (32) and Sweden (33) suggesting that both total and genetic variation of BMI increased during the obesity epidemic. It is, however, noteworthy that we limited our East-Asian cohorts to affluent populations including the affluent Shandong and Guangdong provinces but excluding poorer areas of China. As reported previously, the heritability estimates of BMI were much lower and common environmental estimates higher in other areas of China (11), which may indicate larger differences between families in nutritional status. This emphasizes the importance of collecting data on twins living under different environmental exposures. Our study cannot reveal whether genetic of environmental factors are behind differences in mean BMI between the regions. However, a recent study found the genetic factors explained a part of differences in mean BMI between European populations, and thus genetic factor may contribute to BMI differences also in our study cohorts in addition to environmental factors (34).

The data used in this study have both strengths and weaknesses. The main strength is the very large sample size allowing an investigation of the change of the genetic and environmental contributions to individual differences in BMI in much more detail than in previous studies. We also have twin participants from different countries, thereby making it possible to stratify the analyses by regions of various ethnicities and obesogenic environments. Individual-based data also have many advantages as compared to literature-based meta-analyses, such as better opportunities for statistical modeling and lack of publication bias. However, even when the large majority of the twin cohorts in the world participated in this project, our data still had only limited power for East Asia, especially in adolescence. Another important limitation is that there were only few data sets available from the Middle East and Africa, and a lack of data from South-America. This underlines the need for new data collection in these geographic regions. There were some violations of the assumption of twin modeling due to the larger variation in DZ twins than in MZ twins at some ages (14). The differences in the

292 variation are, however, small and become statistically significant because of the very large sample size
293 of our data. Finally, we did not have any area-level indicators and classified the cultural-geographic
294 areas as less or more obesogenic based on the prevalence of adult obesity (10). Conceptualizing
295 obesogenic environments is difficult, but it has been suggested that both micro- and macro-level
296 environmental factors affect both food intake and physical exercise (35). More detailed measurements
297 of the physical environment are thus needed to analyze the factors in the environment that potentially
298 modify genetic influences on the development of obesity. It is also a clear limitation that only a fraction
299 of BMI values were based on clinical measures and for most of them we needed to rely on parental or
300 self-reported values.
301
302 In conclusion, we found evidence that environmental factors shared by co-twins contribute to BMI
303 variation in early childhood and during puberty, but their role diminishes before the onset of adulthood.
304 Heritability increased from mid-childhood to the onset of adulthood, which may indicate gene-
305 environment correlation processes, whereby an increasing independence of children from their parents
306 led them to express their behaviors according to their genetic background. Genes affecting BMI were
307 partly sex-specific, even in infancy, with their contribution becoming more prominent during and after
308 puberty. Obesogenic environment is associated with variation of BMI in North-America and Australia
309 as compared to East-Asia, but the relative proportions of genetic and environmental variations were
310 roughly similar. Our results suggest that, in spite of different ethnicities and environmental exposures,
311 genetic factors play a major role behind the variation of BMI in adolescence in affluent societies.

Conflicts of interests

None

Authors' contribution

KaSi, JaKa, ThIASø, DoIBo, FiRa, KiOKy, YMHu and YoYo planned the study design of the CODATwins project. AnBu, ChKa, KiJSa, KeLJa, WeCo, AmEHw, ThMMa, WeGa, CaYu, LiLi, RoPCo, BrMHu, KaCh, AxSk, KiOKy, ThIASø, CaADe, RoFVl, RuJFLo, JaKa, KaHe, JaWa, ClHLl, AbFi, ToAMc, ThCEl, AlMGr, MiHe, XiDi, MoBjAn, HeBeNi, MoSo, AdDTa, DaLTa, MaAS, CoFa, CrDI, SyOo, ArKnNo, DaMa, LiAb, SAlBu, KeLKl, HeHMa, LiJEa, JuLSi, RoFKr, MaMc, ShPa, MaGa, DaABu, DoIBo, GoWi, ToCEMBe, MeBa, ChHo, JeMCr, RiSa, DuLFr, JoAMa, FuJi, FeNi, ZePa, LiDu, MiBo, MaBr, GiDi, FrVi, NiGMa, SaEMe, GrWMo, YMHu, BiKi, YoCh, ChHo, HyJSh, JaHGo, SöMö, JaHj, SaAa, ReSu, GaESw, RuKr, PaKEMa, NaLPe, AnKDA, FiRa, PeTy, PaLi, ClMAHa, RoPl, KPaHa, ElMTD, SeYOn, FaAl, GoBa, DaNa, TiSp, MaMa, GeLa, LaABa, CaTu, GlDu, DeBu, YoYo collected the data used in this study. KaSi and AlJe were in charge of data management. KaSi conducted the analyses, wrote the first draft of the manuscript and has primary responsibility of for final content. All authors have commented the manuscript and read and approved the final version of the manuscript.

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(6)(6)Table 1. Number of twin individuals and means and standard deviations (SD) of BMI by age and region in boys and girls.

		All		Europe		North-America and Australia		East-Asia	
Sex	Age	N	BMI ± SD	N	BMI ± SD	N	BMI ± SD	N	BMI ± SD
Boys	1 year	15919	17.1±1.38	13029	17.1±1.36	559	17.6 ±1.74	2238	17.1±1.40
	2 year	13032	16.5±1.39	10677	16.5 ±1.37	617	17.4 ±1.54	1653	16.2±1.26
	3 year	17334	15.9±1.46	14198	15.9 ±1.47	1063	16.4 ±1.79	2020	15.7±1.12
	4 year	10118	15.9±1.82	7593	15.9 ±1.79	1512	16.1 ±2.17	1004	15.5±1.28
	5 year	8255	15.3±1.57	6256	15.2±1.46	1096	16.0±2.09	880	15.2±1.20
	6 year	3322	15.5±1.87	1450	15.5±1.59	811	16.0±2.60	1004	15.1±1.36
	7 year	13767	15.4±1.82	11467	15.4±1.78	716	16.0±2.71	1269	15.3±1.51
	8 year	6502	15.8±1.96	4491	15.7±1.84	695	16.4±2.84	1273	15.6±1.69
	9 year	7066	16.5±2.43	4339	16.4 ±2.22	1430	17.3±3.15	1263	16.0±1.94
	10 year	11531	16.7±2.38	9151	16.6±2.27	863	17.9±3.32	1388	16.6±2.19
	11 year	9149	17.4±2.70	6739	17.3±2.57	963	18.6±3.58	1444	17.2±2.36
	12 year	12140	18.0±2.90	8673	17.6±2.66	2396	19.4±3.54	1071	17.8±2.55
	13 year	5108	18.7±3.06	3629	18.3±2.63	1175	19.9±3.91	304	18.5±2.78
	14 year	9687	19.5±3.07	6994	19.1±2.68	2525	20.6±3.76	168	18.9±2.73
	15 year	5904	20.0±3.18	4341	19.5±2.62	1411	21.5±4.15	140	19.0±3.05
	16 year	8745	20.8±3.02	6387	20.4±2.54	2213	21.9±3.86	128	19.9±3.33
	17 year	11646	21.2±2.78	7681	21.0±2.61	3843	21.8±3.02	106	20.3±2.61
	18 year	17407	21.7±2.66	7332	21.4±2.57	9925	21.9±2.71	123	20.3±2.34
	19 year	11216	22.0±2.72	5605	21.7±2.47	5478	22.3±2.92	122	20.8±2.77
Girls	1 year	15789	16.7±1.37	12709	16.7±1.35	591	16.9±1.53	2381	16.7±1.39
	2 year	12499	16.1±1.37	10081	16.1±1.35	590	16.8±1.49	1731	15.9±1.33
	3 year	17602	15.6±1.51	14257	15.7±1.52	1107	16.0±1.89	2179	15.4±1.18
	4 year	9842	15.7±1.90	7360	15.7±1.99	1442	15.8±2.21	1022	15.3±1.28
	5 year	7984	15.1±1.65	6019	15.0±1.53	1026	15.8±2.33	918	15.1±1.30
	6 year	2852	15.4±1.91	900	15.5±1.70	794	15.8±2.49	1092	15.0±1.38
	7 year	13942	15.5±2.01	11528	15.5±2.03	735	15.6±2.61	1384	15.2±1.46
	8 year	6160	15.8±2.15	4014	15.9±2.13	706	16.5±2.94	1417	15.4±1.60
	9 year	6746	16.6±2.62	3903	16.6±2.49	1402	17.3±3.35	1404	15.8±1.82

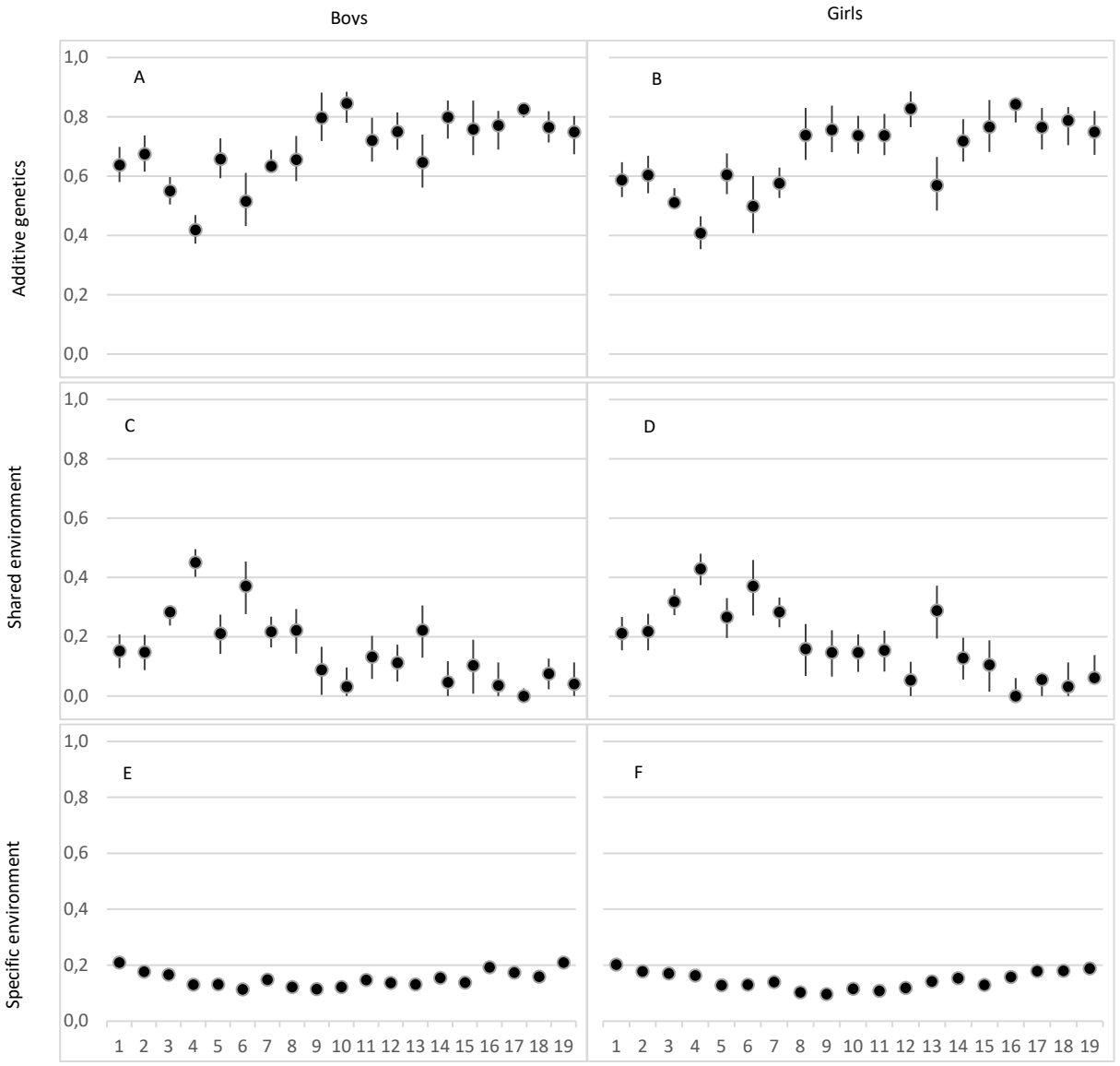
	10 year	11445	16.8±2.58	8975	16.8±2.52	840	18.0±3.50	1494	16.3±2.07
	11 year	8962	17.6±2.95	6460	17.6±2.85	972	19.0±3.95	1527	16.8±2.17
	12 year	12282	18.1±2.98	8572	17.8±2.74	2527	19.6±3.51	1183	17.5±2.32
	13 year	4861	18.9±3.16	3299	18.7±2.87	1255	19.9±3.77	307	18.1±2.51
	14 year	10221	19.8±3.16	7376	19.4±2.73	2677	21.0±3.87	168	18.5±2.43
	15 year	5820	20.3±3.29	4217	19.8±2.78	1414	21.9±4.12	178	19.4±2.43
	16 year	9611	20.7±3.07	7269	20.4±2.78	2180	21.8±3.73	155	19.9±2.25
	17 year	10381	20.8±2.94	8632	20.6±2.68	1599	22.0±3.87	126	20.7±2.64
	18 year	8775	21.2±3.16	6318	20.8±2.66	2291	22.4±4.03	133	19.9±2.35
	19 year	9469	21.4±3.22	6558	21.0±2.75	2765	22.5±3.96	131	20.2±2.20

Figure legends

Figure 1. Proportions of logBMI variation with 95% confidence intervals based on maximum likelihood estimation explained by additive genetic, shared environmental and unique environmental factors by age and sex. The number of twin pairs varied from 2987 at 6 years of age to 17028 at 3 years of age.

Figure 2. Additive genetic correlations with 95% confidence intervals based on maximum likelihood estimation within opposite-sex DZ pairs by age. The number of opposite-sex pairs varied from 753 at 6 years of age to 5272 at 3 years of age.

Figure 3. Proportions of logBMI variation with 95% confidence intervals based on maximum likelihood estimation explained by additive genetic factors by age, sex and region. The number of twin pairs varied from 1107 at 6 years of age to 13855 at 3 years of age in Europe, from 565 at 1 year of age to 5064 at 18 years of age in North-America and Australia and from 111 at 17 to 2284 at 1 year of age in East-Asia.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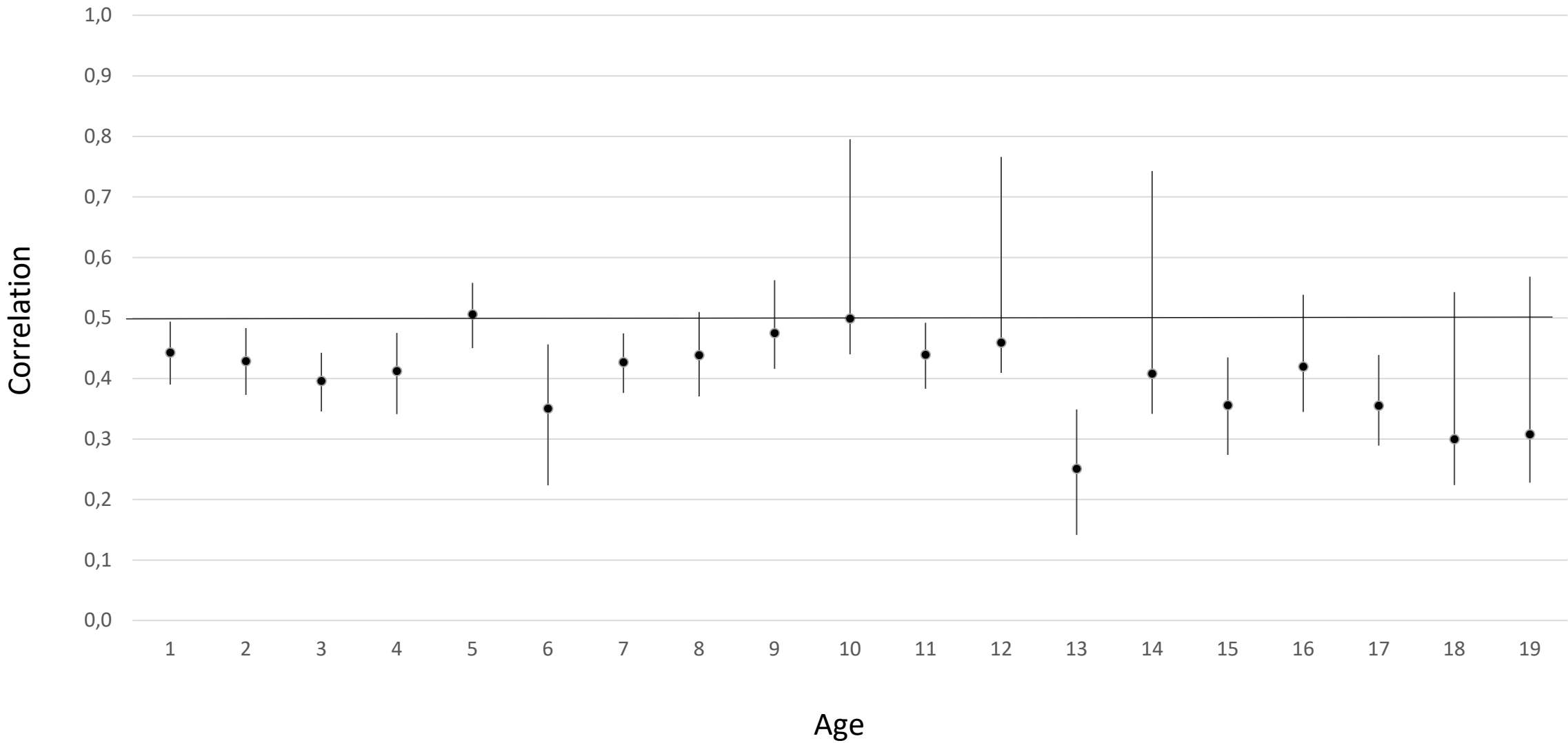
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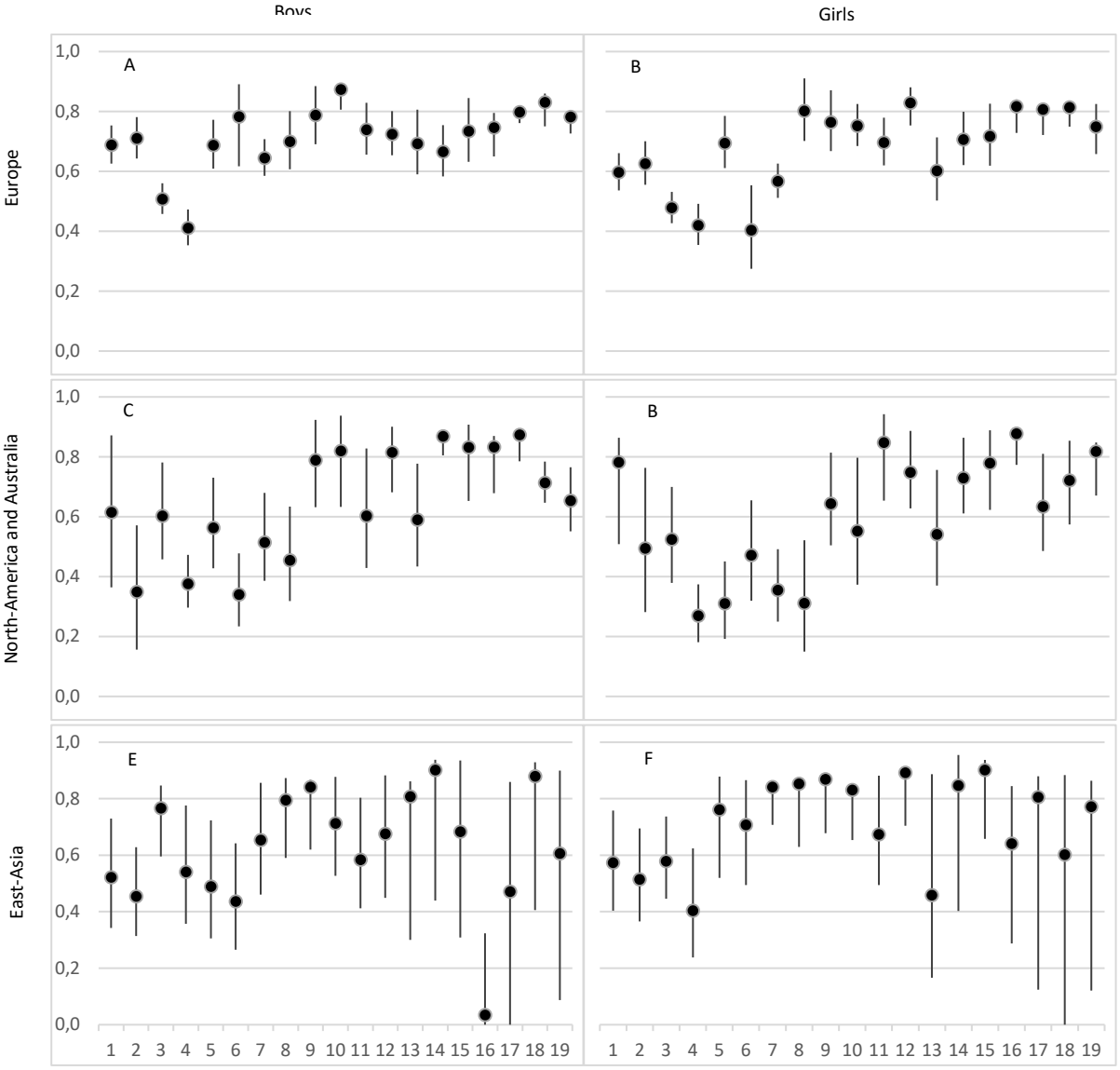
19
Age


Boys
Girls
Europe
North-America and Australia
East-Asia
A
B
C
B
E
F
1,0
0,8
0,6
0,4
0,2
0,0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19