Differences in genetic and environmental variation in adult body mass index by sex, age, time period and region: an individual-based pooled analysis of 40 twin cohorts

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Short Running head: Differences in the heritability of adult BMI

Abbreviations

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
CODATwins = COllaborative project of Development of Anthropometrical measures in Twins
D=dominance genetic variance component
d^2=the proportion of total variance explained by dominance genetic factors
DZ=dizygotic twin
E=unique environmental variance component
e^2=the proportion of total variance explained by unique environmental factors
GWA= genome wide association

logBMI= natural logarithm of body mass index

MZ=monozygotic twin

OSDZ = opposite-sex dizygotic

r_{AOSDZ} = additive genetic correlation for opposite-sex dizygotic pairs

SD=standard deviation

SSDZ = same-sex dizygotic

Abstract

Background: Genes and environment contribute to the variation in adult body mass index (BMI), but factors modifying these variance components are poorly known.

Objective: We analyzed genetic and environmental variation of BMI from young adulthood to old age, between men and women, from the 1940s to the 2000s and between cultural-geographic regions representing high (North America and Australia), moderate (Europe), and low (East Asia) levels of obesity.

Design: BMI in twins 20 years of age or older from 40 cohorts representing 20 countries (140,379 complete twin pairs) was analyzed using genetic structural equation modeling.

Results: The heritability decreased from 0.77 (95% CI 0.77, 0.78) in men and 0.75 (95% CI 0.74, 0.75) in women at 20-29 years of age to 0.57 (95% CI 0.54, 0.60) in men at 70-79 years of age and 0.59 (95% CI 0.53, 0.65) in women at 80 years of age or older. The relative influence of unique environmental factors correspondingly increased. Differences in the sets of genes affecting BMI in men and women increased from 20-29 to 60-69 years of age. The mean and variance increased from the 1940s to the 2000s, being greatest in North America and Australia followed by Europe and East Asia. However, the heritability estimates were largely similar over the measurement years and between the regions. There was no evidence for environmental factors shared by co-twins affecting BMI.

Conclusions: The heritability of BMI decreased and differences in the sets of genes affecting BMI in men and women increased over aging. The heritability of BMI was largely similar between the

cultural-geographic regions and measurement years, despite of the large differences in the means and variances of BMI. Our results show a strong influence of genetic factors on BMI, especially in early adulthood, regardless of the level of obesity in the population.

Key words: BMI, adults, genetics, twins, international comparisons

Introduction

The prevalence of obesity has dramatically increased in the previous decades in the industrialized world and also in many middle-income countries (1). In some geographic areas, the obesity epidemic may have recently levelled off with high rates of obesity, whereas in other areas the increase still continues (2). Estimates of the heritability of BMI, i.e. the proportion of total BMI variation explained by genetic variation, from twin studies vary between 57% and 90% in adult populations (3,4). These values indicate substantial influence of genetic factors on BMI variation but also reveal large heterogeneity in these estimates between populations. Heritability of BMI varies from young childhood to the onset of adulthood (5), but may also vary over adulthood as found in a literature based meta-analysis (4) and in a large Finnish twin study (6). This can be associated with increases in fat mass from early adulthood to late middle-age (7), which is affected by genetic factors (8). Some studies have also analyzed whether the heritability of BMI is different in populations with different mean BMI. Studies in Danish adults (9) and young adult Swedish men (10) have suggested that both genetic and environmental variances have increased during the obesity epidemic leading to rather constant heritability estimates. In a study of twin children and adolescents from different countries based on the same database used in the current study, greater means and variances of BMI were found in North America and Australia than in East Asia, but the heritability estimates were largely constant (5). Previous studies have thus provided evidence that the changes of obesogenic environment over time or differences between geographic regions do not necessarily change the heritability of BMI even when the total BMI variation has increased.

Despite a large body of research, the factors that affect the heritability of adult BMI and the reasons for the large variability of the heritability estimates reported in previous studies (3,4) are poorly

understood. It is known that partially different sets of genes affect lean and fat body mass (11), which may create differences also in the sets of genes affecting BMI in men and women because of different body composition (12). Some evidence exists that these sex differences increase from childhood to adolescence (5) and are also present in adulthood (13), but it is poorly known how they change over adulthood. Using data from a large majority of the existing twin cohorts in the world, we aim to comprehensively examine factors affecting heritability of adult BMI. Our specific aims are to study: 1) how heritability estimates of BMI differ across age, ranging from 20 to 90 years old; 2) how age differences in genetic influences vary between men and women; 3) how the heritability estimates vary between different cultural-geographic regions; and 4) how genetic and environmental variances have changed in BMI measured from the year 1940 to 2014 when the level of BMI has dramatically increased worldwide.

Subjects and Methods

The data were derived from the CODATwins (COllaborative project of Development of Anthropometrical measures in Twins) database described in detailed elsewhere (14). The goal of the CODATwins project is to collect together all available twin data on height and weight in the world. For the current analyses, we selected all BMI measures from those 19.5 years of age or older. Together, we had 40 twin cohorts with adult BMI data from 20 countries. We divided these cohorts into three geographic–cultural regions – Europe, North America and Australia, and East Asia – as described in our previous study on the heritability of BMI in childhood and adolescence utilizing the same database (5). Based on previous population based estimates, East Asia has the lowest and North America and Australia the highest levels of mean BMI and obesity prevalence (1). We had adult BMI data from 18 cohorts from Europe, 14 cohorts from North America and Australia and 6 cohorts from East Asia.

Additionally, we included one cohort from Sri-Lanka and one cohort from Turkey in all pooled analyses; these two countries are distinct genetically and culturally from East Asian and European populations, respectively, and are thus not included in the region specific analyses. The names of participating cohorts are given in the footnotes of **Supplemental table 1**.

Because we focused on the variation of common levels of BMI, we excluded observations consistent with anorexia nervosa (i.e. less than 17.5 kg/m^2; 5706 observations) and morbid obesity (more than 40 kg/m^2; 2880 observations), together representing 1.5% of the total number of observations (**Supplemental figure 1**). Collectively, we had 550,090 BMI measures (54% women) from 140,379 complete twin pairs where 40% were monozygotic (MZ) pairs, 41% same-sex dizygotic (SSDZ) pairs and 19% opposite-sex dizygotic (OSDZ) pairs. In most of the cohorts, the majority of the participants were women. However, Vietnam Era Twin Study of Aging and NAS-NRC Twin Registry cohorts included veterans of Vietnam War and Second World War, respectively. Having these two all-male cohorts resulted in a larger number of measures in North America and Australia done in men in the oldest age groups. The largest number of twin pairs were from Europe (85,715 pairs) followed by North America and Australia (51,882 pairs) and East Asia (1,743 pairs). Further, we had 1039 pairs from Sri-Lanka and Turkey. We adjusted BMI separately in men and women for twin cohort as well as the effects of age, measurement year, and their squares showing statistically significant associations with BMI ($p<0.0001$). Because BMI showed positive skewness after standardization (0.99), we used logarithmic transformation to normalize the distribution when calculating the relative proportions of genetic and environmental variances. Since participating cohorts were asked to provide data on height and weight, no missing cases existed.

The data were analyzed by structural equation modeling of twin data (15). Classical twin modeling exploits the differential degree of biological relatedness between MZ and DZ twins. Specifically, DZ twins share, on average, 50% of their genes identical-by-descent whereas MZ twins are virtually identical at the gene-sequence level. Based on the comparisons of the similarity of MZ and DZ co-twins, the variation of BMI can be decomposed into genetic and environmental variance components. Genetic variation can further be decomposed into additive genetic variation (A) including additive effects of all loci affecting BMI and dominance genetic variation (D) including the non-additive genetic effects. Environmental variation can be decomposed into shared or common environmental variation (C) including all environmental effects making MZ and DZ co-twins similar, and unique environmental variation (E) including the effects of all environmental factors that make co-twins dissimilar. In the modelling, the unique environmental component includes also measurement error. For MZ twins the expected correlations of both additive and dominance genetic effects are 1, whereas for DZ twins they are 0.5 and 0.25, respectively. The expected correlation of shared environment is 1 and unique environment 0 within both MZ and DZ twin pairs. As we had reported previously, there were no systematic differences between MZ and DZ twins in the variances of BMI in adulthood, but especially in early adulthood the mean BMI was somewhat higher in DZ than in MZ twins (16). Thus, we used different means for MZ and DZ twins in the genetic modeling. The modeling was conducted using the OpenMx package, version 2.0.1, of R statistical software (17). All parameter estimates and their 95% confidence intervals (CI) were calculated by the maximum likelihood method. OpenMx was also used to calculate descriptive statistics, i.e. means, standard deviations (SD) and correlations, with their 95% CIs to correctly specify the family structure.

Our data including only twin pairs reared together do not allow estimation of dominance genetic and shared environmental effects simultaneously. Twin correlations did not clearly suggest whether the

126 additive genetic/ shared environment/ unique environment (ACE) model or the additive genetic/
127 dominance genetic/ unique environment (ADE) model would better fit the data (Supplemental table 1).
128 Thus we started the modeling by fitting both of these models as well as a more parsimonious additive
129 genetic/ unique environment (AE) model in each 10-year age and sex group. To secure that the
130 heritability estimates are based on independent observations of twin pairs, we selected one observation
131 per twin pair within each 10-year age group leading to 365,830 BMI measures used in these analyses
132 (Supplemental figure 1). To test the hypothesis that there are differences in the genetic influences on
133 BMI between the sexes, we analyzed sex-limitation models, utilizing information from opposite-sex
134 twin pairs; if the estimated correlation of additive genetic effects for OSDZ pairs is less than the 0.5
135 value expected for SSDZ pairs, it suggests partly different sets of genes affecting BMI in men and
136 women. After these age-specific analyses, we studied how the genetic and environmental variation
137 differed across the measurement years. Again, we secured that each heritability estimate was based on
138 independent observations and selected only measures obtained in the same year for both co-twins
139 leading to 373,924 BMI measures. This set of analyses was based on raw BMI values adjusted for age,
140 birth year and twin cohort effects because we focused on the differences in genetic and environmental
141 variance components rather than relative variation. However, we repeated the analyses by calculating
142 the relative proportions and genetic and environmental variances using logBMI to test the results
143 sensitivity to the logarithmic transformation. Both sets of analyses were based on the same 140,379
144 complete twin pairs implying that slightly more than 30% of measures were repeated, i.e., the same
145 twin pair contributed to more than one estimate. However, because only one measure was used in these
146 independent tests, this does not violate the assumption of independence of observations when
147 calculating CIs.
148

149 The pooled analysis was approved by the ethical board of the Department of Public Health, University
150 of Helsinki. The data collection procedures of the participating twin cohorts were approved by the local
151 ethical boards following the regulations in each country. Only anonymized data with non-invasive
152 measures were delivered to the data management center at the University of Helsinki (14).
153
154 Results
155
156 **Table 1** presents the descriptive statistics by 10-year age and measurement year groups in the whole
157 data set as well as in each geographic-cultural region (95% CIs available in **Supplemental table 2**).
158 Mean BMI increased after 20-29 years of age and then started to decline after 60-69 years of age both
159 in men and women. Across the age groups, there was some increase in the variances of BMI until 60-
160 69 years of age in men and 70-79 years of age in women. Both the means and variances of BMI
161 increased from the measures done before 1960 to those done in 2000 or later in men and women; an
162 exception was the slightly lower mean and variance of BMI measured in 1970-1979. Comparisons
163 between the geographic-cultural regions revealed systematic differences with a higher mean and
164 variance of BMI in North America and Australia in all the age and measurement year groups in men
165 and women. In East Asia, the mean and variance of BMI were lowest, but it is noteworthy that in this
166 region, we only had measures done in 2000 or later.
167
168 We then fitted different genetic models in each 10-year age group (**Table 2;** the sample sizes available
169 in Supplemental table 1). Generally, we found only a little evidence for dominance genetic or shared
170 environmental effects for logBMI. Shared environmental effects were close to zero and statistically
171 significant only in men at 30-39 years of age (c^2=0.05 95% CI 0.01, 0.09) and women at 20-29 years of
172 age (c^2=0.08 95% CI 0.05, 0.11). Dominance genetic effects were statistically significant only in men

at 40-49 years of age (d^2=0.15 95% CI 0.07, 0.23); in men over 80 years of age, the dominance genetic effect was large, but not statistically significant, reflecting the small sample size in this age group. Because our results did not systematically support the presence of shared environmental or dominance genetic effects, we used the AE model in the further analyses. Under this model, the relative proportion of additive genetic variance decreased from 20-29 years of age (a^2=0.77 95% 0.77, 0.78 in men and a^2=0.75 95% 0.74, 0.75 in women) until 70-79 years of age in men (a^2=0.57 95% 0.54, 0.60) and 80 years of age or older in women (a^2=0.59 95% 0.53, 0.65). This decrease corresponded to the increasing proportion of BMI variance explained by unique environmental factors.

The estimates of the genetic correlation for OSDZ pairs were less than the 0.5 value, expected for SSDZ twins, indicating partly different sets of genes affecting logBMI in men and women (**Figure 1**). There was a general trend for the OSDZ genetic correlations to decrease across the age groups from 20-29 years (r_{AOSDZ}=0.34 95% CI 0.32, 0.36) to 60-69 years of age (r_{AOSDZ}=0.28 95% CI 0.23, 0.33), indicating an increasingly greater difference in the sets of genes influencing logBMI in men and women across the age groups. After this age group, the OSDZ genetic correlation was stable or slightly greater, but the 95% CIs were wide.

When we analyzed the heritability of logBMI by region, we found no clear differences (**Table 3**; the sample sizes available in Supplemental table 1). Additive genetic factors explained roughly the same proportion of logBMI variance in Europe as in North America and Australia. The decrease in the contribution of additive genetic factors was found from the age group of 20-29 years to the age groups of 80 years or older (European men and women), 70-79 years (North American and Australian men) or 60-69 years (North American and Australian women); in the oldest age groups the 95% CIs were,

however, wide. In East Asia, the results were roughly similar to the other regions, but once again the 95% CIs were wide.

Finally, we studied how raw additive genetic and unique environmental variances differed across the measurement years (**Figure 2**; estimates with 95% CIs available in **Supplemental table 3**). We limited these analyses only to Europe and North America and Australia, because in East Asia there were no measures done before 2000. We found increase in both additive genetic and unique environmental variances from the earliest measurement year both in men (the earliest measures in 1940) and women (the earliest measures in 1963). Because of the increasing trends in both of these components, the heritability of BMI was largely constant over the measurement years. The heritability estimates calculated by using logBMI were nearly identical to those calculated by using raw BMI (Supplemental table 3).

Discussion

In this large pooled study of around 140,000 twin pairs, we found that the adult BMI variation was caused by additive genetic and environmental factors not shared by co-twins and found only little evidence that shared environmental or dominance genetic factors would affect adult BMI. Our previous twin study of BMI in children and adolescents, also based on the same database, found that shared environmental factors are important in early childhood, but their effect largely disappears in adolescence (5), thus supporting the observations of the present study. It is, however, noteworthy that in studies using only twins reared together, such as in our study, the shared environmental and dominance genetic effects can compensate for each other if both effects are present. An US study using an extended twin design, thus allowing for the estimation of these effects simultaneously, found

evidence on environmental factors shared by twins, explaining however less than 10% of the variance, with the remainder of the BMI variation explained by additive genetic, dominance genetic and unique environmental variation both in men and women (18). A large genome-wide-association (GWA) study estimated that the whole genome wide variation of common variants measured or imputed explained around 20% of the BMI variation (19), which is substantially lower than we found in this study in any age group. It is thus still unclear whether the unknown genetic variation could be due to the effect of dominance as suggested previously (20), or whether it reflects other type of genetic variation, possibly dependent on environmental influences, difficult to measure by current GWA studies.

The heritability estimates of BMI decreased from young adulthood to old age. It is well known that BMI increases from young adulthood to late middle-age largely because of increasing fat mass (7) and then starts to decrease in old age because of a decrease in muscle mass (21). A similar curvilinear association of mean BMI over the age groups from 20-29 years to 80 years and older was also found in our study. Both genetic and environmental factors affect the weight gain trajectories over young adulthood and middle-age as demonstrated by using the twin design (8) and obesity genetic risk score (22), but our results suggest that the role of genetic factors becomes relatively less important while unique environmental effects gain significance by aging. A large, longitudinal Danish population-based study found that the tracking of BMI from childhood decreased from early adulthood to old age also suggesting increasing environmental variation (23). A recent large GWA study on adult body size found that 15 loci had significant age-specific effects from which 11 had a larger effect in adults younger than 50 years as compared to those 50 years or older (24). In the light of this evidence, it is very likely that the heterogeneity of previous heritability estimates of BMI is largely because these estimates are based on cohorts with different age ranges (3,4).

We found clear evidence of partly different sets of genes influencing adult BMI in men and women. These differences are present already in early childhood but become more prominent in adolescence, likely reflecting the major hormonal changes during puberty, which create differences in body composition between men and women (5). Because partly different sets of genes affect lean and fat mass (11), these differences in genes affecting BMI in men and women are expected and probably reflect differences in body composition. In light of this, it is interesting that we found some evidence that the extent of the differences in the genes influencing BMI for men and women becomes more pronounced from early adulthood (20-29 years of age) to late middle age (60-69 years of age) even when this difference was only marginally statistically significant. This may well reflect differences in the hormonal levels between men and women before menopause, which increasingly modifies the expression of genes affecting BMI. In a recent large GWA study, no sex-specific genetic effects were found on BMI (24), but this may be related to the small proportion of BMI variation explained by the known loci in general (19).

There was a strong increase in the mean and variation of BMI from the 1940s to the 2000s, and they were also much larger in North America and Australia than in Europe or East Asia consistent with data from large population-based samples (1). In spite of these differences, the heritability of BMI was largely similar over the measurement years and between these regions. This corresponds well the studies from Denmark (9) and Sweden (10) showing that the heritability of BMI did not change over the measurement years despite the increasing mean and variation of BMI. Furthermore, no major differences in the heritability of BMI were found in childhood and adolescence between these three geographic regions (5). There has been speculation that assortative mating may increase genetic variance of BMI, but there is limited evidence to date to support this (25). Further, it is not likely that there would be changes in gene pools within populations explaining the increasing genetic variance

over the measurement years. Also in a previous study of European populations, no association was found between the values of genetic risk score of BMI and measured BMI values between the populations supporting that the differences in allele frequencies are not the main reason behind the variation of BMI between different populations (26). There is, however, evidence that common genetic variants of BMI are especially expressed in various parts of the brain (19). Changes in obesogenic environment activating these genes may have led to the increasing genetic variance found in this study.

Our study has both strengths and weaknesses. The main strength of our study is the very large sample size with twin data from four continents with substantial geographic variation of BMI measures that were conducted over seven decades. However, this study also clearly demonstrates the limits of current knowledge. Even though the large majority of twin cohorts in the world took part in this study, we still only had a limited number of twin pairs from East Asia, no data from South America or Africa, and only one study from South Asia and one study from the Middle East. All of our cohorts also represent high- or middle-income countries. Thus, our results may be generalized only to relatively affluent populations with low rates of undernutrition or other severe environmental stressors. Moreover, the number of elderly twin pairs was much lower than the number of pairs in younger age groups. Further, we need more data on twins reared apart and extended twin family data to get deeper into the genetic architecture. We did not have any micro-level indicators of environmental influences, which would have helped to further study whether such factors may modify the genetic and environmental variation of BMI.

In conclusion, the heritability of BMI decreased from young adulthood to old age whereas environmental variation increased. At the same time, differences between men and women in the genetic influences became more important with aging. On the other hand, only minor differences in the

heritability estimates were found between the measurement years or cultural-geographic regions despite large differences in the mean and variation of BMI. Our results show the importance of genetic factors behind BMI variation, especially in early adulthood, regardless of the mean BMI of the population.

Authors' contributions

The authors' responsibilities were as follows— KS, YY, Y-MH, FiR, DIB, TIAS and JK planned the study design of the CODATwins project; YY, Y-MH, WC, AH, TM, CH, FI, YI, MW, RT, KP, AR, SS, MH, AS, FR, QT, DZ, ZP, SÖ, JvBH, KC, AxS, KK, JS, TS, JO, JS-R, LC-C, Y-MS, SY, KL, CF, WK, ML, AB, TN, KEW, CK, KJ, MG, DB, MS, CoF, CD, GD, DeB, NM, SM, GW, H-UJ, GES, RK, PM, NP, ADA, TMcA, TE, AG, PT, LB, CT, GB, DN, TiS, MM, GL, SAB, KLK, JH, IB, TSN, RFK, MMcG, SP, BH, RC, BH, MB, TB, GoW, FiR, ADT, DLT, CAD, RV, RL, JLH, JoS, HM, DIB and JK collected the data used in this study; KS and AJ were in charge of data management; KS conducted the analyses, wrote the first draft of the manuscript, and had primary responsibility of for the final content; and all authors commented on the manuscript and read and approved the final version of the manuscript. None of the authors reported a conflict of interest related to the study.

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Table 1. Numbers of BMI measures and means and standard deviations (SD) of BMI by age, measurement year and region in men and women.

	All		Europe		North America and Australia		East Asia	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Men								
Age								
20-29	47668	23.1±2.92	26879	22.9±3.48	20139	23.3±3.14	335	22.4±2.86
30-39	31488	24.7±3.21	20381	24.3±2.91	10311	25.5±3.59	511	24.2±2.85
40-49	36493	25.4±3.16	19241	25.1±3.00	16777	25.7±3.31	313	24.7±2.84
50-59	27127	26.0±3.36	20331	25.8±3.19	6533	26.6±3.79	165	24.1±2.90
60-69	19230	26.0±3.35	11771	26.0±3.27	7355	26.2±3.48	73	23.8±2.83
70-79	9057	25.7±3.22	4213	25.6±3.19	4761	25.8±3.23	77	23.1±2.82
80 or more	1178	24.7±3.26	620	24.6±3.07	481	25.0±3.43	77	22.7±2.83
Measurement year								
Before 1960	10834	22.5±2.57	-	-	10834	22.5±2.57	-	-
1960-1969	16346	24.8±2.69	8082	24.8±2.72	8264	24.9±2.67	-	-
1970-1979	21779	23.7±2.86	20802	23.6±2.83	977	25.2±3.08	-	-
1980-1989	26701	24.7±3.15	11661	24.1±2.90	15040	25.2±3.25	-	-
1990-1990	45413	25.1±3.38	28406	24.7±3.16	17007	25.9±3.61	-	-
2000 or later	45413	25.4±3.66	35055	25.3±3.44	13358	26.1±4.11	1433	23.7±3.02
Women								
Age								
20-29	45762	22.0±3.34	30651	21.7±4.24	14245	22.8±3.93	569	21.0±2.50
30-39	43662	23.1±3.77	26477	22.7±2.47	16131	23.7±4.24	759	22.6±2.87
40-49	37947	24.1±3.90	25749	23.8±3.58	11453	24.5±4.50	521	23.4±3.34
50-59	34309	25.0±3.90	28015	24.9±3.76	5881	25.3±4.49	255	23.3±3.17
60-69	21794	25.4±3.97	16815	25.5±3.88	4827	25.2±4.24	101	22.5±2.74
70-79	8411	25.1±3.92	6289	25.2±3.82	2045	24.9±4.24	63	22.8±2.19
80 or more	1704	24.0±3.68	1208	24.1±3.63	469	24.0±3.81	21	21.8±2.55

Measurement year								
Before 1960	-	-	-	-	-	-	-	-
1960-1969	10216	24.6±3.45	10216	24.6±3.45	-	-	-	-
1970-1979	24157	22.5±3.30	23926	22.5±3.30	231	22.3±2.79	-	-
1980-1989	30101	23.0±3.63	13985	22.7±3.33	16,116	23.4±3.84	-	-
1990-1990	54683	23.9±3.99	37090	23.7±3.77	17,593	24.2±4.41	-	-
2000 or later	70760	24.1±4.20	48069	24.0±4.00	19,582	24.7±4.68	2043	22.4±3.10

Table 2. Relative proportions of logBMI variance explained by genetic and environmental factors by age and sex under different genetic models based on maximum likelihood estimation.[1]

		Additive genetic factors		Dominance genetic factors		Shared environment		Unique environment	
Age	Model	a^2	95% CI	d^2	95% CI	c^2	95% CI	e^2	95% CI
Men									
20-29	AE	0.77	0.77, 0.78	-		-		0.23	0.22, 0.23
	ADE	0.77	0.72, 0.78	0.00	0.00, 0.05	-		0.23	0.22, 0.23
	ACE	0.76	0.73, 0.78	-		0.01	0.00, 0.04	0.23	0.22, 0.23
30-39	AE	0.71	0.69, 0.72	-		-		0.29	0.28, 0.31
	ADE	0.71	0.67, 0.72	0.00	0.00, 0.03	-		0.29	0.28, 0.31
	ACE	0.65	0.60, 0.70			0.05	0.01, 0.09	0.30	0.29, 0.31
40-49	AE	0.69	0.68, 0.70	-		-		0.31	0.30, 0.32
	ADE	0.55	0.47, 0.62	0.15	0.07, 0.23	-		0.30	0.29, 0.32
	ACE	0.69	0.68, 0.70	-		0.00	0.00, 0.01	0.31	0.30, 0.32
50-59	AE	0.64	0.62, 0.65	-		-		0.36	0.35, 0.38
	ADE	0.55	0.45, 0.64	0.09	0.00, 0.19	-		0.36	0.35, 0.38
	ACE	0.64	0.61, 0.65	-		0.00	0.00, 0.02	0.36	0.35, 0.38
60-69	AE	0.60	0.59, 0.62	-		-		0.40	0.38, 0.41
	ADE	0.54	0.43, 0.62	0.07	0.00, 0.18	-		0.39	0.37, 0.41
	ACE	0.60	0.57, 0.62	-		0.00	0.00, 0.03	0.40	0.38, 0.41
70-79	AE	0.57	0.54, 0.60	-		-		0.43	0.40, 0.46
	ADE	0.57	0.48, 0.60	0.00	0.00, 0.09	-		0.43	0.40, 0.46
	ACE	0.51	0.42, 0.59	-		0.06	0.00, 0.14	0.44	0.41, 0.47
80+	AE	0.60	0.52, 0.67	-		-		0.40	0.33, 0.48
	ADE	0.16	0.00, 0.61	0.46	0.00, 0.68	-		0.38	0.32, 0.46
	ACE	0.60	0.48, 0.67	-		0.00	0.00, 0.09	0.40	0.33, 0.48
Women									
20-29	AE	0.75	0.74, 0.75	-		-		0.25	0.25, 0.26
	ADE	0.75	0.73, 0.75	0.00	0.00, 0.01	-		0.25	0.25, 0.26
	ACE	0.66	0.63, 0.70	-		0.08	0.05, 0.11	0.26	0.25, 0.26
30-39	AE	0.72	0.71, 0.73	-		-		0.28	0.27, 0.29
	ADE	0.72	0.68, 0.73	0.00	0.00, 0.04	-		0.28	0.27, 0.29
	ACE	0.69	0.65, 0.72	-		0.03	0.00, 0.06	0.28	0.27, 0.29
40-49	AE	0.70	0.68, 0.70	-		-		0.30	0.30, 0.32
	ADE	0.70	0.64, 0.70	0.00	0.00, 0.05	-		0.30	0.30, 0.32
	ACE	0.68	0.64, 0.70	-		0.02	0.00, 0.05	0.31	0.30, 0.32
50-59	AE	0.67	0.66, 0.69	-		-		0.33	0.31, 0.34
	ADE	0.67	0.60, 0.69	0.00	0.00, 0.07	-		0.33	0.31, 0.34
	ACE	0.67	0.62, 0.68	-		0.01	0.00, 0.04	0.33	0.32, 0.34
60-69	AE	0.67	0.65, 0.68	-		-		0.33	0.32, 0.35
	ADE	0.67	0.60, 0.68	0.00	0.00, 0.07	-		0.33	0.32, 0.35
	ACE	0.65	0.59, 0.68	-		0.02	0.00, 0.07	0.34	0.32, 0.35
70-79	AE	0.65	0.63, 0.68	-		-		0.35	0.32, 0.37

	ADE	0.63	0.46, 0.68	0.03	0.00, 0.20	-		0.34	0.32, 0.37
	ACE	0.65	0.58, 0.68	-		0.00	0.00, 0.07	0.35	0.32, 0.37
80+	AE	0.59	0.53, 0.65	-		-		0.41	0.35, 0.47
	ADE	0.47	0.08, 0.65	0.12	0.00, 0.52	-		0.40	0.35, 0.47
	ACE	0.59	0.43, 0.65	-		0.00	0.00-0.13	0.41	0.35, 0.47

[1]The numbers of complete twin pairs vary from 1441 pairs in the age category of 80 years or older to 46715 pairs in the age category of 20-29 years.

Table 3. Relative proportions of logBMI variance explained by additive genetic and unique environmental factors by age, sex and region based on maximum likelihood estimation.[1]

	Men				Women			
	Additive genetic factors		Unique environment		Additive genetic factors		Unique environment	
	a^2	95% CI	e^2	95% CI	a^2	95% CI	e^2	95% CI
Europe								
20-29	0.77	0.76, 0.78	0.23	0.22, 0.24	0.75	0.74, 0.76	0.25	0.24, 0.26
30-39	0.71	0.69, 0.72	0.29	0.28, 0.31	0.72	0.71, 0.73	0.28	0.27, 0.29
40-49	0.68	0.66, 0.70	0.32	0.30, 0.34	0.69	0.68, 0.71	0.31	0.29, 0.32
50-59	0.64	0.62, 0.66	0.36	0.34, 0.38	0.67	0.66, 0.68	0.33	0.32, 0.34
60-69	0.59	0.57, 0.62	0.41	0.38, 0.43	0.66	0.65, 0.68	0.34	0.32, 0.35
70-79	0.58	0.54, 0.62	0.42	0.38, 0.46	0.62	0.59- 0.65	0.38	0.35, 0.41
80+	0.49	0.33, 0.61	0.51	0.39, 0.67	0.53	0.44, 0.61	0.47	0.39, 0.56
North America and Australia								
20-29	0.78	0.77, 0.79	0.22	0.21, 0.23	0.75	0.73, 0.76	0.25	0.24, 0.27
30-39	0.70	0.68, 0.72	0.30	0.28, 0.32	0.72	0.70, 0.73	0.28	0.27, 0.30
40-49	0.70	0.69, 0.72	0.30	0.28, 0.31	0.70	0.68, 0.72	0.30	0.28, 0.32
50-59	0.64	0.61, 0.67	0.36	0.33, 0.39	0.70	0.67, 0.72	0.30	0.28, 0.33
60-69	0.62	0.59, 0.64	0.38	0.36, 0.41	0.67	0.64, 0.70	0.33	0.30, 0.36
70-79	0.56	0.52, 0.59	0.44	0.41, 0.48	0.73	0.69, 0.76	0.27	0.24, 0.31
80+	0.68	0.58, 0.75	0.32	0.25, 0.42	0.68	0.59, 0.76	0.32	0.24, 0.41
East Asia								
20-29	0.76	0.68, 0.82	0.24	0.18, 0.32	0.78	0.73, 0.83	0.22	0.17, 0.27
30-39	0.66	0.58, 0.73	0.34	0.27, 0.42	0.70	0.64, 0.75	0.30	0.25, 0.36
40-49	0.75	0.67, 0.82	0.25	0.18, 0.33	0.77	0.70, 0.81	0.23	0.19, 0.30
50-59	0.63	0.46, 0.75	0.37	0.25, 0.54	0.71	0.60, 0.80	0.29	0.20, 0.40
60-69	0.34	0.00, 0.69	0.66	0.31, 1.00	0.72	0.54, 0.83	0.28	0.17, 0.46
70-79	0.75	0.45, 0.89	0.25	0.11, 0.55	0.68	0.36, 0.85	0.32	0.15, 0.64
80+	0.50	0.11, 0.76	0.50	0.24, 0.89	0.75	0.09, 0.93	0.25	0.07, 0.91

[1]The numbers of complete twin pairs vary from 914 pairs in the age category of 80 years or older to 28765 pairs in the age category of 20-29 years in Europe; from 475 pairs in the age category of 80 years or older to 17192 pairs in the age category of 20-29 years in North America and Australia; and from 49 pairs in the age category of 80 years or older to 635 pairs in the age category of 30-39 years in East Asia.

Figure 1. Additive genetic correlations for opposite-sex twin pairs by age based on maximum likelihood estimation. The number of opposite-sex pairs per age group: 7102 at 20-29 years, 6028 at 30-39 years, 5549 at 40-49 years, 6285 at 50-59 years, 3472 at 60-69 years, 1247 at 70-79 years and 206 at 80+ years of age.

Figure 2. Additive genetic and unique environmental variances of BMI by measurement year and sex based on maximum likelihood estimation. The number of complete twin pairs per decade varied from 3930 pairs in the 1960s to 22055 pairs in the 2000s (the number of complete twin pairs by measurement year available in Supplemental table 3).