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

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ABSTRACT

Background: Genes and the environment contribute to variation in adult body mass index [BMI (in kg/m^2)], but factors modifying these variance components are poorly understood.

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

Design: We used genetic structural equation modeling to analyze BMI in twins ≥20 y of age from 40 cohorts representing 20 countries (140,379 complete twin pairs).

Results: The heritability of BMI decreased from 0.77 (95% CI: 0.77, 0.78) and 0.75 (95% CI: 0.74, 0.75) in men and women 20–29 y of age to 0.57 (95% CI: 0.54, 0.60) and 0.59 (95% CI: 0.53, 0.65) in men 70–79 y of age and women 80 y of age, respectively. 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 y of age. Mean BMI and variances in BMI increased from the 1940s to the 2000s and were greatest in North America and Australia, followed by Europe and East Asia. However, heritability estimates were largely similar over measurement years and between regions. There was no evidence of 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 from young adulthood to old age. The heritability of BMI was largely similar between cultural-geographic regions and measurement years, despite large differences in mean BMI and variances in BMI. Our results show a strong influence of genetic factors on BMI, especially in early adulthood, regardless of the obesity level in the population. *Am J Clin Nutr* 2017;106:457–66.

Keywords: BMI, adults, genetics, twins, international comparisons

INTRODUCTION

The prevalence of obesity has increased dramatically from 1980 to 2010 in both the industrialized world and in many middle-income countries (1). In some geographic areas, the obesity epidemic may have recently leveled off with high rates of obesity; in other areas, the prevalence of obesity continues to increase (2). Estimates of the heritability of BMI [(in kg/m^2); 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 a substantial influence

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of genetic factors on BMI variation, but they also reveal large heterogeneity in estimates among populations. The 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 variance can be associated with increases in fat mass from early adulthood to late middle age (7), which are affected by genetic factors (8). Some investigators have also analyzed whether the heritability of BMI is different in populations with different mean BMI values. Studies of Danish adults (9) and young adult Swedish men (10) suggested that both genetic and environmental variance 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 CODATwins (Collaborative Project of Development of Anthropometrical Measures in Twins) database used in our study, greater mean BMI and variances in BMI were found in North America and Australia than in East Asia, but heritability estimates were largely constant (5). Previous studies thus provided evidence that changes in the obesogenic environment over time or differences between geographic regions do not necessarily change the heritability of BMI even when total BMI variation has increased.

Despite a large body of research, factors that affect the heritability of adult BMI and the reasons for the large variability in heritability estimates reported in previous studies (3, 4) are poorly understood. Previous research shows that partially different sets of genes affect lean and fat body mass (11), which may also create differences in the sets of genes affecting BMI in men and women as a result of differences in body composition (12). Some evidence shows that these sex differences increase from childhood to adolescence (5) and are also present in adulthood (13), but how they change over adulthood is poorly understood. Using data from the majority of the existing twin cohorts in the world, we aimed to comprehensively examine factors affecting the heritability of adult BMI. Our specific aim was to study the following: *1*) how heritability estimates of BMI differ across age (ranging from 20 to 90 y), *2*) how age differences in genetic influences vary between men and women, *3*) how heritability estimates vary between different cultural-geographic regions, and *4*) how genetic and environmental variances have changed in BMI measurements from 1940 to 2014 when the level of BMI has dramatically increased worldwide.

METHODS

Study data were derived from the CODATwins database, which is described in detailed elsewhere (14). The goal of the CODATwins project is to collect all available data on height and weight from twin cohorts in the world. For the current analyses, we selected all BMI measurements from individuals ≥19.5 y of age. Together, we had 40 twin cohorts with adult BMI data from 20 countries. We divided these cohorts into 3 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, in which we also utilize the CODATwins database (5). Based on previous population-based estimates, East Asia has the lowest and North America and Australia have the highest 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. In addition, we included 1 cohort from Sri Lanka and 1 cohort from Turkey in all pooled analyses; these 2 countries are distinct genetically and culturally from East Asian and European populations, respectively, and were thus not included in the region-specific analyses. The names of participating cohorts are given in the footnotes in **Supplemental Table 1**.

Because we focused on the variation in common levels of BMI, we excluded observations consistent with anorexia nervosa

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Supplemental Figure 1 and Supplemental Tables 1–3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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Abbreviations used: CODATwins, Collaborative Project of Development of Anthropometrical Measures in Twins; GWA, genome-wide association; OSDZ, opposite-sex dizygotic; SSDZ, same-sex dizygotic.

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(i.e., BMI: <17.5; 5706 observations) and morbid obesity (BMI: >40; 2880 observations), together representing 1.5% of the total number of observations (**Supplemental Figure 1**). Collectively, we had 550,090 BMI measurements (54% from women) from 140,379 complete twin pairs, in which 40% were monozygotic pairs, 41% were same-sex dizygotic (SSDZ) pairs, and 19% were opposite-sex dizygotic (OSDZ) pairs. In most of the cohorts, the majority of the participants were women. However, the Vietnam Era Twin Study of Aging and the National Academy of Sciences–National Research Council Twin Registry cohorts included veterans of the Vietnam War and World War II, respectively. Having these 2 all-male cohorts resulted in a larger number of measurements obtained from men in the oldest age groups in North America and Australia. The largest numbers of twin pairs were from Europe (85,715 pairs), followed by North America and Australia (51,882 pairs) and East Asia (1743 pairs). Furthermore, we had 1039 pairs from Sri Lanka and Turkey. We adjusted BMI separately for men and women for twin cohort and for 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. Because participating cohorts were asked to provide data on height and weight, there were no missing cases.

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

Our data including only twin pairs reared together did not allow estimation of dominance genetic and shared environmental effects simultaneously. Twin correlations did not clearly suggest whether the model comprising either *1*) additive genetic variation, shared environment, and unique environment or *2*) additive genetic variation, dominance genetic variation, and unique environment would better fit the data (Supplemental Table 1). Thus, we began by fitting both models and a more parsimonious model comprising additive genetic variation and unique environment in each 10-y age and sex group. To ensure that heritability estimates were based on independent observations of twin pairs, we selected 1 observation/twin pair within each 10-y age group, resulting in 365,830 BMI measurements used in these analyses (Supplemental Figure 1). To test the hypothesis that there are differences in genetic influences on BMI between the sexes, we analyzed sex-limitation models and utilized information from opposite-sex twin pairs; if the estimated correlation of additive genetic effects for OSDZ pairs was <0.5 (the value expected for SSDZ pairs), this suggested that partly different sets of genes affect BMI in men and women. After these age-specific analyses, we studied how genetic and environmental variation differed across measurement years. Again, we ensured that each heritability estimate was based on independent observations and we selected only measurements obtained in the same year for both co-twins, which resulted in 373,924 BMI measurements. This set of analyses was based on raw BMI values adjusted for age, birth year, and twin cohort effects, because we focused on differences in genetic and environmental variance components rather than relative variation. However, we repeated the analyses by calculating the relative proportions of genetic and environmental variances using logBMI to test the results' sensitivity to logarithmic transformation. Both sets of analyses were based on the same 140,379 complete twin pairs, implying that we had >1 measure for slightly >30% of participants (i.e., the same twin pair contributed to >1 estimate). However, because only one measure was used in these independent tests, this does not violate the assumption of independence of observations when calculating CIs.

The pooled analysis was approved by the ethics board of the University of Helsinki Department of Public Health. Data collection procedures of the participating twin cohorts were approved by the local ethics boards following the regulations in each country. Only anonymized data with noninvasive measures were delivered to the data management center at the University of Helsinki (14).

RESULTS

Table 1 presents descriptive statistics by 10-y age groups and measurement year for the whole data set and for each geographic-cultural region (95% CIs are available in **Supplemental Table 2**). Mean BMI increased after 20–29 y of age and then started to decline after 60–69 y of age in both men and women. Across age groups, there was some increase in variances in BMI until 60–69 y of age in men and 70–79 y of age in women. Both mean BMI and variances in BMI increased between measurements performed before 1960 and those obtained in 2000 or later in men and women; the slightly lower mean

TABLE 1
Number of BMI measurements and mean BMI by age, measurement year, and region in men and women[1]

	All		Europe		North America and Australia		East Asia	
Age group, y	*n*	BMI, kg/m^2	*n*	BMI, kg/m^2	*n*	BMI, kg/m^2	*n*	BMI, kg/m^2
Men								
Age, y								
20–29	47,668	23.1 ± 2.92	26,879	22.9 ± 3.48	20,139	23.3 ± 3.14	335	22.4 ± 2.86
30–39	31,488	24.7 ± 3.21	20,381	24.3 ± 2.91	10,311	25.5 ± 3.59	511	24.2 ± 2.85
40–49	36,493	25.4 ± 3.16	19,241	25.1 ± 3.00	16,777	25.7 ± 3.31	313	24.7 ± 2.84
50–59	27,127	26.0 ± 3.36	20,331	25.8 ± 3.19	6533	26.6 ± 3.79	165	24.1 ± 2.90
60–69	19,230	26.0 ± 3.35	11,771	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	1178	24.7 ± 3.26	620	24.6 ± 3.07	481	25.0 ± 3.43	77	22.7 ± 2.83
Measurement year								
Before 1960	10,834	22.5 ± 2.57	—	—	10,834	22.5 ± 2.57	—	—
1960–1969	16,346	24.8 ± 2.69	8082	24.8 ± 2.72	8264	24.9 ± 2.67	—	—
1970–1979	21,779	23.7 ± 2.86	20,802	23.6 ± 2.83	977	25.2 ± 3.08	—	—
1980–1989	26,701	24.7 ± 3.15	11,661	24.1 ± 2.90	15,040	25.2 ± 3.25	—	—
1990–1990	45,413	25.1 ± 3.38	28,406	24.7 ± 3.16	17,007	25.9 ± 3.61	—	—
2000 or later	45,413	25.4 ± 3.66	35,055	25.3 ± 3.44	13,358	26.1 ± 4.11	1433	23.7 ± 3.02
Women								
Age, y								
20–29	45,762	22.0 ± 3.34	30,651	21.7 ± 4.24	14,245	22.8 ± 3.93	569	21.0 ± 2.50
30–39	43,662	23.1 ± 3.77	26,477	22.7 ± 2.47	16,131	23.7 ± 4.24	759	22.6 ± 2.87
40–49	37,947	24.1 ± 3.90	25,749	23.8 ± 3.58	11,453	24.5 ± 4.50	521	23.4 ± 3.34
50–59	34,309	25.0 ± 3.90	28,015	24.9 ± 3.76	5881	25.3 ± 4.49	255	23.3 ± 3.17
60–69	21,794	25.4 ± 3.97	16,815	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	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	10,216	24.6 ± 3.45	10,216	24.6 ± 3.45	—	—	—	—
1970–1979	24,157	22.5 ± 3.30	23,926	22.5 ± 3.30	231	22.3 ± 2.79	—	—
1980–1989	30,101	23.0 ± 3.63	13,985	22.7 ± 3.33	16,116	23.4 ± 3.84	—	—
1990–1990	54,683	23.9 ± 3.99	37,090	23.7 ± 3.77	17,593	24.2 ± 4.41	—	—
2000 or later	70,760	24.1 ± 4.20	48,069	24.0 ± 4.00	19,582	24.7 ± 4.68	2043	22.4 ± 3.10

[1] Values are means ± SDs unless otherwise indicated.

BMI and variance in BMI measured in 1970–1979 was an exception. Comparisons between geographic-cultural regions revealed systematic differences, with a higher mean BMI and variance in BMI in North America and Australia among all age and measurement year groups in men and women. Mean BMI and variance in BMI were lowest for participants in East Asia; however, it is important to note that we had only measurements performed in 2000 or later for participants from this region.

We fitted different genetic models in each 10-y age group (**Table 2**; sample sizes are available in Supplemental Table 1). Generally, both dominance genetic and shared environmental effects for logBMI were very small or did not exist. Shared environmental effects were close to zero and were statistically significant only in men 30–39 y of age (c^2 = 0.05; 95% CI: 0.01, 0.09) and women 20–29 y of age (c^2 = 0.08; 95% CI: 0.05, 0.11). Dominance genetic effects were statistically significant only in men 40–49 y of age (d^2 = 0.15; 95% CI: 0.07, 0.23); the dominance genetic effect in men >80 y of age 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 model comprising additive genetic variation and unique environment in further analyses. Under this model, the relative proportion of additive genetic variance decreased from 20 to 29 y of age in men (a^2 = 0.77; 95% CI: 0.77, 0.78) and women (a^2 = 0.75; 95% CI: 0.74, 0.75) until 70–79 y of age in men (a^2 = 0.57; 95% CI: 0.54, 0.60) and ≥80 y of age in women (a^2 = 0.59; 95% CI: 0.53, 0.65). This decrease corresponded to the increasing proportion of BMI variance explained by unique environmental factors.

Estimates of the genetic correlation for OSDZ pairs were <0.5 (expected for SSDZ twins), indicating that partly different sets of genes affect logBMI in men and women (**Figure 1**). There was a general trend for OSDZ genetic correlations to decrease across age groups from 20–29 y of age (r = 0.34; 95% CI: 0.32, 0.36) to 60–69 y of age (r = 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 age groups. After 60–69 y of age, the OSDZ genetic correlation was stable or slightly greater but the 95% CIs were wide.

We found no clear differences when we analyzed the heritability of logBMI by region (**Table 3**; sample sizes are available in Supplemental Table 1). Additive genetic factors explained

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]

Age group, y	Model	Additive genetic factors, a^2	Dominance genetic factors, d^2	Shared environment, c^2	Unique environment, e^2
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] Values in parentheses are 95% CIs. The number of complete twin pairs varies from 1441 to 46,715 pairs in the groups ≥80 and 20–29 y of age, respectively. ACE, additive genetic variation, shared environment, and unique environment; ADE, additive genetic variation, dominance genetic variation, and unique environment; AE, additive genetic variation and unique environment.

roughly the same proportion of logBMI variance in Europe as in North America and Australia. A decrease in the contribution of additive genetic factors was found between the group 20–29 y of age and the groups ≥80 y of age (European men and women), 70–79 y of age (North American and Australian men), or 60–69 y of age (North American and Australian women); however, the 95% CIs were wide in the oldest age groups. The results for East Asia 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 measurement years (**Figure 2**; estimates with 95% CIs are available in **Supplemental Table 3**). We limited these analyses only to Europe, North America, and Australia, because no measurements were obtained before 2000 in East Asia. We found an increase in both additive genetic and unique environmental variances from the earliest measurement year for men and women (the earliest measurements were from

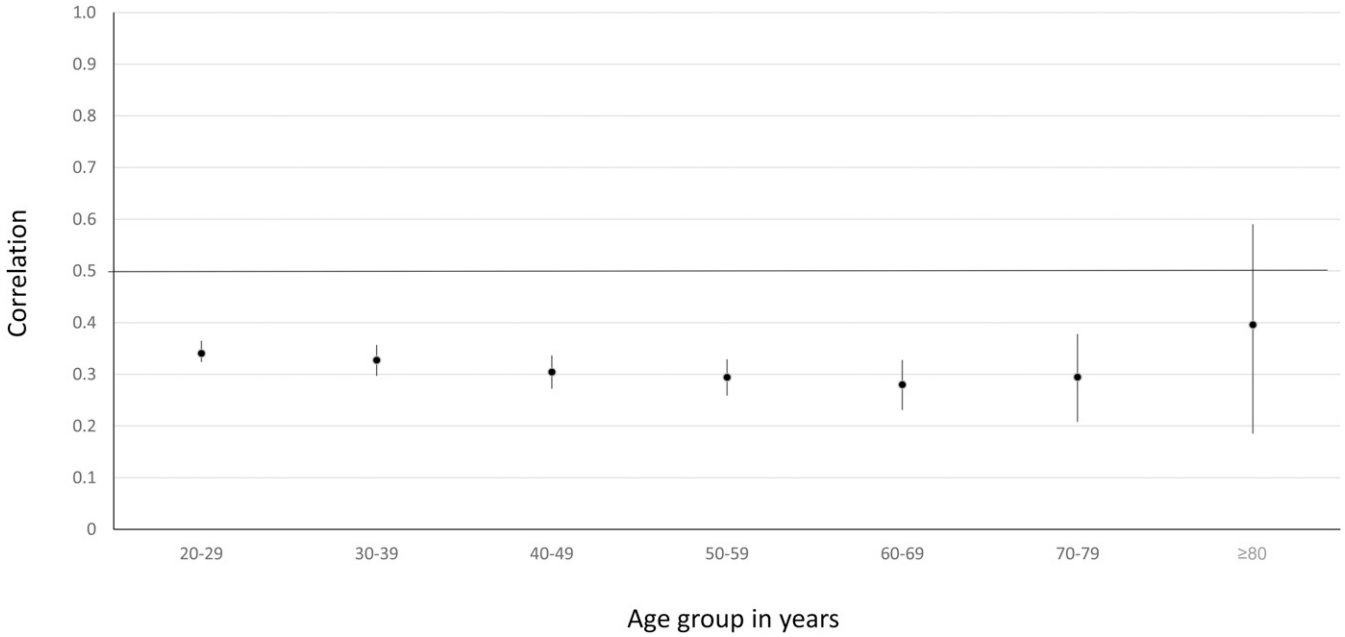

FIGURE 1 Additive genetic correlations for opposite-sex twin pairs by age based on maximum likelihood estimation. The number of opposite-sex pairs per age group is as follows: 7102 at 20–29 y, 6028 at 30–39 y, 5549 at 40–49 y, 6285 at 50–59 y, 3472 at 60–69 y, 1247 at 70–79 y, and 206 at ≥80 y.

1940 and 1963, respectively). Because of the increasing trends in both of these components, the heritability of BMI was largely constant over the measurement years. The heritability estimates we calculated using logBMI were nearly identical to those calculated using raw BMI (Supplemental Table 3).

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	
Age group, y	Additive genetic factors, a^2	Unique environment, e^2	Additive genetic factors, a^2	Unique environment, e^2
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] Values in parentheses are 95% CIs. The number of complete twin pairs varies from 914 to 28,765 pairs for the groups ≥80 and 20–29 y of age, respectively, in Europe; from 475 to 17,192 pairs for the groups ≥80 and 20–29 y of age, respectively, in North America and Australia; and from 49 to 635 pairs for the groups ≥80 and 30–39 y of age, respectively, in East Asia.

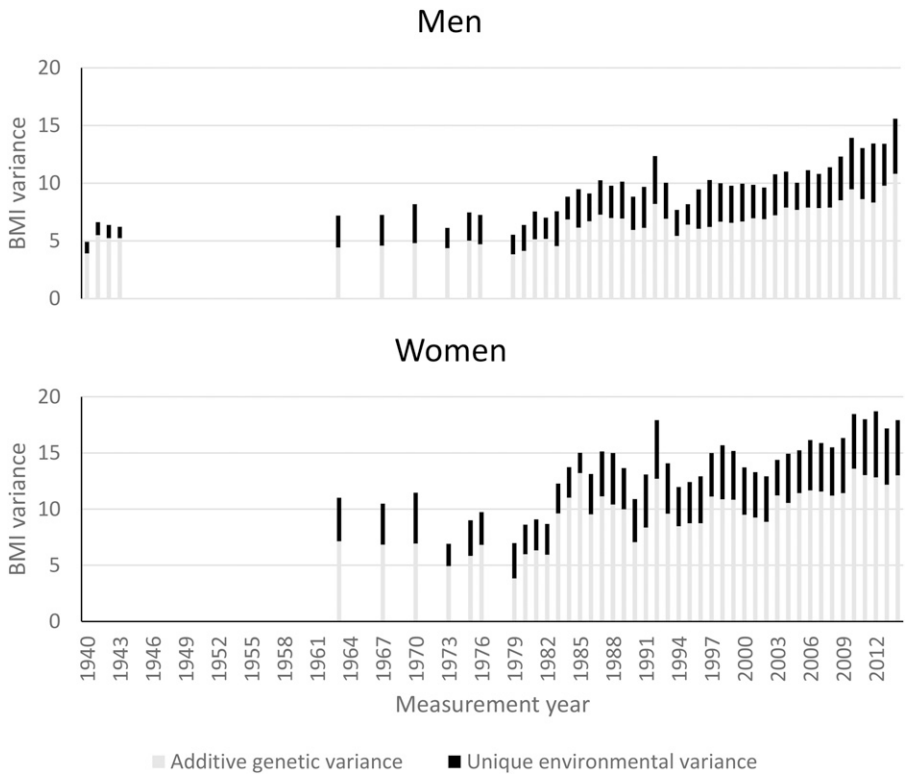

FIGURE 2 Additive genetic and unique environmental variances in BMI by measurement year and sex based on maximum likelihood estimation. The number of complete twin pairs per decade varied from 3930 pairs in the 1960s to 22,055 pairs in the 2000s (the number of complete twin pairs by measurement year is available in Supplemental Table 3).

DISCUSSION

In this large pooled study of ~140,000 twin pairs, we found that variation in adult BMI was caused by additive genetic and environmental factors not shared by co-twins. We found that shared environmental and dominance genetic factors had only a weak effect on adult BMI. Our previous twin study of BMI in children and adolescents, also based on the same CODATwins database, showed that shared environmental factors are important in childhood but their effect largely disappears in adolescence (5), thus supporting the observations of our current study. It is, however, noteworthy that in studies using only twins reared together (e.g., in our study), shared environmental and dominance genetic effects can compensate for each other if both effects are present. A US study using an extended twin design, thus allowing for the estimation of these effects simultaneously, found that environmental factors shared by twins, explaining only <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 whole genome-wide variation in common variants measured or imputed explained ~20% of the BMI variation (19), which is substantially lower than we found in this study in any age group. Therefore, it is still unclear whether unknown genetic variation could be attributable to the effect of dominance, as suggested previously (20), or whether it reflects another type of genetic variation (possibly dependent on environmental influences), which is 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 increased fat mass (7), and then starts to decrease in old age, as a result of decreased muscle mass (21). We also found a similar curvilinear association of mean BMI over the age groups from 20–29 to ≥80 y. Both genetic and environmental factors affect weight gain trajectories over young adulthood and middle age, as demonstrated by studies that used a twin design (8) and obesity genetic risk score (22). However, our results suggest that the role of genetic factors becomes relatively less important, whereas unique environmental effects became stronger by aging. A large, longitudinal Danish population-based study showed 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 showed that 15 loci had significant age-specific effects, 11 of which had a larger effect in adults <50 y of age than in those ≥50 y of age (24). In 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 already present in early childhood but become more prominent in adolescence and they likely reflect 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 showing that the extent of differences in the genes influencing BMI for men and women is more pronounced from early adulthood (20–29 y) to late middle age (60–69 y) even when this difference is only marginally statistically significant. This may well reflect differences in hormonal levels between men and premenopausal women, which increasingly modify the expression of genes affecting BMI. In a recent large GWA study, no sex-specific genetic effects on BMI were found (24), but this may be related to the small proportion of BMI variation explained by the known loci in general (19).

There was a substantial increase in mean BMI and variation in BMI from the 1940s to the 2000s. Mean and variance of BMI were also greater in North America and Australia than in Europe or East Asia, consistent with data from large population-based samples (1). Despite these differences, the heritability of BMI was largely similar over the measurement years and between these regions. This corresponds well with studies from Denmark (9) and Sweden (10), which showed that the heritability of BMI did not change over the measurement years despite the increased mean BMI and variation in BMI. Furthermore, no major differences in the heritability of BMI were found in childhood and adolescence between these 3 geographic regions (5). There has been speculation that assortative mating may increase the genetic variance in BMI, but there is limited evidence to date to support this (25). Furthermore, it is not likely that there would be changes in gene pools within populations explaining the increasing genetic variance over the measurement years. In a previous study of European populations, the values of genetic risk score of BMI did not correlate with the measured BMI values between populations, supporting that the differences in allele frequencies are not the main reason behind the variation in BMI between different populations (26). However, there is evidence that common genetic variants of BMI are expressed in various parts of the brain (19). Changes in the obesogenic environment activating these genes may have led to the increased genetic variance found in this study.

Our study has both strengths and limitations. The main strength of our study is its very large sample size with twin data from 4 continents with substantial geographic variation in BMI measures that were conducted over 7 decades. However, this study also clearly demonstrates the limits of current knowledge. Although the 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 each from South Asia and 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. Furthermore, we need more data on twins reared apart and extended twin family data to to understand better the genetic architecture or BMI. We did not have any microlevel indicators of environmental influences, which would have helped us further study whether such factors may modify genetic and environmental variation in BMI.

In conclusion, the heritability of BMI decreased from young adulthood to old age, whereas environmental variation increased. At the same time, differences in genetic influences between men and women became more important with aging. On the other hand, only minor differences in heritability estimates were found between measurement years or cultural-geographic regions, despite large differences in mean BMI and variation in BMI. Our results show the importance of the genetic factors behind BMI variation, especially in early adulthood, regardless of the mean BMI of the population.

The authors' responsibilities were as follows—KS, YY, Y-MH, F Rasmussen, DIB, TIAS, and JK: planned the study design of the CODATwins project; YY, Y-MH, WC, AEH, TMM, CH, FI, YI, MW, RT, KHP, AR, SHS, MH, A Sumathipala, F Rijsdijk, QT, DZ, ZP, SYÖ, JBH, KC, A Skytthe, KOK, JLS, TDS, JRO, JFS-R, LC-C, Y-MS, SY, KL, CEF, WSK, MJL, AB, TLN, KEW, CK, KLJ, MG, DAB, MAS, CF, CD, GED, DB, NGM, SEM, GWM, H-UJ, GES, RK, PKEM, NLP, AKDA, TAMA, TCE, AMG, PT, LAB, CT, GB, DN, MM, GL, SAB, KLK, JRH, IB, TSN, RFK, MMG, SP, BMH, RPC, MB, CEMvB, GW, F Rasmussen, ADT, DLT, CAD, RFV, RJFL, JLH, JS, HHM, DIB, and JK: collected the data used in the 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 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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