Parental education and genetics of body mass index from infancy to old age: a pooled analysis of 29 twin cohorts

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What is already known about this subject?

1) Low parental education is associated with greater body mass index in offspring from early childhood until adulthood.

2) Genetic factors explain a large proportion of the variation of body mass index, and there is evidence that environmental factors can modify these effects.

What this study adds?

1) Using pooled data from 29 twin cohorts, we showed that low parental education is associated with greater genetic variation of body mass index from early childhood to old age.

2) The interaction effect between parental education and genetic factors on body mass index was stronger in North America and Australia than in Europe and East Asia.

3) Genetic factors intermediate the effect of childhood social position on body mass index seen over the human life course, and this association is strongest in the obesogenic social context.

Abstract

Objective: To analyze how parental education modifies the genetic and environmental variances of body mass index (BMI) from infancy to old age in three geographic-cultural regions.

Methods: A pooled sample of 29 cohorts including 143 499 twin individuals with information on parental education and BMI from 1 to 79 years (299 201 BMI measures) was analyzed by genetic twin modeling.

Results: Until 4 years of age, parental education was not consistently associated with BMI. Thereafter, higher parental education was associated with lower BMI in males and females. Total and additive genetic variances of BMI were smaller in the offspring of highly educated parents than in those whose parents had low education. Especially in North American and Australian children, environmental factors shared by co-twins also contributed to the higher BMI variation in the low educational category. In Europe and East Asia, the associations of parental education with mean BMI and BMI variance were weaker than in North America and Australia.

Conclusions: Lower parental education is associated with higher mean and larger genetic variance of BMI after early childhood, especially in the obesogenic macro-environment. The interplay between genetic predisposition, childhood social environment and macro-social context is important for socio-economic differences in BMI.

Introduction

Mean body mass index (BMI, kg/m^2) has increased all over the industrialized world during the last four decades and currently shows clear geographic differences with the highest BMIs in North America and lowest in East Asia (1). Twin studies have shown that genetic factors explain a substantial proportion of BMI variation over the life course (2,3), and genome wide association (GWA) studies have identified the role of genetic variants behind BMI variation (4,5). There is also strong evidence for a higher BMI in lower socio-economic classes in Western industrialized societies (6). The roots of socio-economic obesity differences may already emerge in childhood since many socio-economic characteristics of childhood family, such as parental education and income, are associated with the BMI of offspring (7). Adoption studies supported these findings by showing that lower socio-economic status of biologically unrelated adoptive families is associated with higher BMI of adopted children as adults (8).

The association of genes and environmental factors with BMI may be modified by socio-demographic characteristics. In our previous study based on the same database as in this present study, we found that the genetic variation of adult BMI increased from the 1940s to the 2010s at the same time when mean BMI dramatically increased (3) confirming the earlier findings based on Danish (9) and Swedish data (10). A Dutch twin study of parental education in children and adolescents (11) as well as studies on Danish (12) and US adults (13) of their own education suggested increased genetic BMI variation associated with lower education. However, a Finnish twin study reported that in adolescence the increased BMI variation in the offspring of parents with lower education was attributable to environmental factors shared by co-twins (14).

To address the question how modification of genetic and environmental influences on BMI develops over the human lifespan requires considerable statistical power. Thus, we analyzed if and how parental education modifies the genetic and environmental variation of BMI from infancy to old age in a very large international database of twins. Further, we analyzed whether the interaction between parental education and BMI varies between three geographic-cultural regions that are characterized by different levels of mean BMI in the population indicating different obesogenic environments.

Methods

The data were derived from the CODATwins (COllaborative project of Development of Anthropometrical measures in Twins) project targeted to collect all available twin data on height and weight in the world (15). We included 29 twin cohorts with additional information on maternal and paternal education. Eleven cohorts came from European countries, five from East Asian countries, eleven from the USA, and single cohorts from Australia and Israel. The names of participating cohorts are given in Table 1 (footnote). Age was classified to one-year age categories from 1 to 19 years of age, and after that 10-year categories were defined. Participants who were 80 years of age or older were excluded (319 measures) because of decreasing muscle mass at old age (16). Together, there were 324 329 BMI measurements. In children and adolescents, we checked the BMI distribution in each age and sex group and removed the extreme, likely erroneous values (658 measures representing 0.3% of the measurements at 19 years of age or younger corresponding to values approximately below or above 3 SD from the mean). In adults, we removed the measurements consistent with anorexia nervosa (BMI<15 kg/m^2, 96 measures representing 0.1% of adult measures) and morbid obesity (BMI>45 kg/m^2, 246 measures representing 0.3% of adult measures). Thus, our results represent the range of normal BMI variation, and not extremely low and very high BMI values, which may be affected

specific factors such as anorexia nervosa or rare monogenic traits. To confirm that all parameter estimates were based on independent observations, we selected one measurement in each age group from cohorts with repeated measures and conducted independent models in each age group. In the present analyses, 299 201 BMI measures from 143 499 twin individuals (52% females) including 66 165 complete twin pairs (39% monozygotic (MZ), 34% same-sex dizygotic (DZ) and 27% opposite-sex DZ) with information on maternal and paternal education were used. All participants were volunteers who gave informed consent when participating in their original studies. The pooled analysis was approved by the ethical committee of the Department of Public Health, University of Helsinki.

The different educational classifications used in the surveys were transformed as educational years as described elsewhere (17). We first calculated regression residuals of maternal and paternal education separately by fitting a regression model with maternal or paternal education as the dependent variable and twin cohort and the birth year of their twin children, used as a proxy indicator for the birth years of parents, as independent variables. Twin cohort was treated as a nominal level variable with a dummy variable for each individual cohort and birth year as a continuous variable. These residuals were then summed up to get combined parental education and divided into three categories (less than -0.5 SD from the mean, from -0.5 until 0.5 SD from the mean and more than 0.5 SD from the mean) to indicate low (31% of participants), average (40% of participants) and high parental education (29% of participants). The SD of parental education was slightly higher in North America and Australia (SD=5.33) than in Europe (SD=4.50) and East Asia (SD=4.10). However, we calculated the residuals in the full cohort and used the same categorization of parental education to avoid changing the educational distribution and to confirm the same distance of education in all geographic-cultural regions. Thus, the residuals indicate how much shorter or longer the parental education is as compared

to the average person having a certain birth year in each twin cohort. Correspondingly, BMI was adjusted for the effects of exact age and twin cohort in each age and sex category by regression models.

In the aggregation of twin cohorts by the geographic-cultural regions, we removed Turkey from all region specific analyses since the Turkish population is genetically distinct from other European populations (18). We also combined the cohort from Australia with North American cohorts since the mean BMI in Australia is closer to North American than European countries (1). Thus, we had three geographic-cultural regions, North America and Australia, Europe, and East Asia representing the high, intermediate and low level of obesogenic environment, respectively, based on the mean BMI of population (1). The same classification was used also in our previous studies on the genetics of BMI in childhood (2) and adulthood (3) based on the CODATwins database. The number of BMI measurements was highest in Europe (196 990 measures) followed by North America and Australia (82 098 measures) and East Asia (18 670 measures). Since there was more ethnic diversity in North America and Australia than in the other cultural-geographic regions, we repeated the main analyses in North Americans and Australians of Caucasian ethnicity based on self-reports (75 973 measures).

We used structural equation modeling to estimate genetic and environmental variance components (19). Genetic twin modeling is based on the different genetic relatedness of MZ and DZ twins: DZ twins share, on average, 50% of their genes identical by descent; MZ twins are virtually identical at the DNA sequence level. Based on this principle, the BMI variation can be decomposed into additive genetic variation (additive effects of all loci affecting BMI), dominance genetic variation (non-additive genetic effects), shared environmental variation (all environmental effects making co-twins similar) and unique environmental variation (all environmental effects making co-twins different and measurement error). Models were fitted separately for each parental education category by age and sex

groups. As we reported previously, slightly higher variances of BMI were found from 6 to 12 years of age in DZ than in MZ twins (20). However, these differences were minor, i.e. 15% of less, and became statistically significant only because of our very large sample size.

As we have previously reported for children (2) and adults (3), there was little evidence for the presence of dominance genetic variation in BMI. Thus, we used the additive genetic/ shared environment/ unique environment model in the analyses, which was also supported by the within pair correlations in all parental education categories in our study cohort (Table S1). We fitted the full model in each age group to get the estimation of the role of shared environmental factors, even when it was not statistically significant in most of age categories. A clear sex-specific genetic effect for BMI was found in childhood (2) and adulthood (3), and thus all models were fitted allowing the opposite-sex DZ genetic correlation to be lower than the 0.5 expected for same-sex DZ twins. Especially in early childhood, DZ twins were slightly heavier than MZ twins (20), and thus a different mean BMI was used for MZ and DZ twins.

Next, we fitted gene-environment interaction models to test the significance of the moderator effect of parental education (21). In these models, parental education, used as a continuous variable, was allowed to modify the genetic and environmental variation of BMI. Since weak but systematic shared environmental effects were found for BMI in this database, especially in childhood (2), we fitted both a more parsimonious additive genetic/ unique environment (AE) model and an additive genetic/ shared environment/ unique environment (ACE) model, which needs more statistical power. The genetic models were fitted to the data by the OpenMx package (version 2.0.1) of R statistical software (22). The effects of parental education on mean BMI were estimated by Stata/SE 13.1 for Windows statistical software. The effect of intra-pair correlations on 95% confidence intervals (CI) was taken

into account by the cluster option of Stata. Further, we adjusted these mean modification effects for zygosity because of slight differences in BMI (20) and parental education between MZ and DZ twins (17).

Results

Table 1 presents the descriptive statistics by age and sex. Mean BMI shows the nadir at 5 years of age and the steady increase until 50-59 years of age with modest sex differences. Mean BMI was highest in North America and Australia and lowest in East Asia (Table S2). Maternal and paternal education decreased from the younger to the older age groups reflecting the increasing education over the birth cohorts. As expected, parental education was virtually identical for males and females.

Figure 1 presents the associations between parental education and BMI. No inverse educational association was seen from 1 to 3 years of age, and the sons of better-educated parents had even a slightly higher BMI. An inverse educational association emerged at 5 years of age in boys and 4 years of age in girls and became stronger until adolescence. In adulthood, the inverse association between parental education and BMI was statistically significant in most of the age groups and stronger in women than in men. In men this association was somewhat weaker in late adulthood as compared with middle-age, but otherwise no systematic differences between the age groups in adulthood were seen.

Figure 2 presents the associations between parental education and BMI in the three cultural-geographic regions. Since most of the BMI measures came from European cohorts, the pattern in Europe followed closely the estimates in the pooled cohort. In North America and Australia, parental education showed stronger associations with mean BMI than in Europe in most of age groups. These differences were

more pronounced in females than in males. In East Asia, similar associations were found in females, but because of wider 95% CIs, they were not statistically significant. However, East Asian males showed no evidence on the association between parental education and BMI.

The total variation of BMI in the three categories of parental education, decomposed to additive genetic, shared environmental and unique environmental variances, is shown in Figure 3 (the exact estimates with 95% CIs are provided in Table S3). The total BMI variation was greatest in the low parental education category and smallest in the high parental education category in all age groups. With a few exceptions, the BMI variation in the intermediate parental education category was between the high and low education categories. In nearly all age groups, the difference in BMI variation between the low and high parental education categories was statistically significant as seen by non-overlapping 95% CIs (Table S3). When we studied the components of variation, a similar pattern was observed with a few exceptions for additive genetic and unique environmental variances. Except in two age groups, the difference was statistically significant for additive genetic variation, but for unique environmental variation, in nearly half of the age groups the 95% CIs overlapped. Shared environmental variance components explained part of the variance, especially in boys and girls of 14 years of age or younger. However, in most of the age groups, they were not statistically significant, and the 95% CIs also overlapped between the educational categories (Table S3).

The gene-environment interaction models confirmed the results of the stratified analyses (Table S4). When we fitted the AE model, in all age groups except 70-79 years old men, additive genetic modification effects were negative, i.e. higher parental education was associated with less genetic variation. However, in men 17 years of age or older and in girls three years or younger and women 50-59 years or older, the modification effects were weaker than in the other age groups and not significant.

Most of unique environmental modification effects were also negative, but weaker than additive genetic modification effects, and around half of them were not statistically significant. In the ACE model, most of the additive genetic and shared environmental modification effects were negative, but there was more fluctuation in the estimates because of lesser statistical power, and only part of them were statistically significant.

Figures 4 and 5 depict the similar decomposition of BMI variance by the cultural-geographic region. Since the results for the intermediate parental educational category were, in general, between the high and low educational categories, they are not shown, but all estimates with 95% CIs are available in Table S5 and Table S6. The total BMI variance was greatest in North America and Australia and smallest in East Asia. In Europe, as well as in North America and Australia, BMI variation was systematically greater in males and females whose parents have low education as compared to the offspring of highly educated parents. In most of the age groups, this difference was statistically significant as seen as non-overlapping 95% CIs (Tables S5 and Table S6). When we restricted the analyses to North Americans and Australians with Caucasian ethnicity, the variances decreased somewhat, but they were still larger than in the other cultural-geographic regions and highest in those with low parental education (Table S5 and Table S6).

The differences in the total BMI variation between the parental educational categories were mainly due to differences in additive genetic variation. An exception was North American and Australian boys and girls 11 years of age or younger, for whom the difference in most age groups was mainly due to shared environmental variation. In Europe, we also observed some evidence for the greater role of shared environment in the low parental education category until 14 years of age, but the differences were not

statistically significant. In East Asia, no systematic differences were seen in the total variance of BMI according to parental education.

The gene-environment interaction models confirmed these results (Table S7). In Europe, the additive genetic modification effects were consistently negative, whereas there was more fluctuation in the common environmental modifications effects. In contrast, in North America and Australia, especially in boys under 12 years of age, the shared environmental modifications were consistently negative. However when using the ACE models, which require more statistical power, only part of these modifications effects were statistically significant. In East Asia, the modification effects fluctuated in both sides of zero and most of them were not statistically significant.

Discussion

In this study of a very large international dataset of twins, we found that higher parental education was consistently associated with lower additive genetic and unique environmental variance of BMI. This result is in accordance with previous twin and molecular genetic studies. In a previous study based on Dutch twin data, children and adolescents whose parents had middle or low education showed greater genetic BMI variance than those whose parents had high education (3). Danish (12) and US (13) studies of adult twins supported this result by showing greater genetic variation in those with lower than in those with higher education. These results are also in line with candidate genes studies in which low maternal education in children (23) and own education in adults (24) reinforced the effect of FTO gene, the major candidate gene of BMI. Similar results were found for other BMI candidate genes (25,26). However, these molecular genetic studies need replications in other populations, and preferably a GWA study using a large sample size should be conducted. Assuming parental education

to be a good proxy indicator of the socio-economic conditions of individuals and their families, our results might indicate that poorer childhood socio-economic environment reinforces the influence of genetic factors affecting BMI. However, parental education is associated also with own education in adulthood (27), which is further associated with other factors such as intelligence and personality (28). Thus, the mediating pathways are complex and may change through the life-course.

Parental education is associated with BMI after early childhood, which parallels previous population based studies showing no association (29) or lower BMI (30) in the offspring of mothers with lower education before two years of age but a clear inverse correlation between the BMI of offspring and maternal education after four years of age. In early childhood, the lack of association between parental education and offspring BMI might be due to low birth weight associated with low parental education affecting BMI over the first years (29). Nevertheless, it may also reflect a change in the genetic architecture of BMI. A negative genetic correlation between education and BMI (r=-0.28, standard error=0.03) was found based on cross-trait linkage-disequilibrium score regression analysis of large GWA studies (31). As we have reported previously, genetic variation in BMI started to increase after 5 years of age in the CODATwins database (2). This result is in accordance with the previous molecular genetic studies showing that the effects of the FTO gene (32), genetic risk scores of top BMI hits (33,34) and polygenic risk scores from GWA studies (35) started to increase only after early childhood. Thus, it seems that after early childhood, new genetic variants affecting BMI activate and parental education can modify the effects of them, which may be independent of the genetic variants regulating body size in infancy.

The mechanisms explaining the interaction effects between genes and socio-economic factors on BMI are not clear. In the present study, the association of parental education with mean and genetic variance

of BMI persisted through adulthood. This trend might be due to behavior. There is evidence that the FTO gene may affect BMI through food-intake self-regulation (36) and eating styles (37), and many genetic risk variants of adult BMI are active in brain areas having an important role in appetite regulation and many cognitive functions (4,5). Findings that the correlations between BMI and a number of personality, cognitive and brain morphological traits were largely explained by common genetic factors further support the mediating role of brain function (38). It is thus possible that the new genetic variance emerging after mid-childhood relates to the child's food-intake self-regulation, with children learning better self-regulation in households with higher parental education. Childhood social position also relates to factors such as diet, adverse childhood experiences and physical activity (39). There is evidence that physical activity can modify the association between the BMI genetic risk-score and BMI (40), and parallel results have been found in a twin study showing greater genetic variance of BMI and other obesity indicators in sedentary persons as compared to those who are physically active (41). However, the background mechanisms may go even deeper in the field of neuro-physiology. Subordinate female rhesus monkeys had higher caloric consumption than dominant monkeys (42). Also starlings with a disadvantaged early life environment were fatter in adulthood and spent more effort for food gathering than those with more advantaged early life environments (43). Although comparisons between species should be treated with caution, these results may suggest deep neurophysiological pathways between early life social position and later eating behavior.

When comparing the geographic-cultural regions, parental education was more strongly associated with BMI in North America and Australia than in Europe and East Asia. Thus, obesogenic environment may reinforce the association between BMI and parental education since the population level mean of BMI is much higher in North America and Australia than in the other two regions (1). This would suggest that the factors affecting BMI at population level have stronger effects on those having social and/or

genetic susceptibility to gain weight. There has been discussion regarding to which specific societal factors are behind these regional level differences in BMI, but the results are inconclusive (44). However, our findings suggest that identifying socio-economic factors associated with the increase of BMI would have beneficial effects especially on those who are most vulnerable to gain weight. Also other societal factors than obesogenic environment may lead to the weaker effect of parental education on BMI in East Asia. For example, because of cultural differences, food consumption may be differently associated with social factors in different cultural-geographic regions even on the same level of obesogenic environment. More detailed measures of macro-environment would be needed to further disentangle the effect of these societal factors.

In most of the age categories, the differences in BMI variance were mainly due to the greater additive genetic variance in the lower parental education category. However, especially in North America and Australia, this difference was due to greater shared environmental variance in boys and girls at 11 years of age or younger. A Finnish twin study also found that environmental factors shared by co-twins explained a share of BMI variation in children for whom parents had limited education at 11-12 and 14 years of age, but this variance component was not present at 17 years of age (14). Disentangling shared environmental and additive genetic effects requires considerable statistical power (45), and, thus, it is possible that these divergent results within Europe are just because of sample variation. However, these results suggest that in childhood shared environmental factors may contribute directly to the socio-economic differences in BMI, at least in some societies, whereas in adolescence and adulthood, parental education affects BMI mainly by modifying genetic effects.

Our data have strengths but also limitations. The main strength is the large sample size allowing us to construct and test models in narrow age groups and offering the required statistical power to analyze

the effect of parental education over the lifespan. Further, we were able to analyze these differences between cultural-geographic regions representing different levels of obesogenic environment. A limitation is that our data is heavily biased toward Caucasian populations following the Westernized life-style thus limiting statistical power in East Asia. New data collections in East Asia and in other non-westernized cultural contexts would thus be warranted, especially because we found evidence that there may be substantial differences in the effect of parental education on BMI between more and less obesogenic societies. Also our data come from multiple sources, which may differ in representativeness and other factors potentially affecting the strength of found associations.

Conclusion

We found clear evidence that higher parental education is associated with lower BMI and less genetic and environmental variation of BMI over the lifespan. The critical period is located just after early childhood when BMI variation started to increase. In addition to genetic variance, especially in late childhood, the environment shared by co-twins and siblings can be important. The educational differences are particularly prominent in North America and Australia. Socio-economic position of the family affects BMI partly by modifying genetic factors, and the effects on BMI are long lasting, being present through adulthood, especially in obesogenic societies.

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Figure legends

Figure 1. Mean BMI modification effects of parental education with 95% confidence intervals from 1 until 70-79 years of age by sex.

Figure 2. Mean BMI modification effects of parental education with 95% confidence intervals from 1 until 70-79 years of age by sex and cultural-geographic region.

Figure 3. Total variation of BMI decomposed to additive genetic (gray), shared environmental (white) and unique environmental variations (black) from 1 until 70-79 years of age by sex and parental education.

Figure 4. Total variation of BMI decomposed to additive genetic (gray), shared environmental (white) and unique environmental variations (black) from 1 until 70-79 years of age by parental education and geographic-cultural region in males.

Figure 5. Total variation of BMI decomposed to additive genetic (gray), shared environmental (white) and unique environmental variations (black) from 1 until 70-79 years of age by parental education and geographic-cultural region in females.

Table 1. The number of twin individuals and means and standard deviations (SD) of body mass index (BMI) and parental education by age.[1]

	Males							Females						
Age	N	BMI (kg/m^2)		Maternal education (years)		Paternal education (years)		N	BMI (kg/m^2)		Maternal education (years)		Paternal education (years)	
		Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD
1	13548	17.1	1.36	13.8	2.31	13.9	2.6	14023	16.7	1.37	13.8	2.33	13.9	2.63
2	11273	16.5	1.37	14.0	2.42	14.0	2.70	11324	16.2	1.37	14.0	2.44	13.9	2.76
3	10907	15.9	1.32	14.2	2.49	14.2	2.73	11460	15.6	1.37	14.2	2.51	14.1	2.76
4	3533	15.9	1.68	15.3	3.39	14.7	3.61	3579	15.7	1.68	15.4	3.38	14.7	3.68
5	6533	15.3	1.58	14.4	2.61	14.3	2.82	6577	15.1	1.66	14.3	2.53	14.3	2.84
6	1898	15.7	1.95	15.1	3.07	14.9	3.23	1998	15.5	1.98	15.2	3.11	14.9	3.32
7	7084	15.4	1.78	14.3	2.44	14.3	2.64	7499	15.4	1.94	14.2	2.48	14.3	2.71
8	4388	15.8	2.06	14.4	2.80	14.3	2.89	4503	15.8	2.22	14.4	2.79	14.3	2.95
9	3497	16.7	2.60	14.7	3.14	14.4	3.23	3471	16.7	2.76	14.8	3.12	14.5	3.28
10	7017	16.6	2.39	14.1	2.57	14.2	2.71	7417	16.7	2.50	14.0	2.46	14.2	2.65
11	3987	17.5	2.69	13.4	3.67	12.9	4.00	4078	17.5	2.92	13.4	3.67	12.9	4.04
12	6760	17.6	2.69	13.8	2.78	13.8	3.13	7023	17.7	2.73	13.7	2.79	13.8	3.18
13	3111	18.6	3.04	14.3	2.87	14.2	3.07	3436	18.7	3.03	14.2	2.81	14.2	3.00
14	5447	19.3	2.94	13.3	3.59	12.9	3.95	6121	19.5	3.02	13.3	3.48	12.9	3.90
15	3278	20.0	3.28	14.3	2.85	14.3	3.02	3603	20.1	3.16	14.2	2.68	14.2	2.93
16	3948	20.8	3.08	13.2	3.19	13.3	3.32	4616	20.6	2.96	13.2	3.07	13.2	3.24
17	5468	21.3	2.91	13.0	3.36	12.8	3.59	6140	20.9	2.95	13.2	3.14	13.0	3.44
18	4224	21.8	2.98	12.0	3.60	11.7	4.10	3775	21.2	3.12	12.7	3.35	12.5	3.74
19	2664	22.0	2.88	12.3	3.04	12.4	3.46	3198	21.5	3.28	13.0	2.78	13.3	3.03
20-29	10005	23.3	3.26	12.0	3.53	11.9	3.91	12096	22.2	3.77	12.5	3.30	12.6	3.62
30-39	7952	25.0	3.45	11.8	2.93	12.0	3.37	11204	23.1	4.18	11.9	2.99	12.2	3.35
40-49	9440	25.7	3.40	11.2	3.22	11.0	3.71	8399	24.3	4.48	11.7	3.00	11.7	3.38
50-59	4720	26.7	3.91	11.0	3.11	10.6	3.54	3274	24.8	4.40	10.8	3.30	10.8	3.41
60-69	4397	26.2	3.54	10.4	3.24	10.0	3.63	2315	24.5	3.90	10.3	3.17	10.3	3.57
70-79	2187	25.6	3.17	10.4	3.40	9.8	3.88	806	24.2	3.93	10.0	3.26	10.4	3.79

[1]Data from the following twin projects have been pooled: Europe (Child and Adolescent Twin Study in Sweden, Netherlands Twin Cohort of Children, FinnTwin12, FinnTwin16, East Flanders Prospective Twin Survey, Gemini, Italian Twin Registry, Norwegian Twin Registry, Portugal Twin Cohort, TCHAD-study, Turkish Twin Study); USA (Boston University Twin Project, California Twin Program, Carolina African American Twin Study of Aging, Colorado Twin Registry, Michigan Twins Study, Mid Atlantic Twin Registry, Minnesota Twin Registry, University of Southern California Twin Study, Texas Twin Project, Vietnam Era Twin Study of Aging, NAS-NRC Study); East Asia (Korean Twin-Family Register, Ochanomizu University Twin Project, Qingdao Twin Registry Children, South Korea Twin Registry, West Japan Twins and Higher Order Multiple Births Registry); and others (Australian Twin Registry, Longitudinal Israeli Study of Twins)