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10.3945/ajcn.116.130252

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

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


† deceased

Author affiliations:

Department of Social Research, University of Helsinki, Helsinki, Finland. (KaSi, AIJe, ReSu, SaAa)

Osaka University Graduate School of Medicine, Osaka University, Osaka, Japan. (KaSi, ChHo)

Department of Genetics, Physical Anthropology and Animal Physiology, University of the Basque Country UPV/EHU, Leioa, Spain. (AIJe, EsRe)
Department of Education, Mokpo National University, Jeonnam, South Korea. (YoMiHu)

Department of Public Health Nursing, Osaka City University, Osaka, Japan. (YoYo)

The Danish Twin Registry, Department of Public Health, Epidemiology, Biostatistics & Biodemography, University of Southern Denmark Odense, Denmark. (JaBHj, SöMö, KaCh, AxSk)

Department of Health Science, Ishikawa Prefectural Nursing University, Kahoku, Ishikawa, Japan. (SyOo)

Department of Public Health, University of Helsinki, Helsinki, Finland. (SaAa, KaHe, JaKa)

Department of Noncommunicable Diseases Prevention, Qingdao Centers for Disease Control and Prevention, Qingdao, China. (FuJi, FeNi, ZePa)

HealthTwiSt GmbH, Berlin, Germany. (AnBu)

Department of Psychology, Bielefeld University, Bielefeld, Germany. (ChKa)

Boston University, Department of Psychological and Brain Sciences, Boston, MA, USA. (KiJSa)

Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada. (KeLJa)

Department of Preventive Medicine, Keck School of Medicine of USC, University of Southern California, Los Angeles, California, USA. (WeCo, AmEHw, ThMMa)

USC Norris Comprehensive Cancer Center, Los Angeles, California, USA. (WeCo, ThMMa)

Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China. (WeGa, CaYu, LiLi)

Institute for Behavioral Genetics, Boulder, Colorado, USA. (RoPCo, BrMHu)

Department of Clinical Biochemistry and Pharmacology and Department of Clinical Genetics, Odense University Hospital, Odense, Denmark. (KaCh)

Department of Clinical Research, University of Southern Denmark, Odense, Denmark. (KiOKy)

Odense Patient data Exploratory Network (OPEN), Odense University Hospital, Odense, Denmark. (KiOKy)

Centre of Human Genetics, University Hospitals Leuven, Leuven, Belgium. (CaADe, RoFVI)
Department of Obstetrics and Gynaecology, Ghent University Hospitals, Ghent, Belgium. (CaADe)

The Charles Bronfman Institute for Personalized Medicine, The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. (RuJFLo)

Health Behaviour Research Centre, Department of Epidemiology and Public Health, Institute of Epidemiology and Health Care, University College London, London, UK. (JaWa, CIHLl, AbFi, ToAMc)

King's College London, MRC Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, London, UK. (ToAMc, ThCEl, RoPl),

Department of Psychology, Goldsmiths, University of London, London, UK. (AlMGr)

State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China. (MiHe, XiDi)

Centre for Eye Research Australia, University of Melbourne, Melbourne, Australia. (MiHe)

Bandim Health Project, INDEPTH Network, Bissau, Guinea-Bissau. (MoBjAn)

Research Center for Vitamins and Vaccines, Statens Serum Institute, Copenhagen, Denmark. (MoBjAn)

Department of Endocrinology, Odense University Hospital, Odense, Denmark. (MoBjAn, HeBeNi, MoSo)

Department of Infectious Diseases, Odense University Hospital, Odense, Denmark.

Department of Radiology and Oncotherapy, Semmelweis University, Budapest, Hungary. (AdDTa, DaLTa)

Hungarian Twin Registry, Budapest, Hungary. (AdDTa, DaLTa)

Istituto Superiore di Sanità - National Center for Epidemiology, Surveillance and Health Promotion, Rome, Italy. (MaASt, CoFa, CrDi)

The Hebrew University of Jerusalem, Jerusalem, Israel. (ArKnNo, LiAb)
Hadassah Hospital Obstetrics and Gynecology Department, Hebrew University Medical School, Jerusalem, Israel. (DaMa)

Michigan State University, East Lansing, Michigan, USA. (SAIBu, KeLKI)

Department of Human and Molecular Genetics, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia, USA. (JuLSi, LiJEa)

Department of Human and Molecular Genetics, Psychiatry & Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia, USA. (HeHMa)

Department of Psychology, University of Minnesota, Minneapolis, MN, USA. (RoFKr, MaMc, ShPa)

Department of Psychology, University of Southern California, Los Angeles, CA, USA. (MaGa, LaABa, CaTu)

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. (MaGa, PaKEMA, NaLPe, PaLi)

Institute of Medicine, National Academy of Sciences Washington, DC, USA. (DaABu)

Department of Biological Psychology, VU University Amsterdam, Amsterdam, Netherlands. (MeBa, ToCEMBe, GoWi, DoIBo)

Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Victoria, Australia. (JeMCr, RiSa)

Department of Paediatrics, University of Melbourne, Parkville, Victoria, Australia. (JeMCr, RiSa)

Department of Physical Education and Sport, University of Madeira, Funchal, Portugal. (DuLFr)

CIFI2D, Faculty of Sport, Porto, University of Porto, Portugal. (JoAnMa)

School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Ontario, Canada. (LiDu)

École de psychologie, Université Laval, Québec, Canada. (MiBo, GiDi)

Institute of Genetic, Neurobiological, and Social Foundations of Child Development, Tomsk State University, Russian Federation. (MiBo)
Département de psychologie, Université du Québec à Montréal, Montréal, Québec, Canada. (MaBr)

École de psychoéducation, Université de Montréal, Montréal, Québec, Canada. (FrVi)

Genetic Epidemiology Department, QIMR Berghofer Medical Research Institute, Brisbane, Australia. (NiGMa, SaEMe)

Molecular Epidemiology Department, QIMR Berghofer Medical Research Institute, Brisbane, Australia. (GrWMo)

Department of Psychology, Pusan National University, Busan, South Korea. (YoCh)

Stanford Prevention Research Center, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA. (GaESw)

Center for Health Sciences, SRI International, Menlo Park, CA, USA. (RuKr)

Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden. (PeTy, FiRa)

MRC Integrative Epidemiology Unit, University of Bristol, Bristol, U.K. (ClMAHa, ThIASø)

Healthy Twin Association of Mongolia, Ulaanbaatar, Mongolia. (GoBa, DaNa)

Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. (DaNa)

Department of Psychology, University of Texas at Austin, Austin, TX, USA. (KPaHa, ElMTuDr)

Department of Statistics, Faculty of Arts and Sciences, Kırıkkale University, Kırıkkale, Turkey. (SeYÖn)

Departments of Psychiatry, Psychology, and Human and Molecular Genetics, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, USA. (FaAl)

Department of Twin Research and Genetic Epidemiology, King's College, London, UK. (TiSp, MaMa, GeLa)

Örebro University, School of Law, Psychology and Social Work, Örebro, Sweden. (CaTu)

College of Medicine, Washington State University – Health Sciences Spokane, Spokane, WA, USA. (GIEDu)

Washington State Twin Registry, Washington State University, Seattle, WA, USA. (DeBu)
Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA, USA (JaHG)

Novo Nordisk Foundation Center for Basic Metabolic Research (Section on Metabolic Genetics) and Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark. (ThIASø)

Institute of Preventive Medicine, Bispebjerg and Frederiksberg Hospitals, Copenhagen, The Capital Region, Denmark. (ThIASø) National Institute for Health and Welfare, Helsinki, Finland. (JaKa)

Institute for Molecular Medicine FIMM, Helsinki, Finland. (JaKa)

No disclaimers or conflict of interests

Author’s last names


Correspondence address:
Karri Silventoinen
University of Helsinki, Population Research Unit, Department of Social Research
P.O. Box 18, FIN-00014 University of Helsinki, Finland
GSM: +358400-620726
E-mail: karri.silventoinen@helsinki.fi
Sources of support

This study was conducted within the CODATwins project (Academy of Finland #266592). Support for participating twin projects: The Boston University Twin Project is funded by grants (#R01 HD068435 #R01 MH062375) from the National Institutes of Health to K. Saudino. California Twin Program was supported by The California Tobacco-Related Disease Research Program (7RT-0134H, 8RT-0107H, 6RT-0354H) and the National Institutes of Health (1R01ES015150-01). Chinese National Twin Registry is funded by Special Fund for Health Scientific Research in the Public Welfare (Project No: 201502006), China. Colorado Twin Registry is funded by NIDA funded center grant DA011015, & Longitudinal Twin Study HD10333; Author Huibregtse is supported by to 5T32DA017637-11. Danish Twin Registry is supported by the National Program for Research Infrastructure 2007 from the Danish Agency for Science, Technology and Innovation, The Research Council for Health and Disease, the Velux Foundation and the US National Institute of Health (P01 AG08761). Since its origin the East Flanders Prospective Survey has been partly supported by grants from the Fund of Scientific Research, Flanders and Twins, a non-profit Association for Scientific Research in Multiple Births (Belgium). Data collection and analyses in Finnish twin cohorts have been supported by ENGAGE – European Network for Genetic and Genomic Epidemiology, FP7-HEALTH-F4-2007, grant agreement number 201413, National Institute of Alcohol Abuse and Alcoholism (grants AA-12502, AA-00145, and AA-09203 to R J Rose, the Academy of Finland Center of Excellence in Complex Disease Genetics (grant numbers: 213506, 129680), and the Academy of Finland (grants 100499, 205585, 118555, 141054, 265240, 263278 and 264146 to J Kaprio). K Silventoinen is supported by Osaka University's International Joint Research Promotion Program. Gemini was supported by a grant from Cancer Research UK (C1418/A7974). Waves 1-3 of Genesis 12-19 were funded by the W T Grant Foundation,
the University of London Central Research fund and a Medical Research Council Training Fellowship (G81/343) and Career Development Award (G120/635) to Thalia C. Eley. Wave 4 was supported by grants from the Economic and Social Research Council (RES-000-22-2206) and the Institute of Social Psychiatry (06/07 – 11) to Alice M. Gregory who was also supported at that time by a Leverhulme Research Fellowship (RF/2/RFG/2008/0145). Wave 5 was supported by funding to Alice M. Gregory from Goldsmiths, University of London. Guangzhou Twin Eye Study is supported by National Natural Science Foundation of China (grant #81125007). Anthropometric measurements of the Hungarian twins were supported by Medexpert Ltd., Budapest, Hungary. Longitudinal Israeli Study of Twins was funded by the Starting Grant no. 240994 from the European Research Council (ERC) to Ariel Knafo.

The Michigan State University Twin Registry has been supported by Michigan State University, as well as grants R01-MH081813, R01-MH0820-54, R01-MH092377-02, R21-MH070542-01, R03-MH63851-01 from the National Institute of Mental Health (NIMH), R01-HD066040 from the Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD), and 11-SPG-2518 from the MSU Foundation. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIMH, the NICHD, or the National Institutes of Health. The NAS-NRC Twin Registry acknowledges financial support from the National Institutes of Health grant number R21 AG039572. Netherlands Twin Register acknowledges the Netherlands Organization for Scientific Research (NWO) and MagW/ZonMW grants 904-61-090, 985-10-002, 912-10-020, 904-61-193,480-04-004, 463-06-001, 451-04-034, 400-05-717, Addiction-31160008, Middelgroot-911-09-032, Spinozapremie 56-464-14192; VU University’s Institute for Health and Care Research (EMGO+ ); the European Research Council (ERC - 230374), the Avera Institute, Sioux Falls, South Dakota (USA). PETS was supported by grants from the Australian National Health and Medical Research Council (grant numbers 437015 and 607358 to JC, and RS), the Bonnie Babes Foundation (grant number BBF20704 to JMC), the Financial Markets Foundation for
Children (grant no. 032-2007 to JMC), and by the Victorian Government’s Operational Infrastructure Support Program. Madeira data comes from the following project: Genetic and environmental influences on physical activity, fitness and health: the Madeira family study Project reference: POCI/DES/56834/2004 Founded by the Portuguese agency for research (The Foundation for Science and Technology [FCT]). The Quebec Newborn Twin Study acknowledges financial support from the Fonds Québécois de la Recherche sur la Société et la Culture, the Fonds de la Recherche en Santé du Québec, the Social Science and Humanities Research Council of Canada, the National Health Research Development Program, the Canadian Institutes for Health Research, Sainte-Justine Hospital’s Research Center, and the Canada Research Chair Program (Michel Boivin). South Korea Twin Registry is supported by National Research Foundation of Korea (NRF-371-2011-1 B00047). The Texas Twin Project is currently funded by grants AA023322 and HD081437 from the National Institutes of Health. The Twins Early Development Study (TEDS) is supported by a program grant (G0901245) from the UK Medical Research Council and the work on obesity in TEDS is supported in part by a grant from the UK Biotechnology and Biological Sciences Research Council (31/D19086). S.Y. Öncel and F. Aliev are supported by Kirikkale University Research Grant: KKU, 2009/43 and TUBITAK grant 114C117. TwinsUK was funded by the Wellcome Trust; European Community’s Seventh Framework Programme (FP7/2007-2013). The study also receives support from the National Institute for Health Research (NIHR) BioResource Clinical Research Facility and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The University of Southern California Twin Study is funded by a grant from the National Institute of Mental Health (R01 MH58354). University of Washington Twin Registry was supported in part by grant NIH RC2 HL103416 (D. Buchwald, PI). The West Japan Twins and Higher Order Multiple Births Registry was supported by Grant-in-Aid for Scientific Research (B) (grant number 15H05105) from the Japan Society for the Promotion of Science.
Running head: Heritability of BMI in childhood and adolescence

Abbreviations

-2LL= -2 log-likelihood

Δ= change

95% CI= 95 percent confidence interval

A=additive genetic variance component

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

BMI=body mass index

C=shared environmental variance component

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

d.f.=degrees of freedom

DZ=dizygotic twin

E=unique environmental variance component

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

logBMI= natural logarithm of body mass index

MZ=monozygotic twin

SD=standard deviation

Not a clinical trial
Abstract

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

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

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

Results: The variance of BMI increased from 5 years of age along with increasing mean BMI. The proportion of BMI variation explained by additive genetic factors was lowest between 4 and 8 years of age ($a^2=0.41-0.74$) and again between 11 and 13 years of age in boys ($a^2=0.65-0.72$) as well as 13 years of age in girls ($a^2=0.57$). This was because of a stronger influence of environmental factors shared by co-twins at these ages. After 15 years of age, the effect of shared environment was not observed. The sex-specific expression of genetic factors occurred already in infancy, but was prominent at 13 years and later ages. Genetic variance of BMI was highest in North-America and Australia and lowest in East-Asia, but the relative proportion of genetic variation to total variation was roughly similar across different regions.
Discussion: Environmental factors shared by co-twins affect BMI in childhood and during puberty, but little evidence for their contribution was found in late adolescence. Our results suggest that genetic factors play a major role in the variation of BMI in adolescence in populations of different ethnicities and exposed to different environmental factors predisposing to obesity.

Key words: BMI, children, genetics, twins, international comparisons
Introduction

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

However, little is known about the universality of these results considering that the two previous multinational analyses were primarily based on Western populations, with the exception of one Korean twin cohort. A multinational study pooling eight cohorts of adolescent twins found that the heritability estimates of BMI were approximately similar in Western and East-Asian populations even when the
mean BMI and total variation of BMI were higher in Western populations (8). However, it is still unknown whether the genetic architecture is similar at earlier ages. Furthermore, because of a lack of data in the previous multinational analyses (5,6), it is still unclear how genetic influences on BMI differ between boys and girls over infancy and childhood.

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

**Subjects and methods**

The data were derived from the CODATwins (COllaborative project of Development of Anthropometrical measures in Twins) database described elsewhere (9). Briefly, the CODATwins project was intended to collect height and weight measurements from all twin cohorts in the world. For the present analysis, we selected 45 twin cohorts from 21 countries having at least 50 measures of height and weight from 0.5 to 19.5 years of age. We divided these cohorts into three geographic-cultural regions: Europe, North-America and Australia, and East-Asia. The prevalence of obesity and overweight is lowest in East-Asia, thus representing a lesser obesogenic environment, and highest in North-America and Australia thus representing a more obesogenic environment (10). We had 20
cohorts from Europe, 15 cohorts from North-America and Australia and seven cohorts from East-Asia. Furthermore, we had one cohort from Africa and two from the Middle-East. However, during the course of the study, we found that in a large Chinese National Twin Cohort Study, the heritability estimates of BMI were substantially lower than in other East-Asian cohorts as also reported previously (11). Given of this heterogeneity, we did not include this cohort in the reported analyses but tested how it would change the results in East-Asia. The names of the cohorts included in the analyses are given in the footnotes of Supplemental table 1, and more information on these cohorts is available elsewhere (9). We eliminated impossible values and outliers in each age and sex group based on visual inspection allowing the BMI distribution to be positively skewed. We removed 1151 measurements as outliers representing 0.3% of the measurements. Further we selected only one observation per twin individual for each 1-year age group. After these exclusions, we had 383,092 BMI values from 180,390 twin individuals (46% females) including 87,782 complete twin pairs (36% MZ twins, 37% same-sex DZ and 27% opposite-sex DZ twins) in the reported analyses. The number of complete twin pairs by age, zygosity and region is presented in Supplemental table 1. The number of BMI measures varied from 6,174 at six years of age to 31,708 at one year of age. The largest number of measures was available from Europe (N=278,479), followed by North-America and Australia (N=66,204), and finally East-Asia (N=36,528). In the additional analyses including the Chinese National Twin Cohort Study, the number of BMI measures in East-Asia was 55,756.

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

BMI showed increasing right skewness from 1 to 18 years of age, and thus we used a log-transformation to normalize the BMI distribution at all ages when calculating the relative proportions of genetic and environmental variation. Further, we adjusted BMI for age and study cohort differences within each 1-year age and sex group by calculating regression residuals. We tested the technical assumptions of twin modeling by comparing the ACE model to the saturated model, which specifies an unconstrained model for trait means, variances and co-variances between co-twins. The fit of nested models was compared by calculating differences in -2 log-likelihood values (Δ-2LL), which follows the \( \chi^2 \)-distribution with a difference in degrees of freedom (Δd.f.) that corresponds to the difference in the number of free parameters estimated. As reported previously, DZ twins had slightly higher mean BMI as well as higher standard deviation (SD) compared to MZ twins at some ages over childhood and adolescence (14). We therefore allowed different means for MZ and DZ twins, but in the genetic models constrained variance components to be the same in all zygosity groups within sex.
The model fit results are presented in Supplemental table 2. At most of the ages, the fit of the full ACE model was significantly poorer than the fit of the saturated model, because of the higher SD of BMI in DZ twins. Even when the differences were small, they were statistically significant because of our very large sample size. Moreover, we tested possible sex differences by constraining the A, C and E parameter estimates to be equal in boys and girls. We found that at most ages, the fit of this model was poor suggesting that these variance components differed between sexes. We also tested whether this difference was because of different variances of logBMI in boys and girls by fitting a scaled model allowing different sizes of variance components but fixing the relative size of these components to be equal. This model also showed significant differences compared to the full ACE model. Accordingly, we presented results separately for boys and girls. Finally, we tested whether a partly different set of genes affects BMI in boys and girls by fitting a sex-limitation model. This model tests whether the genetic correlation of opposite-sex DZ twins is lower than 0.5. We found evidence of a sex-specific genetic effect at some ages seen also as lower opposite-sex DZ correlations (Supplemental table 1 and 2). Therefore, sex-specific genetic effects were allowed at all ages.

We then explored how age modified the genetic and environmental variance components by using gene-environment interaction models (15), where variance components A, C and E were allowed to vary as a function of age. In these models, BMI instead of logBMI was analyzed because we were interested in analyzing how the variance of BMI varies as a contrast to standardized variances studied by univariate models. Given that the parameter estimates differed in males and females (Δ-2LL=514, Δd.f.=15, p-value < 0.0001), we conducted models separately in boys and girls. Because the size of the sex-specific genetic effect varied according to age, we used only same-sex pairs in these age-moderation analyses. In addition to linear effects of age, we also included quadratic age effects on the
variance components because these were highly significant in males ($\Delta-2LL=844, \Delta d.f.=3, p-value < 0.0001$) and females ($\Delta-2LL=495, \Delta d.f.=3, p-value < 0.0001$). In all models, we adjusted mean BMI for the effects of age, age-squared, and study cohort.

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

**Results**

Mean BMI decreased from infancy, reaching a nadir at 5 years of age in boys and girls before increasing until 19 years of age in the pooled data (Table 1). Along with the increasing mean BMI, the variance of BMI also started to increase after 5 years of age. The increase in mean BMI started in Europe after 5 years of age, but slightly later in East-Asia (6 years) and in North-America and Australia (7 years). Boys were slightly heavier than girls from 1 to 4 years of age and again from 17 to 19 years of age, but at other ages sex differences were small. In Europe and North-America and Australia, BMI variances were higher in girls than in boys, especially in adolescence and early adulthood. North-American and Australian boys and girls had the highest mean BMI at all ages, and this difference increased after 7 years of age. European boys and girls had also slightly higher BMI than East-Asians at most ages. Similar differences were also seen in the BMI variation, and at all ages variances were highest in North-America and Australia.
Figure 1 presents the relative proportions of logBMI variation explained by additive genetic, shared environmental and unique environmental factors in the pooled data. The proportion of shared environmental variation was largest between 4 and 8 years of age and subsequently heritability estimates were lower at these ages in boys and girls ($a^2 = 0.41-0.74$). The heritability estimates increased after 8 years of age, but in boys they were somewhat lower again between 11 and 13 years of age ($a^2 = 0.65-0.72$) when the contribution of shared environment was more important again. In girls a lower heritability estimate was seen at 13 years of age ($a^2 = 0.57$). After 15 years of age, the shared environmental variation was no longer present and thus heritability estimates were higher ($a^2 = 0.75-0.84$). The proportion of logBMI variation accounted for unique environmental factors was largely similar at all ages ($e^2 = 0.10-0.20$) and did not show any clear age pattern. The age pattern was similar in boys and girls in spite of the significant sex differences in the relative variance components at most ages (Supplemental table 2). Furthermore, genetic correlations within opposite-sex DZ pairs were generally lower than 0.5, suggesting sex-specific genetic effects, especially in adolescence (Figure 2).

We then fitted similar univariate models for logBMI by region. Only the estimates of additive genetic factors are presented in Figure 3, but all estimates with 95% CIs are available in Supplemental table 3. In Europe and North-America and Australia, the age-related differences in heritability estimates were largely similar to those in the pooled data. Additive genetic factors generally explained the lowest proportion of logBMI between 4 and 8 years of age in boys and girls, which was because of the higher impact of shared environmental factors at these ages. Moderate estimates of shared environmental variation were also seen between 12 and 14 years of age, but after that shared environmental variation diminished (Supplemental table 3). In East-Asia, the pattern was not as clear due to the smaller sample size and larger 95% CIs. However, as in the other regions, the heritability estimates increased in East-Asia after early childhood (6 years in boys and 4 years of girls) because of the diminishing effect of
shared environmental effects. In spite of the roughly similar age patterns, the proportions of logBMI variation explained by genetic and environmental factors were significantly different between the regions at all ages (Supplemental table 2). When the Chinese National Twin Cohort Study was included in the East-Asia region, the proportion of genetic factors decreased and shared environmental factors increased dramatically; the change was from 0.1 to 0.4 unit depending on the age group (data available on request).

Finally, we examined how age modifies the genetic and environmental variances of BMI. Figure 4 presents the results by graphs, and all parameter estimates with 95% CIs are available in Supplemental table 4. In the pooled data, additive genetic variance increased steadily from 1 to 15 years of age in boys and to 19 years of age in girls. Shared environmental variances were largest from 10 to 15 years of age and disappeared after that. When comparing the regions, the general pattern was similar for Europe and North-America and Australia. However, both additive genetic and shared environmental variances were larger in North-America and Australia than in the other two regions, especially in girls. In East-Asia the shared environmental variance was still present at the onset of adulthood, especially in boys. The differences between the regions were highly significant in males ($\Delta-2LL=3490, \Delta d.f.=30, p$-value <0.0001) and females ($\Delta-2LL=3996, \Delta d.f.=30, p$-value <0.0001).

Discussion

In this very large study of nearly 400,000 BMI measures in nearly 88,000 complete twin pairs from 21 countries, we found that the age pattern of the genetic architecture of BMI from infancy to the onset of adulthood was more complex than previously suggested. As in two previous international studies (5,6),
we found that the proportion of BMI variance explained by shared environmental factors was most
prominent from 4 to 8 years of age and it was not present in late adolescence between 15 to 19 years of
age. However, shared environmental variation was also significant in early adolescence between 11 and
13 years of age. The onset of puberty and consequent large changes in body composition take place
between these ages in boys and girls (16). Previous studies have provided evidence that shared
environmental factors partly account for the timing of puberty in girls; for boys the results are less
clear, but this may also be because the onset of puberty is more difficult to assess in boys than in girls
(17,18). It is thus possible that shared environmental factors affect BMI through the timing of puberty
at these ages (19).

The most systematic result of the present study is the increasing role of genetic factors in BMI across
development, starting in infancy and continuing through late adolescence. Previous molecular genetic
studies have indeed found that the variants of FTO gene, which account for the largest fraction of
variance in BMI among the known candidate genes for BMI (20), and other obesity related candidate
genes have increasing effects on BMI after 6 years of age (21-24). Evidence of increasing heritability
of BMI from 4 to 10 years of age has also been reported in genome-wide complex trait analysis (25).
These findings based on molecular genetic studies correspond with our results on the increasing genetic
variation with age. However, this increasing role of genetic factors in BMI with age does not negate the
importance of health behaviors associated with childhood obesity, as genetic factors can affect BMI by
modifying food intake and other behavioral factors. For example, the variants of FTO gene, which act
on the actual functional gene IRX3 (26), were found to be associated with food-intake self-regulation
and eating styles in childhood which are further associated with weight gain (27). Although not yet
conclusive, there is evidence that common genetic risk variants of BMI are active in the hypothalamus,
pituitary gland, hippocampus and limbic system, i.e., areas of brain having an important role in appetite
regulation, learning, cognition, emotion and memory (28). It has also been found that shared
environmental factors have effects on nutritional intake in childhood (29), but they disappear in
adulthood when genetic factors become more important (30,31). The increasing genetic variation in
BMI may thus reflect the increasing independence of children from their parents in eating and other
behavioral factors associated with the variation of BMI. However, the associations between energy
intake and obesity are complex and still an object of debate (32). Differences in DNA methylation have
also been found between lean and obese children (33), and epigenetic processes by themselves are in
part genetically regulated (34). Therefore, it is possible that part of the genetic variation may be
mediated by epigenetic effects.

We found some evidence for sex-specific genetic contributions to BMI. The lowest genetic correlation
within opposite-sex DZ pairs was found at 13 years of age probably coinciding with the onset of
puberty. However, a sex-specific genetic contribution was also clear after puberty, which probably
reflects the increasing differences in body composition between boys and girls with age (16). This is
consistent with the sex-specific genetic contribution in adult BMI found in a study of twin cohorts with
opposite-sex twins from 7 countries (35). However, it is noteworthy that lower genetic correlations for
opposite-sex pairs were found even in infancy, indicating that a partly different set of genes regulates
BMI prior to the major hormonal changes that occur during puberty. This suggests some caution when
interpreting results from genetic studies that have relied upon BMI pooling of boys and girls, even
while focusing on pre-pubertal children. Otherwise, there were relatively minor differences in the
 genetic architecture of BMI between boys and girls, and the general age patterns were largely similar.

When comparing regions, North-American and Australian children and adolescents presented greater
means and larger total variation of BMI than their European and East-Asian peers. The relative
proportions of genetic and environmental sources of variations were, however, roughly similar in these three regions. These results are consistent with those of previous international twin studies showing larger mean and variance of BMI, yet similar heritability estimates in Caucasian and in East-Asian populations in adolescence (8). Thus, increasing BMI was associated with increasing variation in BMI, caused substantially by genetic variation. This suggests that genetic factors have an important role in individual differences in BMI in various populations differing in ethnicity, environmental exposures, as well as in their possible interactions. These results are consistent with studies in Denmark (36) and Sweden (37) suggesting that both total and genetic variation of BMI increased during the obesity epidemic. It is, however, noteworthy that we limited our East-Asian cohorts to affluent populations including the affluent Shandong and Guangdong provinces but excluding poorer areas of China. As reported previously, the heritability estimates of BMI were much lower and common environmental estimates higher in other areas of China (11), which may indicate larger differences between families in nutritional status. This emphasizes the importance of collecting data on twins living under different environmental exposures.

The data used in this study have both strengths and weaknesses. The main strength is the very large sample size allowing an investigation of the change of the genetic and environmental contributions to individual differences in BMI in much more detail than in previous studies. We also have twin participants from different countries, thereby making it possible to stratify the analyses by regions of various ethnicities and obesogenic environments. Individual-based data also have many advantages as compared to literature-based meta-analyses, such as better opportunities for statistical modeling and lack of publication bias. However, even when the large majority of the twin cohorts in the world participated in this project, our data still had only limited power for East Asia, especially in adolescence. Another important limitation is that there were only few data sets available from the
Middle East and Africa, and a lack of data from South-America. This underlines the need for new data collection in these geographic regions. There were some violations of the assumption of twin modeling due to the larger variation in DZ twins than in MZ twins at some ages (14). The differences in the variation are, however, small and become statistically significant because of the very large sample size of our data. Finally, we did not have any area-level indicators and classified the cultural-geographic areas as less or more obesogenic based on the prevalence of adult obesity (10). Conceptualizing obesogenic environments is difficult, but it has been suggested that both micro- and macro-level environmental factors affect both food intake and physical exercise (38). More detailed measurements of the physical environment are thus needed to analyze the factors in the environment that potentially modify genetic influences on the development of obesity.

In conclusion, we found evidence that environmental factors shared by co-twins contribute to BMI variation in early childhood and during puberty, but their role diminishes before the onset of adulthood. Genetic variation increased steadily during childhood and adolescence, which may indicate gene-environment correlation processes, whereby an increasing independence of children from their parents led them to express their behaviors according to their genetic background. Genes affecting BMI were partly sex-specific, even in infancy, with their contribution becoming more prominent during and after puberty. Obesogenic environment is associated with increasing genetic variation of BMI in North-America and Australia as compared to East-Asia, but the relative proportions of genetic and environmental variations were roughly similar. Our results suggest that, in spite of different ethnicities and environmental exposures, genetic factors play a major role behind the variation of BMI in adolescence in affluent societies.
Conflicts of interests

None

Authors’ contribution

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


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

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Figure 1. Proportions of logBMI variation with 95% confidence intervals explained by additive genetic, shared environmental and unique environmental factors by age and sex.

Figure 2. Additive genetic correlations with 95% confidence intervals within opposite-sex DZ pairs by age.

Figure 3. Proportions of logBMI variation with 95% confidence intervals explained by additive genetic factors by age, sex and region.

Figure 4. Changes of additive genetic (dash line), shared environmental (solid line) and unique environmental (dot line) variance with increasing age in quadratic gene–environment interaction model by sex and region.