Association between birthweight and later body mass index

Jelenkovic, Aline; Yokoyama, Yoshie; Sund, Reijo; Pietiläinen, Kirsi H; Hur, Yoon-Mi; Willemse, Gonneke; Bartels, Meike; van Beijsterveldt, Toos Cem; Ooki, Syuichi; Saudino, Kimberly J; Stazi, Maria A; Fagnani, Corrado; D'Ippolito, Cristina; Nelson, Tracy L; Whitfield, Keith E; Knafo-Noam, Ariel; Mankuta, David; Abramson, Lior; Heikkilä, Kauko; Cutler, Tessa L; Hopper, John L; Wardle, Jane; Llewellyn, Clare H; Fisher, Abigail; Corley, Robin P; Huibregtse, Brooke M; Derom, Catherine A; Vliezinc, Robert F; Loos, Ruth Jf; Bierregaard-Andersen, Morten; Beck-Nielsen, Henning; Sodemanni, Morten; Tarnoki, Adam D; Tarnoki, David L; Burt, S Alexandra; Klump, Kelly L; Ordoñana, Juan R; Sánchez-Romera, Juan F; Colodro-Conde, Lucia; Dubois, Lise; Boivin, Michel; Brendgen, Mara; Dionne, Ginette; Vitaro, Frank; Harris, Jennifer R; Brandt, Ingunn; Nilsen, Thomas Sevenius; Craig, Jeffrey M; Saffery, Richard; Rasmussen, Finn; Tynelius, Per; Bayasgalan, Gombojav; Narandalai, Danshiitsoodol; Haworth, Claire Ma; Ploheim, Robert; Ji, Fuling; Ning, Feng; Pang, Zengchang; Rebato, Esther; Krueger, Robert F; McGue, Matt; Pahlen, Shandell; Boomsma, Dorret I; Sørensen, Thorkild I.A.; Kaprio, Jaakko; Silventoinen, Karri

Published in:
International Journal of Epidemiology

DOI:
10.1093/ije/dyx031

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Jelenkovic, A., Yokoyama, Y., Sund, R., Pietiläinen, K. H., Hur, Y-M., Willemse, G., ... Silventoinen, K. (2017). Association between birthweight and later body mass index: an individual-based pooled analysis of 27 twin cohorts participating in the CODATwins project. DOI: 10.1093/ije/dyx031
Early Life and Obesity

Association between birthweight and later body mass index: an individual-based pooled analysis of 27 twin cohorts participating in the CODATwins project

Aline Jelenkovic,1,2* Yoshie Yokoyama,3 Reijo Sund,1 Kirs H Pietiläinen,4 Yoon-Mi Hur,5 Gonneke Willemsen,6 Meike Bartels,6 Toos CEM van Beijsterveldt,6 Syuichi Ooki,7 Kimberly J Saudino,8 Maria A Stazi,9 Corrado Fagnani,9 Cristina D’Ippolito,9 Tracy L Nelson,10 Keith E Whitfield,11 Ariel Knafo-Noam,12 David Mankuta,13 Lior Abramson,12 Kauko Heikkilä,14 Tessa L Cutler,15 John L Hopper,15,16 Jane Wardle,17 Clare H Llewellyn,17 Abigail Fisher,17 Robin P Corley,18 Brooke M Huibregtse,18 Catherine A Derom,19,20 Robert F Vlietinck,19 Ruth JF Loos,21 Morten Bjørregaard-Andersen,22,23,24 Henning Beck-Nielsen,24 Morten Sødemann,25 Adam D Tarnoki,26,27 David L Tarnoki,26,27 S Alexandra Burt,28 Kelly L Klump,28 Juan R Ordoñana,29,30 Juan F Sánchez-Romera,31,30 Lucia Colodro-Conde,29,32 Lise Dubois,33 Michel Boivin,34,35 Mara Brendgen,36 Ginette Dionne,34 Frank Vitaro,37 Jennifer R Harris,38 Ingunn Brandt,38 Thomas Sevenius Nilsen,38 Jeffrey M Craig,39,40 Richard Saffery,39,40 Finn Rasmussen,41 Per Tynelius,41 Gombojav Bayasgalan,42Danshiitsoodol Narandalai,42,43 Claire MA Haworth,44 Robert Plomin,45 Fuling Ji,46 Feng Ning,46 Zengchang Pang,46 Esther Rebato,2 Robert F Krueger,47 Matt McGue,47 Shandell Pahlen,47 Dorset I Boomsma,48,49 Thorkild IA Sørensen,48,49 Jaakko Kaprio,14,50,51 and Karri Silventoinen1,52

1Department of Social Research, University of Helsinki, Helsinki, Finland, 2Department of Genetics, Physical Anthropology and Animal Physiology, University of the Basque Country UPV/EHU, Leioa, Spain, 3Department of Public Health Nursing, Osaka City University, Osaka, Japan, 4Obesity Research Unit, Research Programs Unit, University of Helsinki, Helsinki, Finland and Abdominal Center, Endocrinology, Helsinki University Central Hospital, Helsinki, Finland, 5Department of Education, Mokpo National University, Jeonnam, South Korea, 6Department of Biological Psychology, VU University Amsterdam, Amsterdam, The Netherlands, 7Department of Health Science, Ishikawa Prefectural Nursing University, Kaho, Ishikawa, Japan, 8Boston University, Department of Psychological and Brain Sciences, Boston, MA, USA, 9Istituto Superiore di Sanità—National Center for Epidemiology, Surveillance and Health Promotion, Rome, Italy, 10Department of Health and Exercise Sciences and

International Journal of Epidemiology, 2017, 1488–1498
doi: 10.1093/ije/dyx031
Advance Access Publication Date: 19 March 2017
Original article
Abstract

Background: There is evidence that birthweight is positively associated with body mass index (BMI) in later life, but it remains unclear whether this is explained by genetic factors or the intrauterine environment. We analysed the association between birthweight and BMI from infancy to adulthood within twin pairs, which provides insights into the...
role of genetic and environmental individual-specific factors.

Methods: This study is based on the data from 27 twin cohorts in 17 countries. The pooled data included 78,642 twin individuals (20,635 monozygotic and 18,686 same-sex dizygotic twin pairs) with information on birthweight and a total of 214,930 BMI measurements at ages ranging from 1 to 49 years. The association between birthweight and BMI was analysed at both the individual and within-pair levels using linear regression analyses.

Results: At the individual level, a 1-kg increase in birthweight was linearly associated with up to 0.9 kg/m^2 higher BMI ($P < 0.001$). Within twin pairs, regression coefficients were generally greater (up to 1.2 kg/m^2 per kg birthweight, $P < 0.001$) than those from the individual-level analyses. Intra-pair associations between birthweight and later BMI were similar in both zygosity groups and sexes and were lower in adulthood.

Conclusions: These findings indicate that environmental factors unique to each individual have an important role in the positive association between birthweight and later BMI, at least until young adulthood.

Key words: birthweight, body mass index, twins

Key Messages

- Birthweight is positively and linearly associated with later body mass index (BMI).
- The association between birthweight and BMI from infancy onwards is similar in males and females, and is lower in adulthood.
- Environmental factors unique to each individual have an important role in the positive association between birthweight and later BMI.

Introduction

The increasing prevalence of overweight and obesity over the last decades has grown into a global epidemic that currently affects a large part of the world’s population. The interest in the role of gestational factors behind adult health outcomes has resulted in a number of epidemiological studies analysing the association between birthweight and later body mass index (BMI). Several very large and well-conducted studies have shown a positive association of birthweight with BMI and overweight/obesity in children, adolescents and adults, but J- or U-shaped associations have also been reported. The mechanisms underlying this association are, however, still poorly understood. It has been suggested that the fetal period may be critical for the development of obesity, but it is unclear how far the associations between birthweight and subsequent BMI reflect early developmental factors in the intrauterine environment or whether they are explained by common genetic factors affecting body size from fetal life until adulthood.

Twins create a natural experiment and offer an opportunity to shed light on the mechanisms underlying the association between birth and later BMI. Twins come from the same family, share the same maternal environment, have the same gestational age and, in the case of monozygotic (MZ) twins, are genetically identical. However, each fetus has its own fetoplacental environmental conditions, such as supply of nutrients and oxygen, which may differ substantially from that of its co-twin. The association between the intra-pair differences in birthweight and later BMI cannot be explained by shared family factors, such as maternal nutrition, parental education or socio-economic status. Further, differences within MZ pairs cannot be explained by preconceptional parental influences or genetic factors. The comparison of intra-pair associations in MZ and dizygotic (DZ) twins is thus a strong design to explore within family effects. A stronger association in DZ than in MZ twins is taken as evidence that the relationship between birthweight and later BMI is explained by genetic factors. Differences in birthweight and later BMI within MZ pairs can only be influenced by environmental factors that are unique to individuals (i.e. the intrauterine environment), whereas
differences within DZ pairs can also be influenced by genetic factors.\textsuperscript{13,14}

A few twin studies have performed pair-wise analyses between birthweight and BMI in late adolescence and adulthood, but the results have been somewhat conflicting. Intra-pair differences in birthweight were not related with intra-pair differences in BMI in adults from the USA (Minnesota) and the UK.\textsuperscript{16,17} In young adult Belgian MZ twins, only when the birthweight difference between the twins exceeded 15\%, the heavier twin at birth showed a trend towards a higher BMI.\textsuperscript{18,19} A positive association was observed in Swedish young adult MZ males\textsuperscript{20} and in Finnish MZ and DZ twins of both sexes (aged 16–18.5 years).\textsuperscript{21} This suggests that intrauterine environment may play a role in later BMI, but this is far from settled. Moreover, it is not known whether the effects vary in their importance by age, particularly in childhood. To address these questions, we analysed the association between birthweight and later BMI from infancy to adulthood in MZ and DZ twins of both sexes in multinational twin data from 27 cohorts in 17 countries.

Material and methods

Sample

This study is based on the data from the COllaborative project of Development of Anthropometrical measures in Twins (CODATwins), which was intended to pool data from all twin projects in the world having information on height and weight.\textsuperscript{22} Information on birthweight was available in 27 cohorts; birth length and gestational age were available in 14 and 17 of these cohorts, respectively. The participating twin cohorts are identified in Table 1 (footnote) and were previously described in detail.\textsuperscript{22}

In the original database, there were 122 582 twin individuals with information on birthweight. We excluded 81 individuals with birthweight < 0.5 or > 5 kg. The remaining 122 501 individuals presented a total of 355 650 height and weight measurements at later ages. Age was classified to single-year age groups from age 1 to 19 years (e.g. age 1 refers to 0.5–1.5 years range) and three adult age groups (20–29, 30–39 and 40–49 years). Measurements at ages ≤0.5 and > 49.5 years (which is a proxy for menopausal status in women) were excluded because the sample sizes were too small. BMI was calculated as weight (kg)/square of height (m\textsuperscript{2}). Impossible values and outliers were checked by visual inspection of histograms for each age and sex group and were removed (< 0.3 \% of the measurements) allowing the distribution of BMI data to be positively skewed, resulting in 344 104 measurements. After restricting the analyses to one BMI measure per individual in each age group by keeping the measurement at the youngest age (6\% of the measurements were removed), we had 324 968 observations from 119 323 individuals.

We next excluded unmatched pairs (without data on their co-twins), resulting in 149 435 paired observations. Furthermore, because of the effects of sex differences within a pair on both birthweight and BMI especially during and after puberty, opposite-sex dizygotic twin pairs were excluded (41 733 paired observations). Intra-pair differences in birthweight and later BMI were checked by visual inspection of histograms. We removed birthweight differences greater than ± 1.7 kg (72 paired observations) and outliers for the within-pair BMI difference in each age group (125 paired observations). Together, we had 214 930 observations (107 465 paired observations), 55\% MZ and 45\% same-sex DZ, from 78 642 twin individuals (39 321 complete twin pairs). In summary, after excluding opposite-sex dizygotic twin pairs, the study database (39 321 twin pairs) is 95\% of the eligible sample (41 599 twin pairs).

For secondary analyses, we additionally calculated birthweight standardized by gestational age and ponderal index (PI) at birth. Birthweight was expressed as standard deviation (SD) scores of the respective means/weeks of gestation (z-scores; i.e. mean = 0 and SD = 1) to estimate the relative position of birthweight for a given gestational age. Individuals without data on gestational age, gestational age < 25 or > 45 weeks or with discordant information on gestational age within pairs were excluded. Unrealistic birthweight values for a given gestation were checked by visual inspection of histograms for each gestational week and removed (< 0.2\% of the observations). After these exclusions, we had 84 357 paired observations. For the analyses on PI [weight (kg)/height (m\textsuperscript{3})], we removed those cases without information on birth length, birth length < 25 or > 60 cm, PI < 12 or > 38 or intra-pair difference in PI > 15 kg/m\textsuperscript{3} (from the 107 465 paired observations in the primary analyses), resulting in 68 954 paired observations.

All participants were volunteers and they or their parents gave informed consent when participating in their original studies. Only a limited set of observational variables and anonymized data were delivered to the data-management centre at University of Helsinki. The pooled analysis was approved by the ethical committee of the Department of Public Health, University of Helsinki, and the methods were carried out in accordance with the approved guidelines.

Statistical analyses

Statistical analyses were conducted using the Stata statistical software package (version 12.0; StataCorp, College Station, TX, USA). First, all BMI measurements were adjusted for exact age within each age and sex groups using linear
regression (BMI was used as dependent variable and age as continuous independent variable) and the resulting residuals were used as input variables for the following analyses.

In primary analyses, we studied the association between birthweight and BMI residuals at both the individual and within-pair levels. At the individual level, linear regression models for each age, sex and zygosity group were used with birthweight as the explanatory variable and BMI residuals as the outcome. Associations were adjusted for birth year and twin cohort (treated as continuous and categorical, respectively). The non-independence within twin pairs was taken into account by using the ‘cluster’ option available in Stata. Since regression analyses with log-transformed BMI and untransformed BMI data provided very similar results, we used untransformed BMI data in order to make these results comparable with those from the pairwise analyses. In the within-pair analyses, intra-pair differences with both positive and negative values were created by randomly subtracting the co-twin with the lowest birthweight from the co-twin with the highest birthweight or vice versa. At the within-pair level, we performed linear regression models for each age, sex and zygosity group with intra-pair birthweight difference as the explanatory variable and intra-pair BMI residuals difference as the outcome. Associations were also adjusted for birth year and twin cohort. Next, we ensured that the regression lines passed through the origin by checking that the intercept was not different from zero.

Table 1. Descriptive statistics of birthweight and BMI by zygosity, age and sex

|            | MZ                  | DZ                  | MZ                  | DZ                  |
|------------|---------------------|---------------------|---------------------|---------------------|
|            | N       | Mean | SD    | N       | Mean | SD    | N       | Mean | SD    | N       | Mean | SD    |
| Birthweight (kg) |        |      |       |        |      |       |        |      |       |        |      |       |
| Age 1      | 5572   | 17.15| 1.41  | 5070   | 17.11| 1.35  | 5176   | 16.87| 1.40  | 4692   | 16.78| 1.34  |
| Age 2      | 4448   | 16.54| 1.39  | 4212   | 16.53| 1.43  | 4298   | 16.29| 1.39  | 3666   | 16.15| 1.36  |
| Age 3      | 5490   | 15.94| 1.37  | 5298   | 15.96| 1.50  | 5398   | 15.68| 1.47  | 4968   | 15.68| 1.45  |
| Age 4      | 3042   | 15.85| 1.75  | 2950   | 15.93| 1.86  | 3050   | 15.65| 1.84  | 2750   | 15.69| 1.87  |
| Age 5      | 2488   | 15.25| 1.52  | 2342   | 15.29| 1.61  | 2442   | 15.06| 1.60  | 2078   | 15.18| 1.72  |
| Age 6      | 1058   | 15.43| 1.73  | 660    | 15.47| 1.89  | 722    | 15.18| 1.68  | 530    | 15.32| 2.22  |
| Age 7      | 4536   | 15.34| 1.68  | 3954   | 15.43| 1.89  | 4184   | 15.36| 1.90  | 3826   | 15.46| 2.01  |
| Age 8      | 2066   | 15.57| 1.64  | 1494   | 15.72| 2.01  | 1984   | 15.55| 1.90  | 1264   | 15.79| 2.09  |
| Age 9      | 1982   | 16.24| 2.07  | 1466   | 16.52| 2.48  | 1904   | 16.24| 2.33  | 1290   | 16.50| 2.66  |
| Age 10     | 3776   | 16.56| 2.21  | 3184   | 16.59| 2.32  | 3048   | 16.55| 2.30  | 2892   | 16.79| 2.56  |
| Age 11     | 2992   | 17.21| 2.49  | 2366   | 17.45| 2.65  | 2466   | 17.78| 2.79  | 2052   | 17.70| 3.05  |
| Age 12     | 3934   | 17.70| 2.62  | 3062   | 17.90| 2.88  | 3208   | 18.15| 3.06  | 2980   | 17.98| 2.97  |
| Age 13     | 1198   | 18.41| 2.94  | 1002   | 18.60| 3.22  | 1064   | 18.85| 3.18  | 834    | 18.91| 3.19  |
| Age 14     | 2072   | 19.16| 2.73  | 1848   | 19.45| 3.11  | 2108   | 19.47| 3.00  | 1890   | 19.66| 3.17  |
| Age 15     | 1228   | 19.98| 3.16  | 1094   | 20.20| 3.17  | 1164   | 20.37| 3.44  | 992    | 20.81| 3.75  |
| Age 16     | 1614   | 20.59| 2.88  | 1550   | 20.78| 2.97  | 1674   | 21.04| 3.01  | 1500   | 20.80| 3.11  |
| Age 17     | 1824   | 21.11| 2.80  | 1910   | 21.46| 3.02  | 1988   | 21.69| 3.27  | 1898   | 20.95| 3.00  |
| Age 18     | 2028   | 21.35| 2.55  | 1694   | 21.89| 2.92  | 2078   | 22.12| 3.73  | 2118   | 22.15| 3.51  |
| Age 19     | 814    | 21.57| 2.49  | 784    | 21.82| 2.46  | 798    | 22.12| 3.73  | 734    | 21.49| 3.17  |
| Age 20–29  | 2786   | 23.19| 3.03  | 2290   | 23.45| 2.96  | 2360   | 23.81| 3.12  | 2118   | 22.15| 3.51  |
| Age 30–39  | 1242   | 24.78| 3.34  | 1066   | 25.20| 3.62  | 1144   | 24.91| 3.71  | 1062   | 24.91| 3.71  |
| Age 40–49  | 670    | 26.11| 3.48  | 492    | 26.54| 3.95  | 760    | 26.54| 3.95  | 782    | 23.86| 4.39  |

Names list of the participating twin cohorts in this study: Australian Twin Registry, Boston University Twin Project, Carolina African American Twin Study of Aging, Colorado Twin Registry, East Flanders Prospective Twin Survey, FinnTwin12, FinnTwin16, Gemini Study, Guinea-Bissau Twin Study, Hungarian Twin Registry, Italian Twin Registry, Japanese Twin Cohort, Longitudinal Israeli Study of Twins, Michigan Twins Study, Minnesota Twin Family Study, Minnesota Twin Registry, Mongolian Twin Registry, Murcia Twin Registry, Norwegian Twin Registry, Perinatal Epigenetic Twins Study, Qingdao Twin Registry of Children, Quebec Newborn Twin Study, Swedish Young Male Twins Study of Adults, Swedish Young Male Twins Study of Children, Twins Early Developmental Study, West Japan Twins and Higher Order Multiple Births Registry, and Young Netherlands Twin Registry. All twin cohorts were used in the analyses on the association between birthweight and later BMI (total sample). Twin cohorts used in the analyses involving birth length/PI. Twin cohorts used in the analyses involving gestational age.

Names list of the participating countries (number of twin cohorts per country, % of the total sample): Australia (2, 0.51%), Belgium (1, 0.31%), Canada (1, 1.63%), China (1, 0.32%), Finland (2, 10.88%), Guinea-Bissau (1, 0.08%), Hungary (1, 0.06%), Israel (1, 0.29%), Italy (1, 0.59%), Japan (2, 12.19%), Mongolia (1, 0.04%), Netherlands (1, 35.28%), Norway (1, 1.99%), Spain (1, 0.06%), Sweden (2, 4.60%), United Kingdom (2, 20.47%), USA (6, 10.69%).
An interaction analysis was performed to investigate whether zygosity influenced the associations between birthweight and BMI residuals by introducing a product term of zygosity and birthweight into the regression model. At the individual level, linear regression models for each age and sex group were used with birthweight as the explanatory variable and BMI residuals, zygosity, the product term of zygosity and birthweight, birth year and twin cohort as the regressors. At the within-pair level, linear regression models for each age and sex group were performed with intra-pair birthweight difference as the explanatory variable and intra-pair BMI residuals difference, zygosity, the product term of zygosity and intra-pair birthweight difference, birth year and twin cohort as the regressors. There was no interaction effects between zygosity and birthweight in individual-level analyses (only 2 of 44 tests had $P$-value $< 0.05$ and none of them had $P$-value $< 0.001$ that would correspond to $P$-value $< 0.05$ after Bonferroni correction of multiple testing); similar findings were observed between zygosity and intra-pair birthweight differences in pair-wise analyses (Appendix Table 1). The quadratic effect of birthweight was investigated by introducing the term in the regression models for the association between birthweight and BMI residuals, i.e. by introducing the quadratic term of birthweight in the individual-level analyses and the quadratic term of intra-pair birthweight differences in the pair-wise analyses. No quadratic effect of birthweight or intra-pair birthweight differences was found (results on request).

In secondary analyses, we first analysed the association between birthweight standardized for gestational age and BMI residuals at the individual level. Linear regression models for each age, sex and zygosity group were used with gestational age-standardized birthweight as the explanatory variable and BMI residuals as the outcome. Associations were adjusted for birth year and twin cohort. Finally, we analysed the association between PI at birth and BMI residuals both at the individual and within-pair levels (also adjusted for birth year and twin cohort). At the individual level, linear regression models for each age, sex and zygosity group were used with PI as the explanatory variable and BMI residuals as the outcome. At the within-pair level, linear regression models for each age, sex and zygosity group were used with intra-pair PI difference as the explanatory variable and intra-pair BMI residuals difference as the outcome. Since all analyses were based on BMI residuals, we will refer, except in statistical methods section, to ‘BMI residuals’ as ‘BMI’ for simplicity.

**Results**

Table 1 provides descriptive statistics for birthweight and BMI by zygosity, age and sex. Mean birthweight was slightly greater in males than in females and in DZ than in MZ twins; the same pattern was observed for the SD of birthweight. Regarding BMI, sample size for each zygosity, age and sex group ranged between 530 and 6176 measurements. The 6, 19 and 40–49 years age groups had the smallest sample sizes. Mean BMI declined from the age of 1 to 5 years and then started to increase; these mean values were higher in males than in females from age 1 to 6 years and from the age of 17 years onwards. The SD of BMI generally increased with age. Despite similar values in early childhood, DZ twins had slightly higher mean BMI and greater SD than MZ twins at most ages.

At the individual level, birthweight was generally positively associated with later BMI; regression coefficients showed that a 1-kg increase in birthweight was associated with up to 0.9 kg/m$^2$ higher BMI, ranging between 0.3 and 0.6 kg/m$^2$ at most ages (Table 2). The magnitude of the associations fluctuated more in adolescence and adulthood, probably explained by the smaller sample size, and no association was observed for some age-zygosity groups. When birthweight was expressed as a z-score for gestational age, the associations generally slightly increased in childhood and early adolescence. From middle adolescence onwards, the pattern was not clear, with some decreased associations in boys (Appendix Table 2).

Within MZ twin pairs, greater birthweight was also associated with higher BMI at most ages (Table 3). Regression coefficients generally ranged from 0.6 to 1.0 kg/m$^2$ per kg birthweight (up to 1.2 kg/m$^2$), were similar in males and females, and somewhat greater in childhood than in late adolescence and adulthood; no association was observed at 40–49 years. Supported by the lack of interaction between zygosity and intra-pair birthweight differences, the magnitude of the associations in DZ twins was similar to that of MZ twins; when different, they were generally greater in MZ twins (except at 9 and 19 years in males). A positive association was also observed between PI at birth and later BMI (Figure 1 and Appendix Table 3). A MZ intra-pair difference of a 1-kg/m$^3$ increase in PI generally resulted in a BMI difference of 0.03–0.08 kg/m$^2$, but the effects were somewhat greater in DZ twins at some ages.

**Discussion**

The present study, based on a multinational database of 27 twin cohorts with 107 465 paired observations, showed that birthweight is associated with later BMI in males and females from infancy onwards, but the association tends to be attenuated in adulthood. Because the associations are observed within MZ pairs, our results support the role of environmental factors unique to each individual in the relationship and refine previous findings by considering, in
addition to adult age, childhood and adolescence using 1-year age groups from 1 to 19 years.

At the individual level, the increase in BMI associated with a 1-kg increase in birthweight (0.3–0.6 kg/m² at most ages) was in the range of other twin and singletons studies in late adolescence and young adulthood. The quadratic effects of birthweight were independently tested in each age, zygosity and sex groups, and there was no evidence of non-linearity between birthweight and later BMI. The magnitudes of the associations slightly decreased from late adolescence. For example, the effects at ages 20–29 years (0.41 kg/m² and 0.68 kg/m² per kg in males and females, respectively) were comparable with those reported in other studies; however, none of them analysed the relationship in childhood. These intra-pair associations between birthweight and later BMI observed in different populations suggest that a causal explanation is biologically plausible. The number of fat cells (adipocytes) has shown to be a major determinant of fat mass in adults. Spalding et al. found that the adipocyte number is set during childhood and adolescence and, although there is a high turnover (10% annually), stays constant during adulthood. Further, there is evidence that the number of muscle cells in the body is determined before prematurity, has shown to be an indicator for shortness and lightness in early childhood, we standardized birthweight for gestational age. The magnitude of the associations slightly increased until early adolescence, suggesting that the effect of gestational age on the association between birthweight and BMI remains important, at least until this period.

The pair-wise analysis of MZ twins showed that environmental individual-specific factors are important in the association between birthweight and later BMI, suggesting the role of the intrauterine environment. The magnitude of these individual-specific factors tended to persist during childhood but decreased from late adolescence. For

| Age | MZ B | P-value | 95% CIs | DZ B | P-value | 95% CIs |
|-----|------|---------|--------|------|---------|--------|
| 1   | 0.52 | <0.001 | 0.43 0.61 | 0.40 | <0.001 | 0.32 0.48 |
| 2   | 0.55 | <0.001 | 0.46 0.65 | 0.50 | <0.001 | 0.41 0.59 |
| 3   | 0.53 | <0.001 | 0.44 0.63 | 0.45 | <0.001 | 0.36 0.53 |
| 4   | 0.55 | <0.001 | 0.40 0.69 | 0.42 | <0.001 | 0.27 0.57 |
| 5   | 0.56 | <0.001 | 0.41 0.71 | 0.39 | <0.001 | 0.24 0.53 |
| 6   | 0.46 | 0.002 | 0.16 0.76 | 0.39 | 0.015 | 0.08 0.70 |
| 7   | 0.32 | <0.001 | 0.20 0.44 | 0.41 | <0.001 | 0.29 0.54 |
| 8   | 0.67 | <0.001 | 0.52 0.83 | 0.40 | <0.001 | 0.20 0.60 |
| 9   | 0.40 | 0.001 | 0.17 0.63 | 0.61 | <0.001 | 0.34 0.88 |
| 10  | 0.39 | <0.001 | 0.22 0.56 | 0.40 | <0.001 | 0.22 0.58 |
| 11  | 0.55 | <0.001 | 0.33 0.77 | 0.44 | <0.001 | 0.20 0.69 |
| 12  | 0.50 | <0.001 | 0.30 0.70 | 0.51 | <0.001 | 0.30 0.73 |
| 13  | 0.19 | 0.358 | 0.22 0.60 | 0.21 | 0.364 | 0.24 0.66 |
| 14  | 0.36 | 0.012 | 0.08 0.65 | 0.30 | 0.065 | 0.02 0.62 |
| 15  | 0.20 | 0.329 | 0.20 0.59 | 0.48 | 0.009 | 0.12 0.84 |
| 16  | 0.32 | 0.501 | 0.20 0.83 | 0.66 | <0.001 | 0.29 1.03 |
| 17  | 0.33 | 0.030 | 0.03 0.62 | 0.71 | <0.001 | 0.43 0.98 |
| 18  | 0.28 | 0.046 | 0.00 0.55 | 0.02 | 0.911 | 0.30 0.33 |
| 19  | 0.66 | 0.010 | 0.16 1.15 | 0.86 | <0.001 | 0.52 1.20 |
| 20–29 | 0.41 | 0.003 | 0.14 0.69 | 0.48 | <0.001 | 0.22 0.73 |
| 30–39 | 0.55 | 0.005 | 0.17 0.94 | 0.93 | <0.001 | 0.50 1.35 |
| 40–49 | 0.08 | 0.745 | 0.58 0.41 | 0.77 | 0.013 | 0.16 1.38 |

Table 2. Regression coefficients for the association between birthweight and BMI (BMI units per kg birthweight), with monozygotic (MZ) and dizygotic (DZ) twins treated as individuals (individual level). Birthweight was used as the explanatory variable and BMI as the outcome. Associations were adjusted for birth year and twin cohort. B, regression coefficient; 95% CIs, 95% confidence intervals.
by a lower accuracy of birthweight measurements in individuals born earlier (69% of the individuals with BMI measurements at 40–49 years born before 1950).

There is also evidence that environmental exposures during early life can induce persistent alterations in the epigenome, which may lead to an increased risk of obesity later in life.27 For example, a recent study suggested that both maternal obesity and, to a larger degree, underweight affect the neonatal epigenome via an intrauterine mechanism.28 DNA methylation patterns in cord blood showed some association with altered gene expression, body size and composition in childhood, but the authors found no association between methylation status and birthweight.29 At worst, using childhood, but the authors found no association between gene expression discordance as a proxy measure of epigenetic methylation patterns in cord blood showed some association only when metabolic complications of obesity arise.31

Although the findings from previous studies are contrasting,18,20,21 our data revealed that the magnitude of the associations in DZ pairs was generally similar to that in MZ pairs and thus suggest that genetic factors are not very importantly involved in the relationship between birthweight and later BMI. This is supported by a recent study using linkage-disequilibrium score regression, which estimated a genetic correlation of 0.11 between birthweight and adult BMI.32 However, in the absence of data on choriocity, a possible genetic influence cannot be fully excluded. Approximately two-thirds of MZ twins are monochorionic and thus share the same placenta; an unequal placental sharing is a major cause of fetal growth discordance in MZ twins.33 Therefore, intrauterine factors that could potentially account for our findings are placental differences between MZ and DZ twins and between monochorionic and dichorionic MZ twins.33,34 It has been reported that monochorionic MZ twins are more discordant than dichorionic MZ twins for BMI throughout childhood and adolescence.33 Therefore, it could be argued that, besides genetic factors, these placental differences may increase the intra-pair associations in
MZ pairs, making them thus more similar to those in DZ pairs. Birthweight may not be the ideal measurement of body composition in newborns, since it does not discriminate between those infants of different sizes or body shapes. Thus, we repeated the analyses for PI, a measure of relative weight at birth. The effects were greater in DZ twins at some ages, suggesting that genetic factors may play a role in the association, which is agreement with the findings in Finnish twins. After standardization (to z-scores), the units of weight and PI at birth became comparable. It was then evident that intra-pair differences in BMI were more strongly associated with birthweight than with PI in most zygosity, age and sex groups (results not shown). However, neither PI nor BMI determine fat mass per se. BMI is generally used as a proxy for body fat in epidemiologic studies, but it does not allow the drawing of conclusions about body composition. As reviewed by Rogers, birthweight is usually positively associated with lean body mass and negatively associated with relative adiposity, suggesting that the association between birthweight and BMI/overweight does not necessarily reflect increased adiposity at higher birthweights.

The main strength of the present study is the large sample size of our multinational database of twin cohorts with information on size at birth and height and weight measures from infancy to adulthood. We performed an individual-based pooled analysis to provide results for this sample including the large majority of existing twin cohorts. Generalization for the global population is, however, not possible because countries or regions are not equally represented and the database is heavily weighted towards Caucasian populations following Westernized lifestyle. Another limitation of the data is that most of the measures were parentally reported (birth measures) and self-reported or parent-reported (later measures). However, the accuracy between maternal recall and medical records of birthweights (in singletons) have reached a kappa value of 0.89, and the correlations between measured and self-reported heights and weights have commonly been over 0.90. Finally, it has been questioned whether differences in birth size in twins are a suitable model for differences in birthweight in general, because intrauterine growth in twins is different from that in singletons and fetal growth may be particularly compromised in MZ twins. However, the magnitude of the relationship between birthweight and BMI in twins was at the same level as that reported in singletons. As concluded by Morley, there is no reason to suggest that data from twins cannot be used to shed light on causal pathways underlying the association between birthweight and cardiovascular risk factors.

In conclusion, our findings showed that environmental factors unique to each individual are important in the association between birthweight and later BMI, and thus support the role of the intrauterine environment in the development of later BMI. The association of birthweight with later BMI persists across ages but is attenuated in adulthood. Identifying intrauterine environmental factors affecting later BMI may thus be important when trying to understand the development of obesity across the life-span.

Acknowledgements
This work was supported by the Academy of Finland (grant number #266592). The Australian Twin Registry is supported by a Centre of Research Excellence (grant ID 1079102) from the National Health and Medical Research Council administered by the University of Melbourne. The Boston University Twin Project is funded by grants (#R01 HD068435 & R01 MH062375) from the National Institutes of Health to K.S. The Carolina African American Twin Study of Aging (CAATSA) was funded by a grant from the National Institute on Aging (grant 1RO1-AG13662–01A2) to K.E.W. Colorado Twin Registry is funded by NIDA-funded centre grant DA011015, & Longitudinal Twin Study HD10333; B.M.H. is supported by 5T32DA017637–11. 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.R.), the Academy of Finland Center of Excellence in Complex Disease Genetics (grant numbers: 213506, 129680), Centre of Excellence in Research on Mitochondria, Metabolism and Disease (FinMIT, grant 272376), the Academy of Finland (grants 100499, 203585, 118535, 141054, 265240, 263278 and 264146 to J.K. and grant 266286 to K.F.), the Finnish Diabetes Research Foundation, Novo Nordisk Foundation, Helsinki University Central Hospital and University of Helsinki. K.S. is supported by Osaka University’s International Joint Research Promotion Program. Gemini was supported by a grant from Cancer Research UK (C1418/A7974). 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 A.K. The Michigan State University Twin Registry has been supported by Michigan State University as well as grants R01-MH081813, R01-MH0820–54, R01-MH92377–02, R21-MH07542–01 and R3-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 Murcia Twin Registry is supported by Fundación Séneca, Regional Agency for Science and Technology, Murcia, Spain (08633/PHCS/08, 15302/PHCS/10 & 19479/PI/14) and Ministry of Science and Innovation, Spain (PSI2009–11560 & PSI2014–56680-R.). PETS was supported by grants from the Australian National Health and Medical Research Council (grant numbers 437015 and 607358 to J.C. and R.S.), the Bonnie Babes Foundation (grant number BBF20704 to J.M.C.), the Financial Markets Foundation for Children (grant no. 032-2007 to J.M.C.) and by the Victorian Government’s Operational Infrastructure Support Program. 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 (M.B.). The Twins Early Development Study (Teds) is supported by a program grant (MR/M021475/1) 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). 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. 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, Addicton-3160008, 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). Y.Y., Y.-M.H., F.R., D.I.B., T.I.A.S., J.K. and K.S. planned the study design of the CODATwins project. Y.Y., G.W., M.B., T.C.E.M.v.B., S.O., K.J.S., M.A.S., C.F., C.D., T.L.N., K.E.W., A.K.-N., D.M., L.A., K.H., T.I.C., J.L.H., J.W., C.H.L., A.R., P.R.C., B.M.H., C.A.D., R.E.V., R.J.E.L., M.B.-A., H.B.-N., M.S., A.D.T., D.L.T., S.A.B., K.L.K., J.R.O., J.F.S.-R., L.C.-C., L.D., M.Bs., M.Br., G.D., F.V., J.R.H., I.B., T.S.N., J.M.C., R.S., F.R., P.T., G.B., D.N., C.M.A.H., R.P., F.J., F.N., Z.P., R.F.K., M.M., S.P., D.I.B. and J.K. collected the data used in this study. A.J. and K.S. were in charge of data management. A.J., R.S. and K.S. conducted the analyses. A.J. wrote the first draft of the manuscript and has primary responsibility of the final content. All authors have commented the manuscript and read and approved the final version of the manuscript. A.J. will act as guarantor for the paper.

Conflict of interest: The authors have no conflicts of interest to declare.

References

1. World Health Organization (WHO). Obesity and overweight: Fact sheets. 2015. http://www.who.int/mediacentre/factsheets/ fs311/en/ (15 February 2017, date last accessed).
2. Barker DJ. The fetal and infant origins of adult disease. BMJ 1990;301:1111.
3. Rasmussen F, Johansson M. The relation of weight, length and ponderal index at birth to body mass index and overweight among 18-year-old males in Sweden. Eur J Epidemiol 1998;14:373–80.
4. Sorensen HT, Sabroe S, Rothman KJ et al. Relation between weight and length at birth and body mass index in young adulthood: cohort study. BMJ 1997;315:1137.
5. Seidman DS, Laor A, Gale R et al. A longitudinal study of birth weight and being overweight in late adolescence. Am J Dis Child 1991;145:782–5.
6. Rugholm S, Baker JL, Olsen LW et al. Stability of the association between birth weight and childhood overweight during the development of the obesity epidemic. Obes Res 2005;13:2187–94.
7. Curhan GC, Chertow GM, Willett WC et al. Birth weight and adult hypertension and obesity in women. Circulation 1996;94:1310–15.
8. Curhan GC, Willett WC, Rimm EB et al. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. Circulation 1996;94:3246–50.
9. Pietilainen KH, Kaprio J, Rasani M et al. Tracking of body size from birth to late adolescence: contributions of birth length, birth weight, duration of gestation, parents' body size, and twinship. Am J Epidemiol 2001;154:21–9.
10. Rogers I, EURO-BLCS Study Group. The influence of birth-weight and intrauterine environment on adiposity and fat distribution in later life. Int J Obes Relat Metab Disord 2003;27:755–77.
11. Yu ZB, Han SP, Zhu GZ et al. Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. Obes Rev 2011;12:525–42.
12. Dietz WH. Critical periods in childhood for the development of obesity. Am J Clin Nutr 1994;59:955–9.
13. Boomsma D, Willemsen G, Geus E et al. Twins and the fetal origins hypothesis: an application to growth data. In: Kordon C, Gaillard RC, Christen Y (eds). Anonymous Hormones and the Brain. Springer-Verlag Berlin Heidelberg, 2005, pp. 29–46.
14. Morley R, Dwyer T. Studies of twins: what can they tell us about the fetal origins of adult disease? *Paediatr Perinat Epidemiol* 2005;19(Suppl 1):2–7.

15. Blickstein I, Keith LG, Keith DM. *Multiple Pregnancy*. Taylor and Francis Group, 2005.

16. Allison DB, Paultre F, Heymsfield SB et al. Is the intra-uterine period really a critical period for the development of adiposity? *Int J Obes Relat Metab Disord* 1995;19:397–402.

17. Baird J, Osmond C, MacGregor A et al. Testing the fetal origins hypothesis in twins: the Birmingham twin study. *Diabetologia* 2001;44:33–9.

18. Loos RJ, Beunen G, Fagard R et al. Birth weight and body composition in young adult men: a prospective twin study. *Int J Obes Relat Metab Disord* 2001;25:1537–45.

19. Loos RJ, Beunen G, Fagard R et al. Birth weight and body composition in young women: a prospective twin study. *Am J Clin Nutr* 2002;75:676–82.

20. Johansson M, Rasmussen F. Birthweight and body mass index in young adulthood: the Swedish young male twins study. *Twin Res* 2001;4:400–5.

21. Pietilainen KH, Kaprio J, Rasanen M et al. Genetic and environmental influences on the tracking of body size from birth to early adulthood. *Obes Res* 2002;10:875–84.

22. Silventoinen K, Jelenkovic A, Sund R et al. The CODATwins Project: The cohort description of collaborative project of development of anthropometrical measures in twins to study macro-environmental variation in genetic and environmental effects on anthropometric traits. *Twin Res Hum Genet* 2015;18:348–60.

23. Binkin NJ, Yip R, Fleshood L et al. Birth weight and childhood growth. *Pediatrics* 1988;82:828–34.

24. Spalding KL, Arner E, Westermark PO et al. Dynamics of fat cell turnover in humans. *Nature* 2008;453:783–7.

25. Malina RM. Post-natal growth and maturation. In: Ulijaszek SJ, Johnston FE, Preece MA (eds). *The Cambridge Encyclopedia of Human Growth and Development*, Cambridge University Press, 1998, pp. 176–235.

26. Skidmore PM, Cassidy A, Swaminathan R et al. An obesogenic postnatal environment is more important than the fetal environment for the development of adult adiposity: a study of female twins. *Am J Clin Nutr* 2009;90:401–6.

27. van Dijk SJ, Molloy PL, Varinili H et al. Epigenetics and human obesity. *Int J Obes (Lond)* 2015;39:85–97.

28. Sharp GC, Lawlor DA, Richmond RC et al. Maternal pre-pregnancy BMI and gestational weight gain, offspring DNA methylation and later offspring adiposity: findings from the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* 2015;44:1288–304.

29. Felton CL, Groom A, St Pourcain B et al. DNA methylation patterns in cord blood DNA and body size in childhood. *PLoS One* 2012;7:e31821.

30. Gordon L, Joo JH, Andronikos R et al. Expression discordance of monozygotic twins at birth: effect of intrauterine environment and a possible mechanism for fetal programming. *Epigenetics* 2011;6:579–92.

31. Ollikainen M, Ismail K, Gervin K et al. Genome-wide blood DNA methylation alterations at regulatory elements and heterochromatic regions in monozygotic twins discordant for obesity and liver fat. *Clin Epigenetics* 2015;7:915–0073–5. eCollection 2015.

32. Horikoshi M, Beaumont RN, Day FR et al. Genome-wide associations for birth weight and correlations with adult disease. *Nature* 2016;538:248–52.

33. Marceau K, McMaster MT, Smith TF et al. The prenatal environment in twin studies: a review on chorionicity. *Behav Genet* 2016;46:286–303.

34. Loos RJF, Ridgway CL, Ong KK. Theoretical underpinning of the use of twin studies in life course epidemiology. In: Lawlor DA, Mishra GD (eds). *Family Matters: Designing, Analysing and Understanding Family Based Studies in Life Course Epidemiology*, Oxford University Press, 2009, pp. 57–84.

35. Bouchard C, Perusse L. Heredity and body fat. *Annu Rev Nutr* 1988;8:259–77.

36. McCormick MC, Brooks-Gunn J. Concurrent child health status and maternal recall of events in infancy. *Pediatrics* 1999;104:1176–81.

37. Giacchi M, Mattei R, Rossi S. Correction of the self-reported BMI in a teenage population. *Int J Obes Relat Metab Disord* 1998;22:673–7.

38. Rowland ML. Self-reported weight and height. *Am J Clin Nutr* 1990;52:1125–33.

39. Morley R. Can we generalise from findings in twins? *Paediatr Perinat Epidemiol* 2005;19(Suppl 1):54–9.