Genetic and environmental factors affecting birth size variation: a pooled individual-based analysis of secular trends and global geographical differences using 26 twin cohorts


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Abstract

Background: The genetic architecture of birth size may differ geographically and over time. We examined differences in the genetic and environmental contributions to birthweight, length and ponderal index (PI) across geographical-cultural regions (Europe, North America and Australia, and East Asia) and across birth cohorts, and how gestational age modifies these effects.

Methods: Data from 26 twin cohorts in 16 countries including 57 613 monozygotic and dizygotic twin pairs were pooled. Genetic and environmental variations of birth size were estimated using genetic structural equation modelling.

Results: The variance of birthweight and length was predominantly explained by shared environmental factors, whereas the variance of PI was explained both by shared and unique environmental factors. Genetic variance contributing to birth size was small. Adjusting for gestational age decreased the proportions of shared environmental
variance and increased the propositions of unique environmental variance. Genetic variance was similar in the geographical-cultural regions, but shared environmental variance was smaller in East Asia than in Europe and North America and Australia. The total variance and shared environmental variance of birth length and PI were greater from the birth cohort 1990–99 onwards compared with the birth cohorts from 1970–79 to 1980–89.

Conclusions: The contribution of genetic factors to birth size is smaller than that of shared environmental factors, which is partly explained by gestational age. Shared environmental variances of birth length and PI were greater in the latest birth cohorts and differed also across geographical-cultural regions. Shared environmental factors are important when explaining differences in the variation of birth size globally and over time.

Key words: Birthweight, birth length, ponderal index, twins, genetics, pooled studies

Key Messages

- Additive genetic factors contributing to birth size have a small but consistent effect across geographical-cultural regions (Europe, North America and Australia, and East Asia) and across birth cohorts.
- Environmental factors shared by co-twins importantly contribute to the inter-individual variation in birthweight, length and ponderal index, which is partly explained by gestational age.
- Shared environmental influences were smaller in East Asia than in Europe and North America and Australia.

Introduction

Birth size is an indicator of infant health and is associated with health-related traits in later life such as hypertension, obesity, and psychosocial distress. Moreover, low birthweight is associated with an increased risk of metabolic diseases including type 2 diabetes and cardiovascular diseases in adulthood. Both genetic and environmental factors influence birth size. Associations between fetal genotype and birthweight can in part reflect the indirect effects of the maternal genotype influencing birthweight via the intrauterine environment. Studying monozygotic (MZ) and dizygotic (DZ) twin pairs is a widely used method to decompose total variance into fractions explained by genetic and environmental differences between individuals. The environmental factors shared by co-twins include gestational age, total placental weight and maternal factors, such as maternal body size and smoking. Individual placental characteristics, such as placental function including nutrient capacity, anatomy and perinatal injuries, can lead to differences in birth size between co-twins and are thus part of the environment unique for each individual twin. A previous Dutch study found that the genetic factors explained almost an identical share of the total variation of birthweight and length when estimated by parent-offspring trios of singletons (26% and 26%, respectively), supporting the value of the twin design when studying birth size. Gestational age affects birthweight and, because it is shared by co-twins, may lead to the overestimation of shared environment, if not accounted for.

Genetic and environmental variation of fetal growth may differ between populations because of differences in maternal dietary habits, other environmental exposures and the gene pool of population. A multinational twin study reported that genetic factors explained 17% of the variation of birthweight. This contribution was similar in Western and East Asian populations, but there were differences in the proportions of environmental factors both shared and unshared by co-twins.

It is well known that maternal nutrition and other maternal factors affect birth size, and the determinants of birth size may have changed across birth cohorts over the 20th century. However, there are no previous studies which would have analysed how the roles of genetic and environmental factors on birth size have changed over time. Further, the only international comparison was based only on seven twin cohorts; larger studies would be warranted to get more precise estimates. Finally, it would be important to analyse also indicators of birth size other than birthweight, and gestational age should be adjusted for because otherwise the role of shared environment would be inflated. To address these questions, we used birthweight and length data available in the largest pooled...
database of twin cohorts in the world. We aimed to examine differences in genetic and environmental contributions to birthweight, length and ponderal index (PI) \([\text{PI} = \text{weight (kg)} / \text{height (m}^3\text{)}]\) across geographical-cultural regions (Europe, North America and Australia, and East Asia) and across birth cohorts from 1915 through 2013, and how gestational age modifies these effects.

### Methods

#### Sample

The data were derived from the COllaborative project of Development of Anthropometrical measures in Twins (CODATwins) database. Information on birthweight was available in 26 cohorts from 16 countries, and birth length and gestational age were available in 14 and 17 of these cohorts, respectively. In the majority of cohorts, the birth-related measures were parentally reported (79% for birthweight, 87% for birth length and 83% for gestational age) or self-reported (14%, 2% and 8%, respectively); only in a few cohorts were they based on records from nurses or clinicians (7%, 11% and 9%, respectively). However, birthweights from maternal recall and medical records were found to be highly correlated. The participating twin cohorts are listed in Table 1 (footnote) and were previously described in detail. The prevalence of obesity and overweight is lowest in East Asia, thus representing a less obesogenic environment. Therefore, we divided these cohorts into three geographical-cultural regions: Europe, North America and Australia, and East Asia.

There were 121,997 twin individuals with data on birthweight. We excluded individuals with birthweight <0.5 or >5 kg \(n=79\) or without data on their co-twins \(n=6,606\) as well as those with intra-pair difference in birthweight >2 kg \(22\) pairs or contrasting information on birth year between co-twins \(21\) pairs, leading to 57,613 twin pairs \(38\% \text{MZ}, \text{34\% same-sex dizygotic (SSDZ)}\) and \(28\% \text{opposite-sex dizygotic (OSDZ)}\) twins. For the analyses on birth length and PI, individuals without data on birth length \(n=64,626\), those with birth length <25 or >60 cm \(n=33\), PI <12 or >38 kg/m\(^3\) \(n=675\) or born before 1970 \(n=261\), and co-twins with intra-pair difference in birth length >12 cm \(3\) pairs or PI >15 kg/m\(^3\) \(9\) pairs) were removed, leading to 27,084 twin pairs \(38\% \text{MZ}, \text{33\% SSDZ and 29\% OSDZ twins}\).

#### Table 1. Sample sizes, means and standard deviations of birthweight (kg) by sex, region, birth year, and zygosity

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NA, North America; Aus, Australia.

\(^a\)Includes all cohorts in the footnotes b–d and Africa (one cohort, 108 twin pairs, Guinea-Bissau Twin Study) and Middle East (one cohort, 400 pairs, Longitudinal Israeli Study of Twins).

\(^b\)Europe (11 cohorts, 37,735 twin pairs): East Flanders Prospective Twin Survey, FinnTwin12, FinnTwin16, Gemini Study, Hungarian Twin Registry, Italian Twin Registry, Norwegian Twin Registry, Swedish Young Male Twins Study of Adults, Swedish Young Male Twins Study of Children, Twins Early Developmental Study and Young Netherlands Twin Registry.


\(^d\)East Asia (4 cohorts, 3,433 twin pairs): Japanese Twin Cohort, Mongolian Twin Registry, Qingdao Twin Registry of Children and West Japan Twins Registry.

We further standardized birthweight, length and PI for gestational age separately by sex and within the individuals included in each group of analyses. These three measures of birth size were expressed as standard deviation (SD) scores of the respective means/weeks of gestation (z-scores; i.e. mean = 0 and SD = 1) to estimate their relative value for a given gestational age. Individuals with gestational age <25 or >45 weeks were excluded. Outlying values for
Birthweight, length and PI values for a given gestational age were checked by visual inspection of histograms for each gestational week and removed (0.2% for birthweight and 0.4% for birth length and PI), resulting in 38 806 (birthweight) and 23 742 twin pairs (birth length and PI) for analyses.

All participants were volunteers and gave their informed consent when participating in their original studies. A limited set of observational variables and anonymized data was delivered to the data management centre at the University of Helsinki. The pooled analysis was approved by the ethical committee of the Department of Public Health, University of Helsinki.

Statistical analyses

The data were analysed using genetic structural equations modelling. MZ twins share virtually the same genomic sequence, whereas DZ twins share, on average, 50% of their genes identical-by-descent. On this basis, the total variance was decomposed into variance due to additive genetic factors (A: correlated 1.0 for MZ and 0.5 for DZ pairs), shared (common) environmental factors (C: by definition, correlated 1.0 for MZ and DZ pairs) and unique (non-shared) environmental factors (E: by definition, uncorrelated for MZ and DZ pairs). All genetic models were fitted by the OpenMx package (version 2.0.1) in the R statistical platform.

A full model with A, C and E factors was fitted to the data. We allowed a shared environmental correlation to be less than 1 for OSDZ pairs, as compared with 1 expected for SSDZ and MZ pairs; this would suggest the presence of sex-specific shared environmental factors affecting size at birth. Since boys and DZ twins showed greater birth size than girls and MZ twins, different means for sex and zygosity groups were allowed. We then conducted the analyses in the three geographical-cultural regions and across the birth cohorts from 1915 through 2013, per decade. Moreover, the genetic and environmental variances of birthweight were analysed for each twin cohort. Birthweight, length and PI values (both unstandardized and standardized for gestational age) were first adjusted for twin cohort within each sex and geographical-cultural region/birth year groups using linear regressions, and the resulting residuals were used in the analyses.

Results

Birthweight was greater in European and North American and Australian than in East Asian newborns (Table 1). The variance of birthweight was greatest in North America and Australia and lowest in East Asia. Mean birthweight did not show any clear pattern across the birth cohorts until 1980–89, but started to decrease from 1990–99 onwards. Mean birth length in European and North American and Australian boys and girls was greater than in East Asians (Table 2). The variance showed a less clear pattern, but was greatest in European and lowest in East Asian boys and girls. In MZ and DZ twins, the means of PI in boys were similar to those in girls in all geographical-cultural regions, except for East Asia where MZ girls had the greatest PI. The mean PI of boys was similar between geographical-cultural regions, whereas the mean PI of girls was greater in East Asia than in Europe and North America and Australia. The variances of PI were greatest in Europe and lowest in East Asia in both sexes.

Figure 1 presents the additive genetic, shared environmental and unique environmental variances of birthweight, birth length and PI by cultural-geographical region; the exact point estimates and their 95% confidence intervals (CI) are available in Supplementary Tables 1 and 2, as Supplementary data at IJE online. Shared environmental factors explained the major part of the variation of birthweight and length, whereas shared and unique environmental factors explained roughly equal shares of the variation of PI. When comparing the cultural-geographical regions, the differences in the variances were mainly explained by shared environmental variances. For birthweight, the shared environmental variance was lower in East Asian boys (c^2 = 0.11, 95% CI 0.09–0.14) and girls (c^2 = 0.11, 95% CI 0.09–0.13) than found in Europe (c^2 = 0.19, 95% CI 0.18–0.20 and 0.18, 95% CI 0.17–0.18, respectively) or North America and Australia (c^2 = 0.23, 95% CI 0.22–0.24 and 0.22, 95% CI 0.21–0.23, respectively). Similar differences in the shared environmental variances were also found for birth length and PI. When the results were adjusted for gestational age, in particular the relative contribution of shared environmental variation to birthweight decreased. However, also in these analyses, the shared environmental variation was lower in East Asia than in the other regions. For birth length and PI, the relative decrease in shared environmental variance after the adjustment of gestational age was smaller than for birthweight.

Figure 2 presents the corresponding results by birth cohorts (the exact point estimates and their 95% CIs are available in Supplementary Tables 1 and 2, available as Supplementary data at IJE online). For birth length and PI, the total variances were greater in the birth cohorts 1990–99 onwards as compared with the birth cohorts from 1970–79 to 1980–89. Adjusting the results for gestational age decreased in particular the proportions of shared environmental variance. After the adjustment for gestational age, systematic decrease in the shared environmental variance was found in the cohorts born in 1940–49 (c^2 = 0.55, 0.55,
Discussion

Using data from 57,613 complete twin pairs from 16 countries, the present study revealed that environmental factors shared by co-twins importantly contribute to the inter-individual variation in birthweight, birth length and PI. These factors also explained an important share of regional differences in the birthweight variation, as found also in previous studies.11,15,26 In the classical twin design, maternal effects shared by co-twins, including gestational age, would show up as a shared environmental variance. A previous international study of seven twin cohorts reported that from 50% to 70% of the total variance in birthweight was associated with maternal effects,15 which is close to the relative contribution of shared environmental variance found in our study before standardizing the results for gestational age. The standardization for gestational age decreased in particular the shared environmental variances for birthweight relative to the variances of birth length and PI, suggesting that birthweight is more influenced by the length of gestation than birth length and PI.27

The mean and total variance of birthweight and length were lower in East Asia than in the other regions, which corresponds with previous studies.28,29 The differences in the total variances were especially contributed by differences in shared environmental variance. It has been suggested that part of these maternal effects is due to maternal genes which regulate fetal growth, possibly through the intrauterine environment.30,31 Heritability estimates for the length of gestation were found to be over 30%,31,32 indicating that this is a heritable trait in European ancestry populations. Heritability of the length of gestation for East Asian populations is presently unknown, but if these differ from European ancestry estimates, this may partly explain these regional differences in shared environmental variances.

Table 2. Sample sizes, means and standard deviations of birth length (cm) and ponderal index (kg/m²) by sex, region, birth year, and zygosity

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<th>Ponderal index</th>
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<td>n</td>
<td>Mean</td>
<td>SD</td>
<td>n</td>
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NA, North America; Aus, Australia.

aEurope (eight cohorts, 23,496 twin pairs).
bNorth America and Australia (three cohorts, 872 twin pairs).
cEast Asia (two cohorts, 2614 twin pairs).
Various maternal genes have been shown to influence fetal growth, either directly or indirectly. A study examining genome-wide DNA methylation patterns in term human placentas showed that the patterns of DNA methylation were significantly associated with infant growth.\(^\text{33}\) Moreover, a multi-ancestry genome-wide association study indicated that two loci (INS–IGF2 and RB1), of the 60 genome-wide significant loci from maternal sources, fall within (or near) imprinted genes in fetal growth.\(^\text{12}\) If the frequencies of DNA methylation of gene and/or two loci among Asians differ from those among European ancestry,\(^\text{34}\) the genetic variability in maternal characteristics may explain some of the difference in shared environmental variance of birthweight between European ancestry and East Asians detected in the present study.

Mean PI was similar among boys across the geographical-cultural regions. However, mean PI was greater in East Asia than in European and North American and Australian girls. Gilson \textit{et al.} (2015)\(^\text{27}\) indicated that PI varied between ethnicities. Moreover in the present study, shared environmental variance differed between these regions. The smaller shared environmental variance observed in East Asia than in the other regions may reflect differences in maternal nutrition, smoking and other environmental factors.

The means and variances of birthweight and length were lower in the cohorts born after than before 1990. In

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**Figure 1.** Additive genetic (grey), shared environmental (black) and unique environmental (white) variances of birth size measures before and after standardization for gestational age (GA) by geographic-cultural region.
recent decades, the prevalence of preterm births among singletons and twins has increased in most industrialized countries, while at the same time perinatal mortality has decreased, mainly because of medically indicated preterm births.\textsuperscript{35–44} Gielen \textit{et al.}\textsuperscript{44} (2010) reported that the frequency of infertility treatment and caesarean section, as well as advanced maternal age, have increased over the years, but none of these factors influenced the secular trends in birthweight. The decrease in birthweight and length found in the present study may reflect the decrease in mean length of gestation up to 32 weeks, as suggested by Gielen \textit{et al.} (2010). Another factor with respect to time trends is the increasing survival of twin births. The survivors represent different proportions of twin pregnancies,\textsuperscript{45} and these proportions might be represented differentially in the distributions of birthweight and birth length. We found evidence for these explanations, since the results adjusted for gestational age did not show differences in the total variance of birthweight. This suggests that the increasing total variation over the birth cohorts is affected by increasing survival of babies with early gestational age. In the analyses adjusted for gestational age, shared environmental variance decreased over the birth cohorts. This may suggest that the variation in maternal factors has decreased at the same time as the general standard of living has increased.

When considering how well our results can be generalized, the assumptions made by the twin design need to be

\textbf{Figure 2.} Additive genetic (grey), shared environmental (black) and unique environmental (white) variances of birth size measures before and after standardization for gestational age (GA) by birth cohort.
Figure 3. Total, additive genetic, shared environmental and unique environmental variances of birthweight by twin cohort. Au, Australian Twin Registry; Bo: Boston University Twin Project; Ca, Carolina African American Twin Study of Aging; Co, Colorado Twin Registry; EF, East Flanders Prospective Twin Survey; F12, Finntwin12; F16, Finntwin16; Ge, Gemini Study; GB, Guinea-Bissau Twin Study; Hu, Hungarian Twin Registry; It, Italian Twin Registry; Ja, Japanese Twin Cohort; Is, Longitudinal Israeli Study of Twins; Mi, Michigan Twins Study; MinC, Minnesota Twin Family Study; MinA, Minnesota Twin Registry; Mo, Mongolian Twin Registry; No, Norwegian Twin Registry; PETS, Peri/Postnatal Epigenetic Twins Study; Qi, Qingdao Twin Registry of Children; Qu, Quebec Newborn Twin Study; SwA, Swedish Young Male Twins Study of Adults; SwC, Swedish Young Male Twins Study of Children; TEDS, Twins Early Developmental Study; WJ, West Japan Twins and Higher Order Multiple Births Registry; Ne, Young Netherlands Twin Registry.
considered. MZ twins can either share one chorion and
one amnion, or each fetus can have its own amnion, or
they can each have their own chorion and amnion as for
virtually all DZ twins. Previous Dutch and Belgian stud-
ies\textsuperscript{46,47} have reported somewhat lower correlations for
mono-chorionic than di-chorionic MZ twins, which can
lead to underestimation of additive genetic variance and
overestimation of shared environmental variance.
However, if there was extra variation because of more dis-
similar intrauterine environments of MZ twins, it should
have been seen as the higher trait variance in MZ twins,
which was not the case in our study. One explanation is
that very discordant pairs are not part of our study, be-
cause of higher neonatal mortality or other reasons. It
would be important to estimate the contributions of ge-
netic and environmental factors also by using other meth-
ods available for singleton pregnancies, to confirm how
well our twin study results can be generalized to the whole
population.

The main strength of our study is the very large sample
size, allowing the investigation of differences on the genetic
and environmental contributions to individual differences
in birth size in much more detail than in previous studies.
Pooling data from a large number of twin cohorts also per-
mits analyses by geographical-cultural regions and birth
cohorts born over 100 years. Further, we were able to ana-
lyse also birth length and PI and adjust the results for gesta-
tional age. Lack of information on gestational age, in
particular, is a major limitation in previous studies, since it
inflates shared environmental variation as demonstrated in
our study. However, countries and/or geographical-
cultural regions are not equally represented, and the data-
base is heavily weighted towards populations following the
Westernized lifestyle. There are few data available from
the Middle East and Africa, and no data from South Asia
or South America. It is also noteworthy that all countries
have different historical developments, and thus the same
birth cohorts can have been exposed to different environ-
mental factors. This may well have diluted the differences
between the birth cohorts in this study which reflects the
average variances of different countries.

In conclusion, in contrast to the small contribution of
genetic factors, environmental factors shared by co-twins
importantly contribute to the inter-individual variation in
birth size even after standardization for gestational age.
The contributions of genetic effects on birth size were simi-
lar in the geographical-cultural regions, but unique envi-
ronmental influences were slightly larger and shared
environmental influences smaller in East Asia than in the
other regions. This suggests that in the Westernized social
context, there are features increasing variation in maternal
nutrition and other maternal factors affecting birth size.
Our results thus indicate that maternal factors importantly
contribute to birth size and can then be a target for public
health interventions to improve infant health.

**Supplementary data**

Supplementary data are available at IJE online.

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