

A Comparison of Twin Birthweight Data From Australia, the Netherlands, the United States, Japan, and South Korea: Are Genetic and Environmental Variations in Birthweight Similar in Caucasians and East Asians?

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Birthweight has implications for physical and mental health in later life. Using data from Caucasian twins collected in Australia, the Netherlands and the United States, and from East Asian twins collected in Japan and South Korea, we compared the total phenotypic, genetic and environmental variances of birthweight between Caucasians and East Asians. Model-fitting analyses yielded four major findings. First, for both males and females, the total phenotypic variances of birthweight were about 45% larger in Caucasians than in East Asians. The larger phenotypic variances were mainly attributable to a greater shared environmental variance of birthweight in Caucasians (ranging from 62% to 67% of variance) than Asians (48% to 53%). Second, the genetic variance of birthweight was equal in Caucasians and East Asians for both males and females, explaining a maximum of 17% of variance. Third, small variations in total phenotypic variances of birthweight within Caucasians and within East Asians were mainly due to differences in nonshared environmental variances. We speculate that maternal effects (both genetic and environmental) explain the large shared environmental variance in birthweight and may account for the differences in phenotypic variance in birthweight between Caucasians and East Asians. Recent molecular findings and specific environmental factors that are subsumed by maternal effects are discussed.

Birthweight is a predictor of physical and mental health in later life as well as an indicator of infant health. It has been shown that size at birth is related

to a wide range of variables such as later blood pressure (Ijzerman et al., 2000; Law & Shiell, 1996), height (Ijzerman et al., 2001), body mass index (Johansson & Rasmussen, 2001; Pietilainen et al., 2001; Whitfield et al., 2001), grip strength (Sayer et al., 2002), social adjustment (Brooks-Gunn et al., 1993), psychosocial distress (Cheung et al., 2004), and IQ (Boomsma et al., 2001; Luciano et al., 2004). Although the underlying pathophysiology is not fully understood yet, low birthweight has been demonstrated to be a risk factor for noninsulin-dependent diabetes (Forsen et al., 2000), cardiovascular and lung diseases (Eriksson et al., 2004; Shaheen et al., 1998), hypertension (Eriksson et al., 2000), osteoarthritis (Jordan et al., 2005; Sayer et al., 2003), and schizophrenia (Kungu et al., 2003) in adulthood, and attention-deficit hyperactivity disorder, depressive symptoms (Botting et al., 1997) and autistic disorder (Burd et al., 1999) in childhood and adolescence.

Twin studies are useful to examine the origin of trait variation across populations as well as within a population. In the classical twin design, the total phenotypic variance within a population is partitioned into variance components associated with genetic factors, shared environmental factors (those environmental factors shared by the two members of

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a twin pair), and nonshared environmental factors (those environmental factors not shared by the two members of a twin pair). When comparing the similarity in birthweight of monozygotic (MZ) and dizygotic (DZ) twins, genetic variance represents the variation arising from differences in the fetal alleles. Shared environmental sources for birthweight in twins include gestational age, the physical and physiological characteristics of the uterine environment, and the genotype of the mother who provides the uterine environment. Nonshared environmental factors that can lead to twin pair differences in birthweight include perinatal injuries and the twin-twin transfusion syndrome (TTTS). TTTS is a complication unique to monochorionic twins and is characterized by failure of balance in blood and nutritive sharing. The major features in TTTS are discordance of fetal birthweight, amniotic fluid volumes and fetal hemoglobin concentrations (Lutfi et al., 2004). Measurement errors, if they are uncorrelated within twin pairs, will be confounded in the estimate of nonshared environmental effects. To facilitate interpretation of the sources of variance, genetic and environmental variances are divided by the total phenotypic variance within a population, which yields estimates of heritability, and of the proportion of variance explained by shared and nonshared environmental influences.

Studies of twins' birthweight have found significant, but modest heritability and substantial shared environmental influences on individual differences in birthweight, with heritability estimates generally between 10% and 40%, and shared environmental influences approximately between 40% and 60% (Boomsma et al., 1992; Whitfield et al., 2001). As most twin studies of birthweight have been conducted in western countries using Caucasian twin samples, relatively little is known about genetic and environmental contributions to variations in birthweight in East Asian populations. Recently, Ooki and Asaka (2005) reported MZ and DZ twin correlations for birthweight computed from two large databases of Japanese twins, a subsample of which are used in the present study. Twin correlations in the study by Ooki and Asaka (2005) suggested the heritability of birthweight in Japanese infants ranges from .09 to .32, shared environmental influences range from .41 to .55, and nonshared environmental effects range from .27 to .36. Hur (2005) applied model-fitting techniques to the birthweight data from 433 pairs of South Korean twins that were included in the present study and reported a heritability estimate of 17%, shared environmental effects of 60%, and nonshared environmental effects of 23%. The results of studies by Ooki and Asaka (2005) and Hur (2005) indicate that the magnitudes of heritability and environmental influences on birthweight may be similar in Caucasians and East Asians.

Although proportions of the total phenotypic variance explained by genetic, and shared and nonshared environmental influences on birthweight seem comparable between Caucasians and East Asians, the total phenotypic, genetic, and environmental variances of birthweight may differ between Caucasian and East Asian populations. For instance, if frequencies of fetal alleles contributing to birthweight differ between Caucasians and East Asians, then these differences can lead to a difference in the total phenotypic variance between the two groups by producing differences in genetic variability of birthweight. Also, differences in maternal gene frequencies, maternal dietary habit and lifestyle and the obstetrical care system between Caucasian and East Asian societies can cause differences in the total variance of birthweight. As another example, differences in gene expression arising from exposure to particular environments can result in difference in the phenotypic variance between the two groups.

So far, few studies have explored the question of variability in total phenotypic, genetic and environmental variances of birthweight at the population level. The goals of the present study are twofold. First, we aimed to determine whether the total phenotypic variance of birthweight differs between Caucasians and East Asians. Second, by comparing genetic and environmental variances in birthweight between the two groups, we attempted to understand why the total phenotypic variance of birthweight varies between Caucasians and East Asians. To fulfill these goals, we analyzed Caucasian and East Asian twin data collected from five countries, namely Australia, the Netherlands, the United States (US), Japan and South Korea.

Materials and Methods

Sample

Table 1 summarizes the characteristics of the twin samples from five countries. We conducted analyses only on the same-sex twin pairs because not all the samples included opposite-sex twin pairs. We excluded twin pairs with birthweight lighter than 1000 g from data analyses as the focus of the present investigation was on the etiology of the normal variation of birthweight. Whereas several twin cohorts were available in some countries, we chose twins born after 1978 to minimize cohort effects. For the cohorts selected for the present study, the correlations between birthweight and birth year were near zero in all except the Japanese sample, where younger cohorts tended to be lighter ($r = -.18$). The negative relationship observed in the Japanese sample may be largely due to the obstetrical practice currently prevalent in Japan intended to prevent maternal overweight problems (Ooki & Asaka, 2005).

In the Dutch, Japanese and US samples, twin zygosity was determined primarily from the twins' parents' responses to a zygosity questionnaire that included questions on physical similarities and the frequency of confusion of the twins by family members

Table 1
Characteristics of the Twin Samples

	Caucasians			East Asians	
	Australia	The Netherlands	United States	Japan	South Korea
# of pairs					
Total	670	941	1068	1045	1289
MZM	190	212	308	380	337
DZM	152	234	168	128	289
MZF	185	274	374	395	380
DZF	143	221	218	142	283
Birth cohorts	1978–1992	1988–1997	1978–1993	1980–2003	1986–2003
Measure	P	P	P	O	P = 686, O = 603
Zygosity	B, DNA	B, DNA, Q	Q	Q	Q

Note: P = parental report; O = obstetric records; Q = questionnaire method; B = blood group analysis.

and others. This method has been previously demonstrated to be over 90% accurate in determining zygosity as compared to results from DNA analyses (Rietveld et al., 2000). In the Australian twin sample, zygosity was determined by blood-group analysis (ABO, MN and Rh) and DNA analysis with a probability of error less than 10^{-4} . In the South Korean twin sample, zygosity was determined by the questionnaire method and chorionicity (see below).

Australia. The Australian twin sample was drawn from ongoing studies of adolescents in Brisbane (Wright et al., 2001). Twins were initially recruited in 1992 from schools in Brisbane and surrounding areas of southeastern Queensland, with most twins participating in a study of melanocytic naevi at ages 12 and 14 (Zhu et al., 1999), and others involved in a study of cognition at age 16 (Wright et al., 2004). Ancestry was reported by the parents of the twins, primarily of grandparents identified as being of northern European ancestry, mainly from Britain and Ireland. For the purpose of the present study, we chose twins whose grandparents were reported to be Caucasians. The sample used in the present analyses included 670 twin pairs (342 male and 328 female pairs) born between 1978 and 1992. Birthweight was obtained from a questionnaire completed by the twins' parents (primarily by mothers) when the twins were 12, 14 or 16 years old. For a subsample of the participants, mothers reported birthweight twice (2-year interval) and the correlation between these reports was .96.

The Netherlands. The Netherlands sample was drawn from the Netherlands Twin Register (NTR). The NTR is a longitudinal twin family study that currently contains over 60,000 twins and multiples recruited nationwide. The recruitment procedures and other details of the NTR are described in detail elsewhere (Boomsma et al., 2002). The sample used in the present study consisted of 941 twin pairs (446 male and 495 female pairs) born in the Netherlands between 1988 and 1997. To keep the sample as homogeneous as pos-

sible, we only chose twins whose parents were both born in the Netherlands. Information on birthweight was obtained from questionnaires that were sent to twins' parents within half a year of birth of the twins.

The United States. The US sample consisted of 1068 twin pairs (476 male and 592 female pairs) born between 1978 and 1993 who were derived from the Minnesota Twin Family Study (MTFS). The MTFS is a longitudinal, population-based study of genetic and environmental influences on substance abuse and related problems. The MTFS recruits twins born in Minnesota from birth records obtained through the Minnesota State Health Department, and therefore twin participants of the MTFS are broadly representative of Minnesota preadolescent and adolescent children (Iacono & McGue, 2002). Although almost all the twins in the MTFS were Caucasians (over 95%) with the majority having German and Scandinavian ancestry, in the present study we only included twins whose parents identified themselves as Caucasian. Information on birthweight was collected from birth records. Because the three Caucasian samples came from countries where the majority of the population is also Caucasian, for ease of presentation we designate these countries as Caucasian countries in the following.

Japan. The Japanese sample was drawn from two separate twin registries. The first registry consists of twins who applied for the secondary school attached to the Faculty of Education at the University of Tokyo between 1981 and 2003. Twins lived in the Tokyo metropolitan area at the time they applied for the school. The second registry comprised twins recruited from several associations for parents of multiples throughout Japan. For the present analyses, we chose twins born between 1980 and 2003, which resulted in 1045 twin pairs, consisting of 508 male and 537 female pairs. For further details of the two twin registries, see Ooki and Asaka (2005). Twins' birthweights were obtained from the Maternal and Child Health Handbook completed by obstetricians at the time of delivery. In

Japan, the Ministry of Health, Labor and Welfare provides the Maternal and Child Health Handbook to all pregnant women.

South Korea. The South Korean sample also consisted of two independent sources. The first source, derived from the ongoing Seoul Twin Family Study (STFS), included 686 twin pairs. The STFS is a large, longitudinal twin family study of genetic and environmental influences on the behavioral development of children and adolescents in Seoul, South Korea (Hur, 2002). Twins in the STFS were recruited from all private and public elementary, middle and high schools in Seoul. In the STFS, twin zygosity is determined by the questionnaire method. For the STFS twins, information on birthweight was obtained from parents of the twins whose age ranged from 8 to 18 years. The second source comprised 603 twin pairs who were born in two major hospitals in South Korea between 1998 and 2003. For the present analyses, only dichorionic twins conceived by Assisted Reproductive Technologies (ART) and monochorionic twins were chosen to accurately classify twin zygosity. Birthweights for these twins were obtained from the obstetric records. While the mean and standard deviation for birthweight were lower in the hospital than in the STFS sample, only the difference in the standard deviation between the two samples was statistically significant.

Data Analysis

First, we computed descriptive statistics and twin intraclass correlations. Next, we conducted model-fitting analyses using Mx 1.50 (Neale, 1999) software designed for analysis of twin and family data. We applied the standard univariate twin model (Neale & Cardon, 1992) to the variance-covariance matrices derived from the male and female MZ and DZ twin data. The full model included additive genetic (A), shared environmental (C), and nonshared environmental (E) variances. In the full model, parameter estimates were allowed to differ across gender and across all five countries. We compared the full model to submodels (e.g., leaving out A or C) to determine the best fitting, most parsimonious model. Model fit was judged using the likelihood ratio chi-square test.

Results

Descriptive Statistics

Table 2 provides means and standard deviations of birthweight by country, sex and zygosity. Levene's tests and *t* tests were conducted to compare means and standard deviations for birthweight to test the effects of sex, zygosity, birth order and race. Within each zygosity group, males tended to be heavier than females in all five countries. The difference in mean birthweight between males and females was statistically significant in all groups except the DZ twins in the US sample. Within each sex, DZ twins weighed significantly more than MZ twins in the Dutch and US samples. However, in the Australian, Japanese and South Korean samples DZ twins were not consistently heavier than MZ twins. First-born twins tended to weigh more than second-born twins in all five countries, but this difference was significant only in the Japanese and South Korean samples. None of the five countries showed significant differences in variances between males and females, between MZ and DZ twins, or between first- and second-born twins.

Within each zygosity group, means and variances for birthweight were uniformly higher in Caucasian than in East Asian samples. When we combined the three Caucasian samples and two East Asian samples separately (see Table 2), the means and standard deviations for birthweight were 2613.3 g and 541.3 g for Caucasian males, 2485.5 g and 457.4 g for East Asian males, 2514.6 g and 535.4 g for Caucasian females, and 2378.6 g and 441.4 g for East Asian females. The differences in means and standard deviations between Caucasians and East Asians were statistically significant ($p < .001$) in both males and females. In males, the variance in birthweight was 40% larger in Caucasians than in East Asians, whereas in females it was 47% larger in Caucasians than in Asians.

Twin Correlations

Table 3 presents twin intraclass correlations for birthweight for each zygosity group. The pattern of twin correlations was similar in males and females. For both males and females, MZ correlations were

Table 2

Means and Standard Deviations of Birthweight (g) by Country, Sex, and Zygosity

	Caucasians			East Asians	
	Australia	The Netherlands	United States	Japan	South Korea
MZM	2575.8 (548.1)	2540.4 (534.5)	2604.6 (541.8)	2449.4 (421.1)	2531.9 (487.6)
DZM	2678.8 (533.3)	2626.3 (526.2)	2686.5 (556.4)	2468.1 (443.6)	2486.5 (469.2)
MZF	2458.2 (531.8)	2432.6 (520.6)	2514.6 (542.8)	2359.9 (427.1)	2391.4 (452.3)
DZF	2533.5 (568.2)	2513.7 (514.6)	2654.0 (516.2)	2330.7 (436.9)	2411.5 (446.4)
Total (M)		2613.3 (541.3)		2485.5 (457.4)	
Total (F)		2514.6 (535.4)		2378.6 (441.4)	

Note: Standard deviations are in parenthesis. MZM = male monozygotic twins; DZM = male dizygotic twins; MZF = female monozygotic twins; DZF = female dizygotic twins.

Table 3
Twin Intra-class Correlations for Birthweight by Country, Sex, and Zygosity

	Caucasians			East Asians	
	Australia	The Netherlands	United States	Japan	South Korea
MZM	.74	.69	.77	.61	.69
DZM	.67	.67	.73	.50	.55
MZF	.76	.76	.76	.69	.70
DZF	.81	.69	.68	.53	.58

Note: MZM = male monozygotic twins; DZM = male dizygotic twins; MZF = female monozygotic twins; DZF = female dizygotic twins.

consistently higher than DZ correlations, with the exception of female Australian twins where the MZ correlation was slightly lower than the DZ correlation. These higher MZ than DZ correlations suggested the existence of fetal genetic influences on birthweight. Substantial shared environmental influences on birthweight were also indicated by the DZ twin correlations being greater than half the MZ correlations across all five countries and genders.

Model Fitting

Estimates of the raw variance components for the full model are shown in Figure 1. The chi-square test statistic was not statistically significant ($\chi^2_{30} = 14.43$) for the full model, indicating that it explains the data satisfactorily. Table 4 summarizes the results of fitting submodels of the full model. When we equated A, C and E variances for males and females within countries (Model 1), the fit worsened significantly ($\Delta\chi^2_{15} = 28.7, p < .05$). However, when we equated only

A and C variances across sex within countries while allowing the E variance to vary (Model 2), the resulting change in chi-square was not significant ($\Delta\chi^2_{10} = 6.9$). From Model 2, we further constrained the A and C variances to be equal across all five countries (Model 3), which led to a significant reduction in model fit ($\Delta\chi^2_{18} = 123.0, p < .01$). Our next step, therefore, was to constrain only the A variance to be the same across five countries, while fixing the C variance to be equal within the three Caucasian countries and within the two East Asian countries (Model 4). This yielded a satisfactory model-fit ($\chi^2_{47} = 38.35, \Delta\chi^2_{17} = 23.9, ns$). Further attempts to reduce parameters did not improve model-fit. On the basis of these model-comparisons, we chose Model 4 as the best fitting model where genetic variances were the same across all five countries and across gender, shared environmental variances were the same within Caucasians and within East Asians, but different between Caucasians and East Asians, and nonshared environmental variances varied across all five countries and across sex.

Figure 2 presents the raw variance component estimates for the best fitting model. In Caucasian countries, the total phenotypic variance ranged from 284,876 g² in the US to 298,536 g² in the Netherlands for males, and from 276,948 g² in Australia to 286,787 g² in the US for females. In contrast, the total phenotypic variances were only 201,691 g² in Japan and 210,071 g² in South Korea for males, and 190,123 g² in Japan and 194,880 g² in South Korea for females. As the estimates of genetic variance were constrained to be equal to 31,944 g² for all five countries and as estimates of non-shared environmental variance did not vary much across countries, the striking difference in the total phenotypic variance between Caucasian and East Asian countries was attributed to the difference in shared environmental variance between the two groups, that is, 184,570 g² versus 101,670 g².

Nonshared environmental variances tended to be slightly larger in Caucasian than in East Asian countries. For males, the means for nonshared environmental variances were 75,910 g² for Caucasian and 72,267 g² for East Asian countries; for females, the corresponding means were 65,293 g² and 58,888 g², respectively. As these differences were relatively small, it was unlikely that nonshared environmental factors

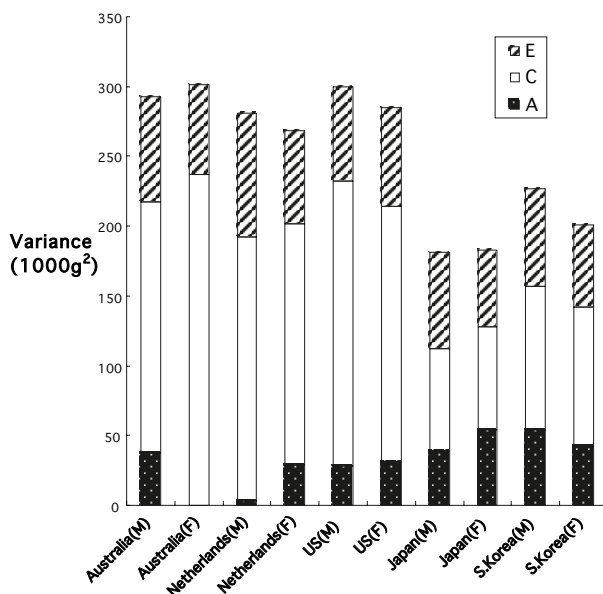


Figure 1
Unstandardized parameter estimates of the total phenotypic, additive genetic (A), shared environmental (C), and nonshared environmental (E) variances of birthweight for five countries by gender in the full model. M = males; F = females.

Table 4

Model-Fitting Results

Model	Description	χ^2	df	χ^2_a
Full	A, C and E vary across sex and across 5 countries	14.43	30	
1	No sex difference for A, C and E within countries	43.13	45	28.7*
2	For A and C, males = females within countries For E, males \neq females within countries	21.39	40	6.9
3	Same as model 2, but A & C are equated across 5 countries	137.38**	48	123.0**
4	Same as model 2, but A equated across 5 countries C equated within Caucasians and within East Asians but not between them E varies across 5 countries.	38.35	47	23.9

Note: a = difference in chi-square between the full model and the reduced model.

A = additive genetic variance; C = shared environmental variance; E = nonshared environmental variance.

The best fitting model is indicated in bold.

* $p < .05$, ** $p < .01$.

explained the large difference in total variance between Caucasians and East Asians. There were also small variations in nonshared environmental variance within Caucasian countries and within East Asian countries. These variations in nonshared environmental variances explained the modest size of variation observed in total phenotypic variances within Caucasian and within East Asian countries.

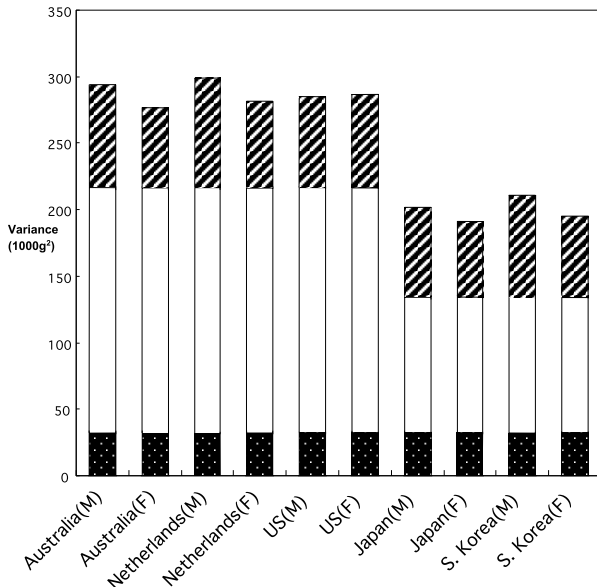
Table 5 presents percentages of genetic, and shared and nonshared environmental variance of birthweight

for males and females across five countries in the best fitting model. Heritability estimates and nonshared environmental influences were slightly higher and shared environmental influences were lower in East Asian than in Caucasian countries. Heritability estimates ranged from 15% to 17%, shared environmental influences from 48% to 53%, and nonshared environmental influences from 30% to 36% in Japan and South Korea. In Australia, the Netherlands, and the US, heritability estimates varied from 11% to 12%, shared environmental influences from 62% to 67%, and nonshared environmental influences from 22% to 27%. These estimates generally conformed to the conclusions reached from the observation of the twin correlations in Table 3.

Discussion

Like many other quantitative phenotypes, birthweight is likely to be a complex character determined by multiple genes and environmental factors. To our knowledge, the present study is the first to compare the phenotypic, genetic, and shared and nonshared environmental variances for birthweight between Caucasians and East Asians. There were significant and substantial differences in the phenotypic variance for birthweight between Caucasians and East Asians for both males and females. Interestingly, however, genetic variances were the same in the two groups. Whereas differences in the nonshared environmental variance between Caucasians and East Asians were very small, differences in the shared environmental variance were substantial, indicating that it is shared environmental factors that explain the large difference in the total phenotypic variances of birthweight between Caucasians and East Asians.

The finding that shared environmental factors largely determine the difference in the phenotypic variance of birthweight between Caucasians and East Asians is consistent with other studies suggesting the importance of shared environmental factors in explaining within-group variation in birthweight (Boomsma et al., 1992; Whitfield et al., 2001). In the

**Figure 2**

Unstandardized parameter estimates of the total phenotypic, additive genetic (A), shared environmental (C), and nonshared environmental (E) variances of birthweight for five countries by gender in the best fitting model.

A = 31,944 g² for all five countries; C = 184,570 g² for Australia, the Netherlands, and the United States; C = 101,670 g² for Japan and South Korea; and E varies from 56,509 g² for Japanese female twins to 82,022 g² for the Dutch male twins.

M = males; F = females.

Table 5

Percentage of Additive Genetic (A), and Shared (C) and Nonshared (E) Environmental Variances of Birthweight and Their 95% Confidence Intervals for Males and Females in the Best Fitting Model

Parameter	Sex	Caucasians			East Asians	
		Australia	The Netherlands	United States	Japan	South Korea
A	M	11 (7–15)	11 (7–16)	11 (7–15)	16 (10–22)	15 (9–21)
	F	12 (7–16)	11 (7–16)	11 (7–16)	17 (10–23)	16 (10–23)
C	M	63 (58–67)	62 (60–69)	65 (57–66)	50 (44–57)	48 (42–54)
	F	67 (62–71)	66 (60–69)	64 (61–70)	53 (47–60)	52 (46–58)
E	M	26 (23–30)	27 (21–27)	24 (24–31)	34 (30–37)	36 (33–40)
	F	22 (19–25)	23 (22–27)	25 (20–26)	30 (27–33)	31 (28–35)

Note: M = male; F = female.

classical twin design, ‘maternal effects’ including gestational age would show up as shared environmental factors because these are shared by both MZ and DZ twin pairs. Maternal effects occur when the mother contributes to her offspring over and above that which results from the genes she contributes to her offspring (Mather & Jinks, 1971). On the basis of children of female and male MZ twins, Nance et al. (1983) demonstrated that maternal half-siblings were much more similar than paternal half-siblings in birthweight, indicating the importance of maternal effects on fetal growth. Nance et al. (1983) also reported that 41% to 54% of the total variance in birthweight was associated with maternal effects, which is close to the size of shared environmental effects found in our study. Unfortunately, however, Nance et al. (1983) were not able to decompose the maternal effects into genetic and environmental components because they examined offspring of only MZ twins.

Considered from an evolutionary perspective, it has been suggested that part of these maternal effects are due to maternal genes which regulate fetal growth, perhaps through physical and physiological characteristics (e.g., of uterus) of the mother (Nance et al., 1983; van den Oord & Rowe, 2001), and which may also include genetic influences on gestational length. For example, Clausson et al. (2000) and Van Den Oord and Rowe (2001) in studies of offspring of twins and siblings reported that heritability estimates for gestational length were over 30%, whereas shared environmental estimates were zero, indicating that gestational length is a heritable trait in Caucasians. Heritability and shared environmental influences on gestational length are presently unknown for East Asian populations but if these vary from Caucasian estimates, then this may partly explain the difference in shared environmental variance in birthweight between Caucasians and East Asians. Factors that influence the uterine environment and hence resulting birthweight may include maternal socioeconomic level, lifestyle, behavioral factors, blood pressure, dietary habits, glucose concentration, stature and prepregnancy weight. Given that these maternal variables have been demonstrated to be genetically

influenced traits (Plomin et al., 2000), it is likely that the larger shared environmental variance of birthweight in Caucasians as compared to East Asians found in the present study may largely reflect greater genetic variability in maternal characteristics in Caucasians than in East Asians. A recent study that genotyped 71 Americans of European, African and Asian ancestry reported that genetic variances were greater in individuals of African and European descents than in those of Asian descent (Hinds et al., 2005).

Various maternal genes have been shown to influence fetal growth, either directly or indirectly. For instance, Petry et al. (2005) found that an exclusively maternally expressed gene, *H19*, was associated with birthweight and with cord blood IGF-II levels especially in first pregnancies. The *H19* 2992 T allele as opposed to C variant was related to heavier birthweight and more elevated cord blood IGF-II levels, and these associations were independent of maternal weight. Petry et al. (2005) proposed that the *H19* 2992 T allele may confer reduced fetal growth restraint either by influencing mother’s glucose metabolism and thereby affecting placental glucose transfer or by regulating insulin-like growth factor IGF-II expression in maternally derived placental tissues. Thus, the difference of the frequency of *H19* 2992 allele between Caucasians and East Asians, if it exists, may account for some of the difference in shared environmental variance of birthweight between the two racial groups found in the present analyses.

In Caucasians, the maternal G protein $\beta 3$ subunit is another gene that shows association with birthweight (Hochoer et al., 2000), with the 825T allele lowering offspring birthweight. As this gene is known to be associated with obesity (Siffert et al., 1999), the effect on birthweight may be related to prepregnancy weight, a major determinant of fetal growth (Negggers et al., 1995; Rossner & Ohlin, 1990; Shapiro et al., 2000). A study by Masuda et al. (2002) in a Japanese sample found that the 825T allele lowered the fetal head circumference, but the association of the 825T allele with birthweight was not replicated. As the frequency of the 825T allele has been shown to be higher

among Asians than among Caucasians (Siffert et al., 1999), this variability may explain some of the difference in shared environmental variance of birthweight between Caucasians and East Asians detected in the present study.

Maternal smoking was not controlled for in our study as not all the samples collected data on smoking during pregnancy. However, it appears that the prevalence of smoking during pregnancy is generally higher in the Caucasian than in the East Asian countries that participated in the present study. For example, in a sample of over 3500 pregnant women who received prenatal care at a major maternity hospital in South Korea, Han (2002) found the rate of smoking to be 4.1%. In contrast, Hamilton et al. (2004), on the basis of the US national data, found the rates of female smoking during pregnancy to be 11.4% in 2002 and 11.0% in 2003. In the Netherlands, 34% of mothers expecting twins smoked between 1986 and 1989 (Van Baal & Boomsma, 1998). Thus, the difference in shared environmental variance of birthweight between Caucasians and East Asians found in the present study may in part be attributable to the difference in the prevalence of maternal smoking between Caucasians and East Asians.

It is noteworthy that the effects of fetal genes that determine birthweight were approximately equal in magnitude in Caucasians and East Asians in spite of the difference in the genetic background between the two racial groups. It may be that the majority of the fetal genes and their major molecular pathways that lead to the variation in birthweight may be largely common to Caucasians and East Asians. But this awaits detailed molecular genetic analyses.

Recently, several molecular genetic studies have successfully identified genes associated with birthweight in Caucasian and Chinese samples. In Caucasian samples, for example, the insulin gene (*INS*) variable number of tandem repeats (VNTR), which regulates the expression of a major fetal growth factor, IGF-II, has been repeatedly associated with birthweight, in particular with head circumference at birth and also with IGF-II protein levels in cord blood at birth (Dunger et al., 1998; Ong et al., 2004). As another example, Adkins et al. (2005) found an association between fetal growth restriction and the presence of C alleles at sites -1 and +3 of the pituitary growth hormone gene on chromosome 17 in a Caucasian sample. Although the underlying mechanism of this association is not fully understood, the authors speculated that late in gestation, when the fetal pituitary growth hormone gene is expressed, the hormone begins to play a growth stimulatory role leading to a difference in birthweight between genotypes for the A/C polymorphism at -1 and +3 sites.

Few studies have been conducted to search for birthweight genes for East Asian populations. Chen et al. (2005) have shown that the maternal and infantile Cytochrome P450 gene variability was asso-

ciated with increased risk of low birthweight in a Chinese sample. In the analyses of both mothers and children's genotypes in the Chen et al. (2005) study, homozygous carriers of the variant alleles (C/C6235 as compared to T/T6235 for CYP1A1 MspI) were at increased risk for low birthweight. One should note that the results of the gene identification studies for birthweight were published only very recently. Replication studies, therefore, need to be performed across Caucasian and East Asian populations as well as within each of these two populations.

In order to study the etiology of the normal variation of birthweight, we excluded twins who weighed less than 1000 g in the present analyses. One could argue that the differences in phenotypic variance in birthweight between Caucasians and East Asians found in the present analyses may have disappeared if we had excluded twins lighter than, for example, 1500 g or heavier than 4000 g. However, the differences in phenotypic variance in birthweight between the two racial groups were still statistically significant ($p < .0001$) and substantial even when we eliminated twins who weighed less than 1500 g or more than 4000 g from data analyses.

In the present study, Caucasian data were collected from only three countries where the majority of the population has northern and western European ancestry. In addition, East Asian data were collected from Japanese and South Koreans only. Genetic background and environmental characteristics may be very similar among the three Caucasian countries and among the two East Asian countries selected. To strengthen our findings, therefore, further studies that include samples from such regions as the Middle East, Latin America, mainland China, Hong Kong and Taiwan will be necessary. Future studies should also include the birthweight covariates of mother's height and weight, and gestational age of the twins in the analysis so that the shared environmental variance can be decomposed even further. Moreover, to study the effects of maternal genes a twin design is needed in which the birthweights of the offspring of MZ and DZ twins are compared. A comparison between Caucasian and Asian samples will enable evaluation of the hypothesis that greater maternal genetic variability in Caucasians than Asians is the strongest determinant of birthweight variance differences between the two racial groups.

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