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Etiology of individual differences in birth weight of twins as a function of maternal smoking during pregnancy

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Birth weight is in large extent influenced by gestational age. In addition genetic and environmental factors determine intrauterine growth and birth weight. The contributions of these factors may be influenced by maternal smoking during pregnancy. We examined birth weight and maternal smoking in a sample of 2930 twin pairs from the Netherlands Twin Register using structural equation modelling. Gestational age accounted for 27–44% of the variance in birth weight. A lower variability of birth weight and a lower association of birth weight with gestational age was found in twins whose mothers smoked during pregnancy. The variance not associated with gestational age was independent of maternal smoking during pregnancy. A systematic smaller part of the variability in birth weight was associated with variability in gestational age in second born twins compared to first born twins. The heritability of interindividual differences in birth weight was modest (10% for twins with non-smoking mothers and 11% for twins with smoking mothers). Common environmental influences other than gestational age accounted for a slightly larger part of the variance not associated with gestational age (17–20%).

Keywords: birth weight, genetics, gestational age, maternal smoking, twins

Introduction

Intrauterine growth as indexed by birth weight is an important determinant of physical and mental development and is positively associated with height in children at school age,[1,2] with reading abilities at ages 7 and 11,[1] with mental retardation,[2] with neurological abnormalities,[3–5] and with speech development at ages 6 to 12 years.[6] Although brain weight of growth retarded children is generally less affected than the rest of the body, other indices of brain development are retarded somewhat when intrauterine growth is reduced, for instance cell migration and differentiation.[6] Thus, birth weight is a highly informative measure of physical and mental development.

Birth weight is influenced by a number of factors. An important source of influence is gestational age. In addition, studies of individual differences in birth weight showed that genetic as well as environmental influences affect birth weight. Genetic influences comprise two main sources: maternal genes and foetal genes. Regulation of the foetal weight by maternal genes would have an important survival function, as it would prevent a genetically unfit mother from having a very large baby.[7] Cross-breeding studies in horses suggest that maternal factors regulate offspring birth weight.[8] Human embryo transfer studies have shown that offspring birth weight is more associated with the recipient mother than the donor mother.[9] But there is no absolute consensus as to whether the maternal genetic effect exists. In a study of first cousins and twins, Penrose[10] estimated that maternal genes explain 20% of variance in birth weight. Nance and colleagues[11] estimated the effect of maternal genes on birth weight of offspring to be 40% in a study with 1694 offspring of monozygotic (MZ) twins. Magnus found a contribution of 12% of maternal genes to birth weight of 13970 offspring of monozygotic (MZ) and dizygotic (DZ) twins,[12] and no contribution of maternal genes in his study with 5625 grandchildren of the same MZ and DZ twins.[13] In a classical twin design (comparing birth weight correlations of MZ co-twins with those of DZ co-twins), the effect of maternal genes cannot be estimated, but would show up as a common environmental factor, because the effect would be the same within a twin pair, but different between pairs. Vlietinck and colleagues[14] compared birth weights of 1855 MZ and DZ twins, but did not find a common environmental factor, suggesting no effect of maternal genes. The familial resemblance in their study was of foetal genetic origin, with a heritability of 22.5%.

A number of other studies have reported different estimates of foetal genetic influences on birth weight. Older studies[10,15] (1174 sibs, 198 halfsibs and 442 children with consanguinous parents) and

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Robson[16] (1517 first cousins) showed no or only a marginal effect of foetal genes on birth weight. This agreed with the results of Nance and colleagues,[11] but was in contrast with the studies of Magnus *et al*, who found the effect of foetal genes to be very high (60–70%) in a Norwegian parent–offspring study with 3130 children,[17] in a study of 13970 children of twins,[12] and in a study of 5625 grandchildren of the same twins.[13] Langhoff-Roos and colleagues[18] reported a moderate effect of foetal genes of 30% on birth weight of 276 Swedish children. In the latter study variation in birth weight due to gestational age was taken into account. Vlietinck and colleagues[14] also looked for gestational age. They showed that as much as 41.8% of variation in birth weight could be explained by variation in gestational age. A third important source of variance in birth weight were random environmental effects, which explained 22.8% of the variation.

In the present paper we examine the effect of maternal smoking during pregnancy on interindividual variability in birth weight. Maternal smoking is an important factor affecting mean birth weight. Goldstein,[19] using data from the British Perinatal Mortality Survey (17 000 offspring) showed an effect of maternal smoking after the 20th week of gestation on mean birth weight. Cnattingius[20] showed in a study with 280 809 offspring that smoking mothers have significantly more often a 'small for gestational age' infant (SGA) than non-smoking mothers. Orlebeke *et al*[21] reported that maternal smoking significantly reduced birth weight in 5376 Dutch twins. Magnus *et al*[17] showed that maternal smoking during pregnancy explained a small but significant part of variance in birth weight in a parent–offspring study with 3130 offspring of Norwegian twins, as did Langhoff-Roos *et al*[18] in another parent–offspring study in 276 Swedish children. In all these studies maternal smoking during pregnancy reduced birth weight in offspring.

Little and Sing[22] analysed data on 377 nuclear families with information on birth weights of mother, father, an index infant and a sibling. Maternal smoking was dichotomised into smoking or non-smoking. Infant birth weights were corrected for tobacco use by regression, and standardised residuals were used for model fitting. For male offspring, maternal smoking during pregnancy resulted in lower heritabilities of birth weight. For female offspring heritabilities were the same for smoking and non-smoking mothers. Such a reduced heritability of birth weight can indicate a reduced genetic variance or an increased environmental variance. Maternal smoking may inhibit the expression of particular foetal genes. It is also possible that the influence of environmental factors is amplified because of maternal smoking. A third possibility is an increased variance in birth weight due to a larger effect of gestational age on birth weight which would result in a smaller relative effect of genetic variance in total variance. In Little and Sing's study no data on gestational age were available.

The aim of the present study is to estimate the (foetal) genetic and environmental contributions to variance in birth weight in a multivariate model with gestational age as covariate, and to determine whether maternal smoking during pregnancy changes the genetic architecture of birth weight.

Materials and methods

Subjects

Data on 3064 pairs of twins born in 1987, 1988 or 1989, with complete information on zygosity, birth weight, gestational age and maternal smoking during pregnancy, were obtained from questionnaires by the Netherlands Twin Register (NTR).[23] Twenty-three pairs were left out because their mothers were diabetic, and four pairs because they were triplets, of which only two children survived. Two pairs of twins were excluded because one of the twins had heart failure, or the twins suffered from transfusion syndrome. Since this paper concerns genetic influences on normal birth weight, we discarded twin pairs with the most extreme gestational ages (shorter than 32 weeks or longer than 42 weeks, $n = 105$) and birth weights (lighter than 1000 grams or heavier than 4000 grams, $n = 20$). This left 2930 pairs. Birth weight was measured by a doctor or nurse in the hospital shortly after birth. Parents were asked to report these birth weights in a questionnaire which they received within half a year of birth of the twins. When the parents indicated that the twins were born by Caesarian section, and that the 'first born' really was the second born twin, the birth order was reversed. Questions about gestational age (number of weeks from last menstrual period to birth) and maternal smoking during pregnancy (yes or no) were answered in this questionnaire as well. 1004 of 2930, ie 34%, mothers smoked during pregnancy. Zygosity information was obtained from similarity questions in other questionnaires, which were completed when children were about 5 years old.[24] A discriminant analysis of these data on a larger sample of these twins yielded a 92.71% correct classification.[24] Same-sex twin pairs were distributed over 8 different groups: MZ versus DZ, male versus female and maternal smoking versus no maternal smoking during pregnancy. Opposite-sex twin pairs were distributed over 4 groups: pairs with a male first born (MOS) and pairs with a female first born twin (FOS),

Table 1

	N	*Birth weight, oldest, gm*		*Birth weight, youngest, gm*		*Gestational age, wks*	
		Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Males							
Non-smoking, MZ	343	2565	469	2511	471	36.98	2.24
Non-smoking, DZ	307	2731	464	2635	446	37.42	2.14
Smoking, MZ	130	2471	467	2390	480	36.97	2.33
Smoking, DZ	190	2602	465	2540	455	37.63	2.01
Females							
Non-smoking, MZ	373	2516	476	2468	508	37.20	2.20
Non-smoking, DZ	286	2665	485	2623	489	37.55	2.23
Smoking, MZ	142	2303	452	2280	429	36.89	2.47
Smoking, DZ	179	2470	455	2370	490	37.55	2.03
DZ opposite sex							
Non-smoking, MF	322	2716	475	2530	497	37.36	2.17
Non-smoking, FM	295	2595	457	2694	501	37.36	2.17
Smoking, MF	194	2644	466	2430	435	37.81	2.06
Smoking, FM	169	2408	449	2444	500	37.23	2.22

MF=male first born, female second born; FM=female first born, male second born

with smoking mothers and with non-smoking mothers. The number of subjects are depicted in Table 1.

Statistical analysis

Differences in mean values of birth weights between zygosity, sex, maternal smoking and birth order were tested using the GLM procedure (repeated measures) in SPSS for Windows (alpha = 0.05). Because data of first and second born twin are not independent, a twin pair was taken as a case, and birth order effects (oldest and youngest) were tested as a within subjects factor. Between subject factors were zygosity (MZ and DZ), sex (male and female), and maternal smoking during pregnancy (non-smoking and smoking). The effect of gestational age was tested as a covariate. For same-sex twins, sex is a between subjects factor, but for opposite-sex twins sex is a within subjects factor (note that a subject is a twin pair in these analyses). For that reason, these analyses were conducted on the same-sex twin pairs only (n = 1950).

Data were further analysed using the statistical package PRELIS 2[25] to calculate means, standard deviations and twin correlations. LISREL 8[26] was used for path analysis.[27] For every group a variance–covariance matrix was calculated between 3 observed variables: gestational age of both children, birth weight of the oldest child, and birth weight of the youngest child. These matrices were used to conduct two different kinds of analysis: a model fitting approach for testing heterogeneity in variances and regression coefficients, and genetical model fitting.

Heterogeneity testing

We first estimated the variance of gestational age, the effect of gestational age on birth weight in first and second born twins, the residual variance in birth weight in both twins, and the residual correlation between birth weights. This yielded 6 estimates for each zygosity group. Next, it was tested whether heterogeneity in variability of gestational age and birth weight, and association between birth weight and gestational age existed between oldest and youngest of the twins, between male and females, between MZ and DZ twins, and between offspring of smoking and non-smoking mothers. Lastly, we tested whether the residual twin correlations were different between sexes and between offspring of smoking and non-smoking mothers. These effects were tested using structural equation modelling with nested models. A path diagram of the model used in these analyses is shown in Figure 1.

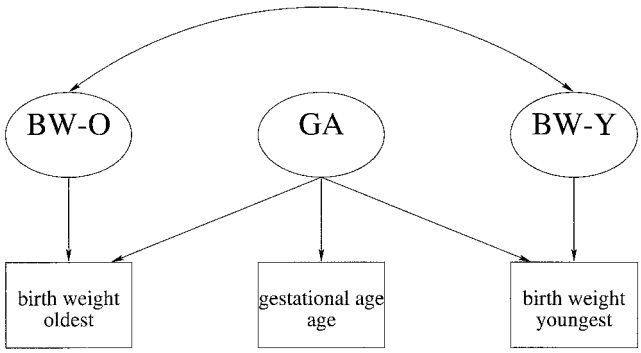

Figure 1 Model for heterogeneity testing. The squares represent the observed variables (birth weights of oldest and youngest of the twins and gestational age). The circles represent latent factors influencing the observed variables. The latent factor gestational age (GA) is the sole contributor to variation in the observed gestational age, and also influences variation in birth weights of the twins. For birth weight, a second latent factor accounts for a part of the variability (BW-O for oldest of the twins and BW-Y for youngest of the twins). BW-O and BW-Y may be correlated.

Genetic model fitting

The relative magnitudes of (foetal) genetic (G), common environmental (C), and unique environmental factors (E) were determined in a twin design. This design is based on the fact that identical, monozygotic twins (MZ) share all their genes, whereas fraternal, dizygotic twins (DZ) share 50% of their genes on average. A larger resemblance between MZ twins than between DZ twins thus yields evidence for genetic influences. Since twins grow up in the same uterus, they are exposed to largely the same environment, which may increase the resemblance between both MZ and DZ twins.

The model in Figure 2 was used to examine genetic architecture of birth weight. Again, three variables were observed in each group, birth weight of both children, and gestational age. Variability in birth weight can have different causes. Part of the variance is explained by differences in gestational age (GA). The remainder of the variance is caused by genetic factors (G), environmental factors which are common to both twins (C), and environmental factors unique to both twins (E). Because the analyses for heterogeneity indicated higher variance in birth weight of the youngest of the twins, an additional source of variance was modelled, – birth order effect (BO) – for second born twins (youngest). The relative importance of these factors was estimated by maximum likelihood method. The best model has the most degrees of freedom, but is not significantly worse than a model with fewer degrees of freedom. Using parameter estimates from the best fitting model, a number of descriptive statistics were calculated: heritability (h^2, ie the percentage genetic variance over total variance), common environmentability (c^2, ie percentage common environmental variance over total variance), and percentage variance explained by gestational age.

Results

Table 1 contains means and standard deviations for birth weights and gestational ages for oldest and youngest of the twins in 12 groups. Mean gestational age is 37.3 weeks. Gestational age was the same for males and females. Maternal smoking during pregnancy did not influence the duration of gestation: gestational age was the same for offspring of smoking and non-smoking mothers. However, gestational age differed for MZ and DZ twins ($F(1,1949) = 21.91$, $P < 0.000$). Mean gestational age for MZ twins is 37.1 weeks, and for DZ twins 37.5 weeks. Birth weight of twins was 2549 grams on average. Birth weights were significantly higher for first born than for second born twins ($F(1,1941) = 9.80$, $P = 0.002$), for males than for females ($F(1,1941) = 39.66$, $P = 0.000$), for DZ twins than for MZ twins ($F(1,1941) = 24.45$, $P = 0.000$) and for twins with non-smoking mothers than for twins with smoking mothers ($F(1,1941) = 101.20$, $P = 0.000$). The effect of gestational age on birth weight was highly significant: a higher gestational age resulted in a higher birth weight ($F(1,1941) = 1623.08$, $P = 0.000$). Two

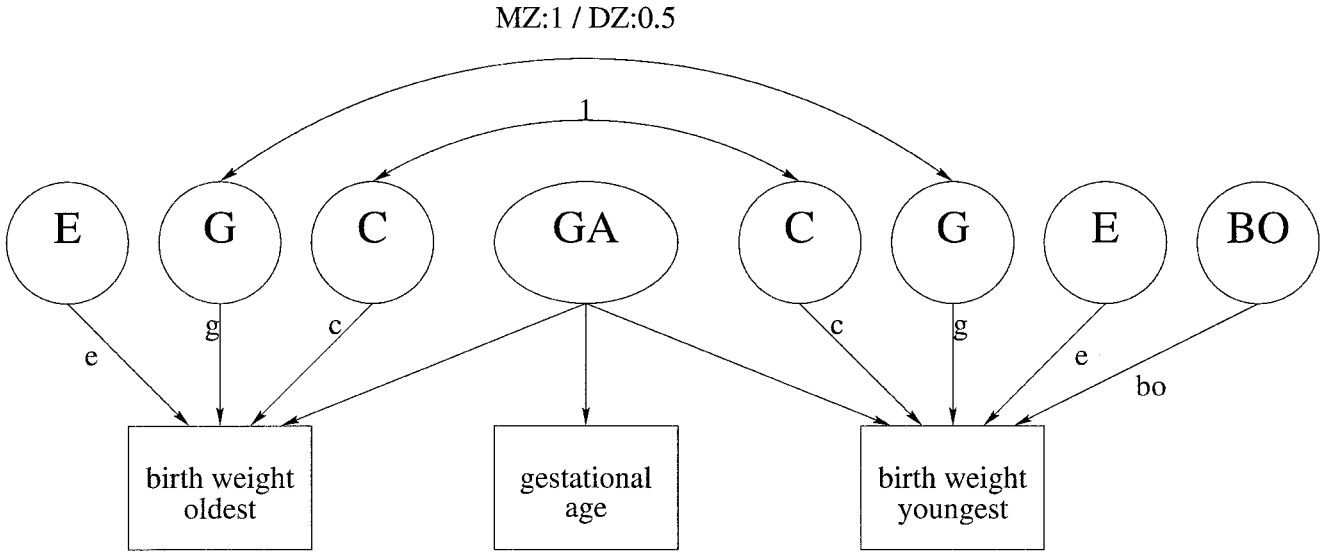

Figure 2 Genetic model for path analysis. Birth weight is influenced by a genetic factor (G), a common environmental factor (C), a unique environmental factor (E), gestational age (GA) and a birth order factor (BO, second born twin only). Their relative importance is estimated. bo = factor loading of birth order, g = genetic factor loading, c = common environmental factor loading, e = unique environmental factor loading. Correlation between C of co-twins is 1, correlation between G of MZ co-twins is 1, correlation between G of DZ co-twins is 0.5.

interaction effects of these factors were found. The effect of gestational age on birth weight was larger in the oldest of the twins than in youngest (birth order × gestational age, ($F(1,1941) = 12.56$, $P = 0.000$). And the difference between birth weights of daughters of smoking mothers and daughters of non-smoking mothers was larger than the difference between birth weights of sons of smoking mothers and sons of non-smoking mothers (sex- × maternal smoking, ($F(1,1941) = 4.07$, $P = 0.044$).

Correlations between birth weight of the oldest twin with birth weight of its co-twin are shown in Table 2. Since gestational age has a large effect on birth weight, its correlation with birth weight of both infants is also shown. The last column shows partial correlations between birth weight of the twins, when calculated in a multivariate model with gestational age as covariate. This is done by fitting the LISREL model for heterogeneity testing, shown in Figure 1. The correlations shown in Table 2 are correlations in the full model (without any equality constraints). They depict the residual correlations between birth weights of the co-twins when correlations due to a shared gestational age are taken into account.

Heterogeneity testing

Table 3 shows test statistics (χ^2, df and P) for a number of models in which the variabilities and associations of birth weights of twins and gestational age were estimated. Best fitting model (B) was one with the same variance for gestational age in all 12 groups (sd = 2.19 weeks), different residual variances for birth weights of oldest versus youngest children – sd = 356 grams (oldest) and 394 grams (youngest), and different regressions of birth weight on gestational age for oldest versus youngest of the twins, and for twins with non-smoking mothers versus twins with smoking mothers (317, 289, 276 and 237 for oldest and youngest twins of non-smoking mothers and oldest and youngest twins of smoking mothers respectively). Correlations were the same for all MZ twins (0.46), and for all DZ twins (0.38), but significantly higher in MZ twins than in DZ twins.

Model B shows that maternal smoking does not influence variance of birth weight once birth weight has been corrected for gestational age, but that it influences the regression of birth weight on gestational age. An additional source of variance of birth weight in youngest twins exist, which causes them to be more variable than oldest twins. However, variability in birth weight which is associated with gestational age was less in youngest twins compared with oldest twins. No differences in all parameter estimates between male and female offspring were found. SDs of birth weight and gestational age were not different for MZs and DZs, but MZ correlations between birth weights of oldest and youngest were significantly higher than DZ correlations, indicating that at least some degree of heritability (h^2) exists. However, MZ correlations were not twice as high as DZ correlations, which points to an additional influence of the common environment.

Genetic model fitting

To test for the genetic and common environmental influences, a genetic model was fitted to the data. Variance in birth weight was decomposed into variance associated with gestational age (GA), variance influenced by (foetal) genetic factors (G), variance influenced by common environmental factors (C), and variance influenced by unique environmental factors (E). Since the variance of birth weight in the youngest twin was larger than that of the oldest, an extra source of variance was introduced for this group: birth order.

Table 2

	N	*Twin correlations*	*Correlation, birth weight/ gestational age: first born*	*Correlation, birth weight/ gestational age: second born*	*Twin correlation corrected for gestational age*
Males					
Non-smoking, MZ	343	0.65	0.66	0.61	0.43
Non-smoking, DZ	307	0.54	0.66	0.57	0.27
Smoking, MZ	130	0.64	0.57	0.54	0.48
Smoking, DZ	190	0.57	0.59	0.51	0.39
Females					
Non-smoking, MZ	373	0.67	0.72	0.63	0.41
Non-smoking, DZ	286	0.67	0.67	0.59	0.47
Smoking, MZ	142	0.70	0.61	0.49	0.58
Smoking, DZ	179	0.57	0.58	0.53	0.38
DZ opposite sex					
Non-smoking, MF	322	0.62	0.67	0.58	0.39
Non-smoking, FM	295	0.64	0.67	0.61	0.38
Smoking, MF	194	0.59	0.60	0.53	0.41
Smoking, FM	169	0.54	0.63	0.46	0.36

Table 3 Test of heterogeneity

Model		χ^2	*Df*	*P*
A:	The variance of gestational age is the same in all 12 groups; the variance of birth weight is different for oldest and youngest twin, but the same in all 12 groups; regressions of birth weight on gestational age differ for oldest and youngest of the twins and for offspring of smoking and non-smoking mothers, but are the same for males and females and for MZ and DZ twins; the residual correlations between birth weights are different for every sex × zygosity group (12 groups).	50.51	53	0.57
B:	Same as model A, but correlations are the same for all MZ twins, and for all DZ twins (including OS twins).	63.79	63	0.45
C:	Same as model B, but the variance of birth weight is the same for oldest and youngest twin.	101.28	64	0.00
D:	Same as model B, but the regression of birth weight on gestational age is the same for oldest and youngest twins of smoking mothers, and for oldest and youngest twins of non-smoking mothers.	78.27	65	0.12
E:	Same as model B, but the regression of birth weight on gestational age is the same for oldest twins of smoking and non-smoking mothers, and for youngest twins of smoking and non-smoking mothers.	80.86	65	0.09
F:	Same as model B, but with the same correlation of MZ and DZ twins.	71.19	64	0.25

The best fitting model was one with the same factor loadings of genetic, common environmental and unique environmental factors (indicated by their parameter estimates g, c and e) for twins with smoking mothers and twins with non-smoking mothers. No sex differences were found. Regressions of birth weight on gestational age were different for oldest and youngest of the twins, and for twins with smoking and twins with non-smoking mothers, but the same for males and females. Leaving out additive genetic effects or common environmental effects significantly decreased the fit of the model (difference-$\chi^2(1) = 7.54$ (without G) or 41.64 (without C)). Parameter estimates of the best fitting model ($\chi^2 = 63.84$, df = 63, $P = 0.45$) were: g = 152, c = 203, e = 249 and bo (birth order) = 171. Standard deviation of gestational age and regressions of birth weights on gestational age were the same as in model B of the heterogeneity model.

Because the influences of gestational age are different in first and second born twins, heritabilities of birth weights were different for these twins, and for twins with smoking mothers and twins with non-smoking mothers. This is not a result of a difference in genetic variance, but of a difference in total variances, due to a different regression of birth weight on gestational age or due to the additional source of variance in the younger twin. Heritabilities of birth weights were: 10% for oldest and for youngest of the twins with non-smoking mothers and 11% for oldest and youngest of the twins with smoking mothers. Common environmentabilities were 18%, 17%, 20% and 19% for oldest and youngest of non-smoking mothers and oldest and youngest of smoking mothers, respectively. The additional variance in the youngest of the twins explained 12% of the variance in birth weights of twins with non-smoking mothers, and 14% of the variance in birth weights of twins with smoking mothers. The regression of birth weight on gestational age explained 44%, 35%, 37% and 27% for oldest and youngest of non-smoking mothers and oldest and youngest of smoking mothers respectively.

Discussion

In this paper, the genetic architecture of birth weight as a function of maternal smoking during pregnancy was studied using a twin design. For offspring of smoking and non-smoking mothers we found the same low heritability of birth weight ($h^2 = 10\%$). A very large part of the variability was accounted for by gestational age. An interesting result of this study was that, although maternal smoking during pregnancy did not influence gestational age, the association between birth weight and gestational age was smaller when mothers smoked during pregnancy.

Because maternal smoking during pregnancy is a serious hazard to intrauterine growth, we studied whether maternal smoking resulted in a reduced birth weight of twins. Results showed that mean values of birth weight of offspring of smoking mothers and non-smoking mothers were different. This finding agrees with the literature (eg ref. 28). Tobacco smoke contains a number of teratogenic substances, which can all be responsible for foetal growth retardation. An increased level of carbomonoxide results in oxygen deprivation, because it has a 200 times greater affinity to bind with the oxygen transporting haemoglobin. This can cause a 200 to 300 gram reduction in birth weight.[29] In addition, nicotine may decrease the utero–placental blood flow and thus reduce birth weight.[30] In smoking adults, nicotine causes a higher basal metabolism. This effect may also take place in the foetus, because nicotine is transported through the placenta, and thus may reduce the weight gain during pregnancy. These, and possible other effects can accumulate during pregnancy. Due to these teratogenic effects, the foetus may not develop optimally during pregnancy, resulting in a lower birth weight of offspring of smoking mothers. It is important to recognise that

such effects will be stronger when children have spent more time in uterus, that is when gestational age at birth is higher. We argue that this will show up as a lower regression of birth weight on gestational age for twins whose mothers smoked during pregnancy, which is exactly what we found in our model-fitting approach.

Twins of non-smoking mothers have a more optimal development of weight, because they are in a situation where the circumstances were not subject to teratogenic effects of tobacco, so that the largest part of the inter-individual variance will be associated with the restrictions of the uterus, and the time spent there. Therefore, birth weight of twins with non-smoking mothers should be associated more with gestational age than birth weight of twins with smoking mothers, whose circumstances were less optimal during pregnancy.

A second indication of this combination of low birth weight and a lower association between birth weight and gestational age is seen when the effect of birth order is taken into account. First born children are heavier than second born children, which coincides with a higher regression of first born birth weight on gestational age than of second born birth weight on gestational age.

Returning to the other main interest of this paper, when the effect of gestational age is included in the analysis it is shown that the relative effects of foetal genes, common environment and unique environment on birth weight was not altered when mothers smoked during pregnancy. For both groups we found a low influence of foetal genes on inter-individual differences in birth weight of twins, and a low influence of common environmental influences other than gestational age. The genetic influences were smaller than those found in most studies.[12–14,17,18] We may have slightly underestimated the heritability because we could not distinguish between monochorial and dichorial MZ twins. This may be important, because monochorial twins may have suffered from a milder form of the transfusion syndrome, so that they were not detected as such, but were more discordant in birth weight than would have been expected based on their genetic predisposition. Corey *et al*[31] showed that chorionicity and placentation influence intra-pair variation. Therefore, the data presented here may have yielded an underestimated heritability and an overestimated common environmentability.

The common environmental influences found in the present study could be an indication of maternal genetic effects. The genetic predisposition of a mother to give birth to lighter or heavier offspring was found in some studies[11] but not in others.[12,13] In our twin design it cannot be estimated directly, but would show up as common environmental influences on birth weights of both twins. Therefore, our results show that maternal genetic influences on birth weight of their twin offspring may be present. One could argue that a maternal genetic influence could also be shown in a high effect of gestational age. However, animal research has shown that the moment of birth is probably instigated by the foetus, not by the mother.[32]

In conclusion, this study has shown that in Dutch twins foetal genetic influences on birth weight are minor, and of equal magnitude for twins whose mothers smoked during pregnancy and twins whose mothers did not smoke during pregnancy. Maternal smoking during pregnancy did not affect gestational age. However, maternal smoking did influence the association between birth weight and gestational age. Mothers who smoke have lighter children, which may be especially harmful for twins, since they already have lower birth weights than singletons.

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