Brothers and Reduction of the Birth Weight of Later-born Siblings

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It has been speculated whether maternal immune responses against male-specific minor histocompatibility (H-Y) antigens affect pregnancies negatively. This study explores, on a population level, whether previous births of boys compared with girls are associated with a decrease in birth weight of later-born siblings. The population was identified in the Danish Birth Registry and consisted of all Danish women who gave birth to their first-born singleton from 1980 to 1998. The women were followed until 2004, and their subsequent births were recorded. A total of 545,839 second- to fourth-born children were identified. The authors used linear regression to analyze the association between sex of preceding children and birth weight of subsequent siblings. Brothers compared with sisters reduced the birth weight of later-born siblings. One or two brothers, respectively, reduced the mean birth weight of later-born boys by 29 g (p = 0.0001) and 38 g (p = 0.0001) and later-born girls by 17 g (p = 0.0001) and 21 g (p = 0.0001) compared with later-born siblings with no brothers. Part of this association was due to a shorter gestation among later-born siblings with brothers. An explanation for these results could be maternal immune reactions directed against the H-Y antigens initiated during pregnancies with boys. The findings might add to the understanding of both normal and pathologic pregnancies.

birth weight; general linear model; H-Y antigen; minor histocompatibility antigens; siblings

Pregnancies with boys prime maternal immune responses against male-specific minor histocompatibility (H-Y) antigens (1–3), and anti-H-Y immunity in women can be demonstrated up to 22 years after the birth of a boy (2). These immune responses are normally well tolerated by the fetus, as more than half of the population comprises males. A 172-g reduction in the mean birth weight of second-born siblings with an older brother compared with those with an older sister has previously been reported, when the mothers between the two births had had a minimum of three consecutive miscarriages (4). In the same study, a first-born boy compared with a first-born girl was also related to a significantly poorer prognosis of achieving the second desired child. These findings, in patients with recurrent miscarriages, were suggested to be caused by an abnormal immune response against H-Y antigens initiated in the first pregnancy with a boy. We undertook the present population-based study to explore whether previous birth of boys also impacts the birth weight of subsequent siblings in the general population.

MATERIALS AND METHODS

Population

The Danish Birth Registry records all births in Denmark. Every newborn is given a personal and unique identification number. The history of pregnancies and births and any change of partner that may occur can be monitored through the mother’s and father’s identification numbers. From the registry, we identified all women who gave birth to their first-born singleton from January 1, 1980, to December 31, 1998.
Among these women, 393,120 gave birth to a minimum of one more child on or before December 31, 2004. The women gave birth to a total of 552,443 second- to fourth-born children, of whom 6,604 (1.2 percent) were excluded because of missing information on the variables of interest, resulting in an effective sample size of 545,839.

All livebirths were counted as births regardless of gestational week. Pregnancy losses before gestational week 28 were considered miscarriages. Background details on later-born siblings stratified on sex, number of siblings, and number of brothers are shown in table 1. To test whether women who previously have given birth to boys have different lifestyle habits than women who previously have given birth to girls, linkage to the Danish National Cohort provided information on alcohol intake, smoking habits, and body mass index during pregnancy for 25,484 (6.5 percent) of the women included in the present study (5).

Permission to perform this register-based study was given by the National Data Protection Agency according to Danish legislation.

### Statistical analysis

The association between sex of previous siblings and birth weight of later-born siblings was analyzed by linear regression. Birth weight as a continuous variable was used as the dependent variable, while the pattern of sex of older siblings was used as the independent variable. Adjustments were performed in two steps, of which the first adjusted for interpregnancy interval, calendar year, and maternal age by use of piecewise linear splines with predefined knots (6) and for parity, which was entered as a categorical variable. The second step adjusted additionally for gestational age modeled as a fourth-degree polynomial (7). Analyses were stratified on paternity and the sex of later-born siblings, because these variables interacted significantly in the prediction of birth weight. The assumption of equality of variance was confirmed by Levene’s test for homogeneity of variances as described in the book by Olkin et al. (8).

### RESULTS

Brothers significantly reduced the mean birth weights of both later-born boys and girls. The differences in mean birth weight of later-born siblings with one, two, or three brothers compared with no brothers and the associated p values are shown in table 2. Later-born boys with one or two brothers weighed an unadjusted 29 g (p = 0.0001) and 38 g (p = 0.0001) less and later-born girls weighed 17 g (p = 0.0001) and 21 g (p = 0.0001) less compared with later-born siblings with only sisters in sibships with the same father. Adjustments for interpregnancy interval, maternal age, calendar

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<th>No. of older brothers</th>
<th>Total no.</th>
<th>Mean birth weight (g)</th>
<th>Mean gestational age (weeks)</th>
<th>Mean time to pregnancy (years)</th>
<th>Mean age of mother (years)</th>
<th>Mean age of father (years)</th>
<th>New father (%)†</th>
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* Second- to fourth-born children born until 2004 are included.
† Compared with preceding sibling.
year, and parity did not change the discrepancy in birth weight. Adjustments for gestational age, however, attenuated the association of brothers on the mean birth weight of later-born siblings, indicating that part of the lower mean birth weight of later-born siblings with brothers is due to a shorter gestation compared with later-born siblings with only sisters (table 2).

We found no significant differences in the mean birth weight of later-born girls with two or three brothers compared with girls with only sisters when parity in that pregnancy was changed compared with the previous pregnancy. In later-born boys, change of parity seemed to have a different effect, depending on the number of older brothers (table 2). A new father compared with the same father almost reduced the discrepancy in birth weight with close to 50 percent for later-born boys with one brother, while this was not seen for boys with two or three brothers.

A stillbirth preceded a total of 1,255 second-born siblings, in sibships with the same father. The mean birth weight of second-born boys preceded by a stillborn brother was 77 g less than the mean birth weight of a boy preceded by a stillborn sister ($p = 0.18$). Second-born girls preceded by a stillborn brother compared with a stillborn sister weighed 15 g ($p = 0.79$) less.

Smoking habits, alcohol intake, and body mass index did not differ significantly between women who previously had given birth to boys compared with girls (data not shown).

### DISCUSSION

We found that brothers compared with sisters reduce the mean birth weight of later-born siblings of both sexes. Adjustments for gestational age showed that part of the difference in mean birth weight is accounted for by a shorter gestation among later-born siblings with brothers compared with those with only sisters. Adjustments for other important determinants of birth weight (9, 10), such as maternal age, interpregnancy interval, parity, and calendar year, did not change the discrepancies in mean birth weight between later-born siblings with brothers compared with those with only sisters. Maternal smoking habits, body mass index, and alcohol intake during pregnancy are known to be strong determinants of birth weight (11). Although these determinants are not intuitively associated with the sex of previous siblings, smoking has been proposed to decrease the male/female sex ratio (12), but this was not confirmed in the Swedish Birth Registry (13). The Danish Birth Registry provided no or insufficient information on these determinants, but detailed information was obtained for a subpopulation in the present study, and these lifestyle habits did not differ for women with first-born boys compared with those with first-born girls.

One other population-based study has previously reported the finding of a lower birth weight of later-born siblings with brothers (14). This was an unexpected finding in a study with a different aim. Results from three other studies (15–17) with considerably smaller numbers of children (0.05 percent of the children included in this study) have been published on this topic. Two of these studies (15, 16) found an effect of brothers only on later-born boys but not on later-born girls. The methodology used in the above-mentioned studies differed from ours in several ways. In contrast to our study, stillbirths, children with birth weight of less than 2,500 g, and children with gestational age of less than 37 weeks were excluded. No information concerning change of father was given in two of the studies (15, 17), one study included only sibships with the same father (16),...
and the population-based study pooled all sibships irrespective of change of paternity (14). In our study, we addressed paternity and found that the influence of brothers on the birth weight of later-born siblings was affected by change of father. Our study also addressed the influence of known strong birth weight determinants, such as parity, interpregnancy interval, maternal age, calendar year, gestational age and, for a subgroup, also maternal body mass index, smoking habits, and alcohol intake. Finally, this study explored the difference in birth weight of later-born siblings in relation to number of brothers.

As this is a registry study, no firm conclusions with respect to causality can be made. However, the reported reduction in mean birth weight in later-born siblings with brothers is consistent throughout birth orders over a 25-year period. Except for an association with gestational age, the estimates are almost unaffected by adjustments for known strong determinants of birth weight, indicating a fundamental biologic mechanism. If the sex of preceding siblings influences the birth weight of subsequent children, such a mechanism is suggested to possess memory. Involvement of the immune system, which possesses memory, is in our view the most plausible physiologic explanation for our findings. Pregnancies with boys are known to prime maternal immune responses against male-specific minor histocompatibility H-Y antigens, and anti-H-Y immunity in women can be demonstrated up to 22 years after the birth of a boy (1–3). An explanation for the findings in this study could be maternal immune responses against H-Y antigens. Such immune responses lead to inflammatory processes, which theoretically can reduce the invasion of the placenta in the uterus, leading to insufficient placental function causing a decrease in birth weight (18). An inflammatory process may also promote liberation of inflammatory cytokines, causing increased prostaglandin production in the uterus that may lead to a shorter gestation (19, 20).

Change of paternity affected the differences in birth weight, which further supports the H-Y immune hypothesis. With change of paternity, the maternal immune system is exposed to different fetal H-Y antigens, since the ability of fetal cells to present H-Y antigens depends on the fetal repertoire of HLA alleles (what is known as “the HLA system”) is the officially recognized nomenclature for antigens and alleles determined by the World Health Organization and is available at http://www.anthonyolan.com/HIG/lists/nomenc.html. Paternal HLA-linked genes have previously been shown to reduce birth weight in children whose father shared these genes with a sister suffering recurrent miscarriage (21).

If H-Y immunity is responsible for the findings in the present study, we consider some women more likely to be immunized, such as women who carry HLA alleles with H-Y antigen-presenting abilities. Two observations support the notion that some women might be immunized more heavily: 1) The difference in mean birth weight of second-born boys preceded by a stillborn brother compared with a stillborn sister tended to be larger than the difference in mean birth weight in the large cohort of second-born boys with brothers compared with only sisters, and 2) a 172-g reduction in mean birth weight of siblings born following a minimum of three consecutive miscarriages has previously been reported when the child prior to the miscarriages was a boy compared with a girl (4).

In the present study, we did not have any information on preeclampsia, placental abruptions, or intervening miscarriages, which could confound the results, especially since these complications are shown to be more common in pregnancies with boys (4, 22, 23). On the other hand, some of these obstetric complications could also be caused by an exaggerated anti-H-Y immunity, so we may be dealing with a shared mechanism instead of confounding. This is supported by the observation that recurrent placental abruption is associated with first-born boys and maternal HLA alleles capable of presenting H-Y antigens to immune-competent cells (24).

The mean birth weight of later-born girls with brothers compared with later-born girls with sisters was also reduced, although to a smaller extent than for later-born boys with brothers. This attenuated effect is likely to be ascribed to the immunologic mechanism of determinant spreading, which is a recognized and common feature in a series of autoimmune diseases (e.g., insulin-dependent diabetes mellitus) (25, 26). The initial reaction specific against H-Y antigens, which we suggest is induced by the first pregnancy with a boy, may lose specificity with time and become directed toward non-sex-specific proteins on the fetus or trophoblast that have achieved immunogeneity through the inflammatory processes initiated by the anti-H-Y reaction.

The consistent finding of a reduced birth weight in later-born siblings with brothers compared with sisters could be explained by anti-H-Y immunity. These epidemiologic results have no direct public health implications but may add to our understanding of both normal and pathologic pregnancies.

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