Original Contribution

Cryptorchidism and Hypospadias in a Cohort of 934,538 Danish Boys: The Role of Birth Weight, Gestational Age, Body Dimensions, and Fetal Growth

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Early delivery and low birth weight are strong predictors of the urogenital anomalies cryptorchidism (undescended testis) and hypospadias. Understanding these associations may lead to important etiologic clues. Therefore, the authors revisited the prevailing hypotheses regarding fetal growth restriction as a risk factor for urogenital anomalies. They studied a population of 934,538 Danish boys born alive between January 1, 1980, and December 31, 2008. Cryptorchidism and hypospadias were associated with low weight-for-gestational-age, an indicator of fetal growth restriction, and furthermore the authors observed strong interaction with early delivery. Low birth weight in a singleton compared with the mean birth weight of all singleton brothers in the family or in a twin compared with the male co-twin was associated with higher risk of urogenital anomalies, suggesting an effect of relative fetal growth restriction within families. Contrary to previous reports, newborns’ body dimensions assessed independently of birth weight were not associated with urogenital anomalies. The hypothesis that shared factors cause both fetal growth restriction and urogenital anomalies was supported by comparison of urogenital anomaly risks in singletons and twins and by patterns of cryptorchidism and hypospadias co-occurrence in individuals. These novel insights might also extend to other male reproductive conditions with prenatal etiology.

anthropometry; birth weight; cryptorchidism; fetal growth retardation; gestational age; hypospadias; siblings; twins

Abbreviations: CI, confidence interval; ICD, International Classification of Diseases; SGA, small for gestational age.

Early delivery and low birth weight are well-known and strong predictors of the urogenital anomalies cryptorchidism (undescended testis) and hypospadias (1–8). Boys born small for gestational age (SGA) face especially high risks (2–5, 9), which has directed attention to impaired fetal growth as a risk factor (9, 10). Risk estimates have been quite similar for cryptorchidism and hypospadias (2, 3). This fact has puzzled researchers because, until recently, these two anomalies were thought to have different etiologic time windows (2, 9, 11). Emerging evidence from rat models suggests a programming window for reproductive tract masculinization that relates to gestational weeks 8–14 in humans (12). Normal androgen action seems crucial during this time (13), and disruption leads to both cryptorchidism and hypospadias in rats (12). It thus seems that this puzzle may have been resolved, but several other questions regarding fetal growth restriction and urogenital anomalies have as yet defied solution: Is the association with low birth weight due to fetal growth restriction or due to a small constitution? In addition, do the associations indicate a continuous biologic link between low birth weight and each urogenital anomaly? Further, are other aspects of a newborn’s body size or proportion associated with urogenital anomalies when assessed independently of birth weight? Finally, do causal factors shared by fetal growth restriction and urogenital anomalies create the associations? Failure to properly address such questions may have led to misconceptions about the etiology of urogenital anomalies. Advancements in our understanding may also extend to other male reproductive conditions with prenatal etiology, including testicular cancer and poor semen quality (11). Therefore, we revisited the prevailing hypotheses regarding fetal growth restriction as a risk factor for cryptorchidism and hypospadias.
Newborns weighing below the 10th percentile for their gestational age are commonly defined as SGA and are regarded as “growth-restricted” (14). The growth potential of each fetus is unknown, however, which limits the usefulness of SGA as a measure of poor fetal growth. Not all small newborns are in fact growth-restricted, and many larger newborns could be growth-restricted from a heavier target weight (14). Whether growth restriction might predict urogenital anomalies independently of absolute birth weight is not known. Therefore, we studied the associations between the relative birth weight of male singletons compared with the mean of all singleton brothers in the family and the relative birth weight of twins compared with their male co-twins and urogenital anomalies. In addition, associations with SGA are usually reported collectively for all gestational ages, although the consequences may vary by gestational age. Two studies have found associations between male urogenital anomalies and low birth weight (or SGA) according to gestational age (1, 2). We explored whether associations between growth restriction, early delivery, and urogenital anomalies might be of a dose-response type, indicating a biologic continuum.

Growth restriction coinciding with the suggested programming window for masculinization is of particular interest. Symmetric reduction in newborns’ body proportions has been suggested as a way to identify early growth restriction (starting in the first trimester) (15, 16). Other authors have questioned this (17–19). Body proportions are also inherently related to body weight. To clarify the predictive value of newborns’ body proportions, we studied their association with the risk of the urogenital anomalies when assessed independently of birth weight.

Shared causes of fetal growth restriction and urogenital anomalies have been hypothesized (3, 9). Explaining the associations by the alternative hypotheses, that fetal growth restriction causes urogenital anomalies or vice versa, might also seem even less attractive. We compared urogenital anomaly risks in twins and singletons, as well as the co-occurrence of cryptorchidism and hypospadias in singletons, to further investigate this suggested shared causal pathway.

MATERIALS AND METHODS

Study population

We studied the entire population of 934,538 Danish boys born alive between January 1, 1980, and December 31, 2008. Each boy was identified in the Danish Civil Registration System by a unique personal identifier given at birth (20). The Civil Registration System automatically stores dates of emigration and death for all citizens. The personal identifier further facilitated linkage to the Danish Medical Birth Registry and the Danish National Registry of Patients (21). The Danish Medical Birth Registry provided information on pregnancy and delivery. Data on birth weight, crown-heel length at birth, gestational age at birth, and maternal age at birth were available for the entire study period (1980–2008). Data on head circumference and abdominal circumference were available only from 1997 onwards. The completeness of the obstetric and anthropometric data was approximately 95% during the study period. Midwives recorded the data just after delivery and reported them to the register. Gestational age was estimated from the first day of the last menstrual period or from ultrasound. By 1990, ultrasound dating was performed in approximately 80% of pregnancies, and it was used in case of a discrepancy of more than 2 weeks between the two measures (22).

Information on cryptorchidism, hypospadias, other congenital malformations, and surgical procedures was obtained from the Danish National Patient Registry. This registry contains information on all inpatient diagnoses and surgeries performed during the follow-up period, and it covered all hospitals in Denmark. Boys with a diagnosis of cryptorchidism (International Classification of Diseases, Eighth Revision (ICD-8), codes 75210, 75211, and 75219; International Classification of Diseases, Tenth Revision (ICD-10), codes DQ53, DQ531, DQ531A, DQ532, DQ532A, and DQ539) who also underwent corrective orchiopexy (codes 55600, 55640, KKFH00, KKFH01, and KKFH10 in the Nordic Classification of Surgical Procedures) were considered cryptorchidism cases. Orchiopexy indicates that the cryptorchidism persisted until the time of surgery (mean age, 6.3 years; interquartile range, 3.7–9.3). Boys with a diagnosis of hypospadias were considered cases (ICD-8 codes 75220, 75221, 75222, 75228, and 75229; ICD-10 codes DQ540, DQ541, DQ542, DQ548, and DQ549). Boys with other congenital malformations (ICD-8 codes 74000–75999; ICD-10 codes Q00–Q99) diagnosed during follow-up were excluded.

Statistical analyses

Cryptorchidism and hypospadias are considered congenital anomalies, but some cases are diagnosed throughout childhood (23, 24). In most analyses, we estimated crude and adjusted hazard ratios and 95% confidence intervals by means of Cox regression models, using boy’s age as the time variable. The boys entered the risk set at birth and were followed until their age at first diagnosis, death, emigration from Denmark, or the end of follow-up (October 21, 2009), whichever came first. We adjusted for calendar year of birth (7 categories) and maternal age at birth (6 categories) in all unpaired analyses.

Anthropometric characteristics at birth (crown-heel length (cm), head circumference (cm), and abdominal circumference (cm)) were recorded in whole numbers. We added a random decimal digit to enable categorization into quintiles. (For example, a recorded head circumference of 34 cm was assigned a random value from 33.5 cm to 34.4 cm.) All anthropometric measures were strongly correlated with gestational age (see Web Figure 1 (http://aje.oxfordjournals.org/)), and therefore we present quintiles of weight, length, head circumference, and abdominal circumference for gestational age. Outlying pairs of gestational age and birth weight were excluded on the basis of Alexander’s criteria (25). Hazard ratios for cryptorchidism and hypospadias were estimated according to quintiles of each anthropometric-for-gestational-age measure, as well as by birth weight group, gestational age group, and weight-for-gestational-age group. We considered possible interaction between weight-for-gestational-age and gestational age at birth in the risk of urogenital anomalies.

We identified term-born (≥37 weeks) singleton brothers to estimate the effects of fetal growth restriction among siblings. The mean birth weight of all singleton brothers served as a measure of each family’s constitutional growth potential.
The ratio of each brother’s birth weight to this family mean was calculated, and ratios were categorized into groups of <85%, 85%–94.9%, 95%–104.9%, 105%–114.9%, and ≥115%. Families with at least 1 affected boy (cryptorchidism or hypospadias) and 1 unaffected boy were informative in a conditional logistic regression analysis using the mother as an identifier. Unaffected boys with a longer follow-up period than their affected sibling’s age at first diagnosis served as controls in this analysis. We estimated odds ratios for urogenital anomalies according to the ratio categories using 95%–104.9% as the reference group and adjusting for gestational week of birth, mother’s parity, and calendar year of birth. For male twin pairs, we estimated differences in birth weight by discordance of urogenital anomalies using the paired t test.

Body dimensions (length, circumference) are inherently associated with body weight, and estimated effects of body dimensions can easily be confounded by birth weight. We generated categories of each body dimension independent of birth weight, as follows. Within each gestational week (weeks 22–45), we modeled the body dimension as the response variable with birth weight and squared birth weight as explanatory variables in a generalized linear least-squares regression (Figure 1). This was done with body dimension measures and birth weight on a log scale (natural logarithm) to reduce curvature for a better fit. Body dimensions more than 5 standard deviations from the mean were excluded from all analyses. Predicted cutoff values for the 20th, 40th, 60th, and 80th percentiles of the body dimension were estimated at each birth weight, assuming a normally distributed variance around the mean. As intended, the mean birth length, head circumference, and abdominal circumference varied by body weight, and estimated effects of body dimensions can easily be confounded by birth weight. We generated categories of each body dimension independent of birth weight, as follows. Within each gestational week (weeks 22–45), we modeled the body dimension as the response variable with birth weight and squared birth weight as explanatory variables in a generalized linear least-squares regression (Figure 1). This was done with body dimension measures and birth weight on a log scale (natural logarithm) to reduce curvature for a better fit. Body dimensions more than 5 standard deviations from the mean were excluded from all analyses. Predicted cutoff values for the 20th, 40th, 60th, and 80th percentiles of the body dimension were estimated at each birth weight, assuming a normally distributed variance around the mean. As intended, the mean birth length, head circumference, and abdominal circumference varied by body weight, and estimated effects of body dimensions can easily be confounded by birth weight. We estimated the risk of urogenital anomalies in twins compared with singletons and then stratified by gestational age at birth (or birth weight), allowing interaction with twin or singleton status. We compared the observed co-occurrence of urogenital anomalies in individuals with the expected co-occurrence from the marginal distributions of cryptorchidism and hypospadias. In logistic regression analyses, we estimated the overall and stratified co-occurrence ratios (odds ratios) for each possible 2 × 2 table in 4 groups of weight-for-gestational age and by term and preterm birth. Co-occurrence ratios above 1 indicate higher co-occurrence than could be explained from the marginal distributions of cryptorchidism and hypospadias within each group.

We performed secondary analyses 1) restricting our sample to the years 1997–2008, to ensure that associations with birth weight and gestational age were comparable to those presented for the entire study period and 2) excluding 1,067 (9%) cryptorchidism cases with a diagnosis of inguinal hernia, because this condition is associated with early delivery, low birth weight, and cryptorchidism (26).

The Danish National Board of Health and the Danish Data Inspectorate approved the study protocol. Statistical analyses were performed using Stata 11 software (StataCorp LP, College Station, Texas).

RESULTS

Between 1980 and 2008, 934,538 boys were born alive in Denmark. For analyses of singletons, we excluded 27,507 boys with missing or invalid birth weight or gestational age data (2.9%), 61,250 boys with other congenital malformations (6.6%), 25,885 twins (2.8%), and 785 higher multiples, leaving 819,111 boys (87.6%). Of these, 459,657 were born between 1980 and 1996, when only data on gestational age, birth weight, and birth length were available. The remaining 359,454 singleton boys were born between 1997 and 2008, when the register also included data on head circumference and abdominal circumference. Of the latter, 350,258 (97%) had a valid measure of head circumference and 340,980 (95%) had a valid measure of abdominal circumference. During follow-up, 11,586 cryptorchidism cases (14.1/1000) and 3,268 hypospadias cases (4.0/1000) were identified among singletons.

Earlier birth and lower birth weight were both strongly associated with urogenital anomalies (Table 1). Hypospadias showed a steady risk increase with decreasing birth weight, whereas cryptorchidism risk increased only at birth weights below 3,000 g. Boys in the smallest weight-for-gestational-age quintile had the highest risks of cryptorchidism (hazard ratio = 1.4, 95% confidence interval (CI): 1.3, 1.5) and hypospadias (hazard ratio = 1.9, 95% CI: 1.7, 2.1) compared with the largest quintile. These associations were strongly modified by gestational age at birth (Figure 2). Boys in the 2 heaviest weight-for-gestational-age quintiles (60%–100%) experienced limited (if any) increased risk of urogenital anomalies with early delivery. In contrast, boys in the lowest weight-for-gestational-age quintile (0%–<20%) experienced the highest risks with early delivery, reaching a hazard ratio of 7.8 (95% CI: 6.0, 10) for cryptorchidism.
Table 1. Risks of Cryptorchidism and Hypospadias According to Gestational Age, Birth Weight, and Anthropometric Characteristics at Birth Among 819,111 Danish Singleton Boys, 1980–2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total No.</th>
<th>Cryptorchidism</th>
<th>Hypospadias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of Cases</td>
<td>HR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Gestational age, weeks&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;28</td>
<td>1,412</td>
<td>31</td>
<td>3.7</td>
</tr>
<tr>
<td>28–31.9</td>
<td>3,936</td>
<td>136</td>
<td>3.0</td>
</tr>
<tr>
<td>32–34.9</td>
<td>10,060</td>
<td>248</td>
<td>1.9</td>
</tr>
<tr>
<td>35–36.9</td>
<td>24,025</td>
<td>478</td>
<td>1.5</td>
</tr>
<tr>
<td>37–38.9</td>
<td>125,892</td>
<td>1,845</td>
<td>1.2</td>
</tr>
<tr>
<td>39–39.9</td>
<td>168,711</td>
<td>2,163</td>
<td>1.0</td>
</tr>
<tr>
<td>40–41.9</td>
<td>414,435</td>
<td>5,695</td>
<td>1.0</td>
</tr>
<tr>
<td>≥42</td>
<td>70,640</td>
<td>990</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Birth weight, g&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1,500</td>
<td>4,538</td>
<td>221</td>
<td>5.5</td>
</tr>
<tr>
<td>1,500–1,999</td>
<td>5,997</td>
<td>179</td>
<td>2.4</td>
</tr>
<tr>
<td>2,000–2,499</td>
<td>17,999</td>
<td>478</td>
<td>2.1</td>
</tr>
<tr>
<td>2,500–2,999</td>
<td>78,426</td>
<td>1,383</td>
<td>1.4</td>
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<tr>
<td>3,000–3,499</td>
<td>244,253</td>
<td>3,471</td>
<td>1.1</td>
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<td>3,500–3,999</td>
<td>156,430</td>
<td>2,891</td>
<td>1.4</td>
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<td>4,000–4,499</td>
<td>162,335</td>
<td>2,305</td>
<td>1.1</td>
</tr>
<tr>
<td>4,500–4,999</td>
<td>170,435</td>
<td>2,293</td>
<td>1.0</td>
</tr>
<tr>
<td>≥5,000</td>
<td>158,593</td>
<td>1,948</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Percentile of weight for gestational age&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;20</td>
<td>68,337</td>
<td>734</td>
<td>1.1</td>
</tr>
<tr>
<td>20–39.9</td>
<td>69,512</td>
<td>667</td>
<td>1.0</td>
</tr>
<tr>
<td>40–59.9</td>
<td>68,466</td>
<td>677</td>
<td>1.0</td>
</tr>
<tr>
<td>60–79.9</td>
<td>71,173</td>
<td>622</td>
<td>0.9</td>
</tr>
<tr>
<td>≥80</td>
<td>72,770</td>
<td>750</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Percentile of birth length for gestational age&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;20</td>
<td>70,474</td>
<td>768</td>
<td>1.1</td>
</tr>
<tr>
<td>20–39.9</td>
<td>67,294</td>
<td>628</td>
<td>1.0</td>
</tr>
<tr>
<td>40–59.9</td>
<td>68,422</td>
<td>654</td>
<td>1.0</td>
</tr>
<tr>
<td>60–79.9</td>
<td>66,438</td>
<td>590</td>
<td>0.9</td>
</tr>
<tr>
<td>≥80</td>
<td>68,352</td>
<td>672</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

<sup>a</sup> Adjusted for maternal age at birth and calendar year of birth.

<sup>b</sup> 1980–2008 (n = 819,111 for gestational age and birth weight; n = 809,876 for birth length).

<sup>c</sup> 1997–2008 (n = 350,258 for head circumference; n = 340,980 for abdominal circumference).
and 10.4 (95% CI: 6.9, 16) for hypospadias at a gestational age below 32 weeks.

Inferred growth restriction was studied using the relative birth weights of singleton brothers in 3,939 families with at least 1 cryptorchidism case and in 1,221 families with at least 1 hypospadias case (Table 2). Lower relative birth weight showed a dose-response-type association with higher risk of hypospadias. For cryptorchidism, no such pattern was seen, but brothers with birth weights below 85% of the family mean had an increased odds ratio of 1.6 (95% CI: 1.1, 2.4).

Among 9,801 male twin pairs, we identified 238 pairs discordant for cryptorchidism and 99 pairs discordant for hypospadias. Compared with the unaffected twin, the twin with cryptorchidism was on average 136 g lighter (95% CI: 70, 202) and the twin with hypospadias was 164 g lighter (95% CI: 45, 283).

Hypospadias was associated with short crown-heel length, head circumference, and abdominal circumference for gestational age, while these associations were weaker or absent with cryptorchidism (Table 1). However, we observed no association between length, head circumference, or abdominal circumference independent of birth weight and the urogenital anomalies when using the constructed quintiles (Web Table 1). Stratification by prematurity did not modify the associations.

We compared the risk of urogenital anomalies in twins with that in singletons. Twinning was associated with a hazard ratio for cryptorchidism of 1.2 (95% CI: 1.1, 1.3), but this was reduced to 0.9 (95% CI: 0.8, 1.0) when adjusted for gestational age and to 0.8 (95% CI: 0.7, 0.8) when adjusted for birth weight. Likewise, twinning was associated with a hazard ratio for hypospadias of 1.4 (95% CI: 1.1, 1.6), which was reduced to 1.0 (95% CI: 0.8, 1.2) when adjusted for gestational age and to 0.8 (95% CI: 0.6, 0.9) when adjusted for birth weight. Differences between singletons and twins were most clear for birth weight when allowing interaction between singleton versus twin status and gestational age or birth weight (Figure 3).

The co-occurrence of cryptorchidism and hypospadias was higher in boys with a high risk of fetal growth restriction (low weight for gestational age). Taken together, these data strongly suggest that fetal growth restriction is associated with urogenital anomalies and, further, that this association is due to shared causes.

A few studies have explored the possible interaction between gestational age and birth weight or SGA in the risk of urogenital anomalies (1, 2). We extended this to show continuous effects of weight for gestational age modified by gestational age at birth (Figure 2). Short gestation had little if any effect on the risk of urogenital anomalies among normal-to-heavy boys.

Few studies have found higher risk of hypospadias in the smaller of twin or singleton brother pairs (27, 28). We observed

**DISCUSSION**

We revisited the roles of birth weight, gestational age, body dimensions, and fetal growth in the risks of cryptorchidism and hypospadias using a large population-based cohort. We observed an association between low birth weight for gestational age and urogenital anomalies that was strengthened by early delivery. Estimated fetal growth restriction, identified by low birth weight in a singleton compared with the mean of all singleton brothers in the family and in a twin compared with the male co-twin, was associated with a higher risk of urogenital anomalies. Body proportions, when assessed independently of birth weight, had no impact on risk of the anomalies. Twins had higher crude urogenital anomaly risk than singletons, but twinning became “protective” after adjustment for birth weight or gestational age. The co-occurrence of cryptorchidism and hypospadias was higher in boys with a high risk of fetal growth restriction (low weight for gestational age). Taken together, these data strongly suggest that fetal growth restriction is associated with urogenital anomalies and, further, that this association is due to shared causes.

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lower birth weight in the urogenital anomaly-affected twin than in the unaffected twin among discordant pairs. We had no information on zygosity, chorionicity, or twin-twin transfusion syndrome with which to explain the weight differences. We corroborated the reported association of lower birth weight in hypospadias-affected singleton brothers (27) and extended it to cryptorchidism (Table 2). However, unlike the case with hypospadias, brothers heavier than the family mean (the mean of all

<table>
<thead>
<tr>
<th>Birth Weight Ratio, %</th>
<th>No. of Cases</th>
<th>Total No.</th>
<th>ORb</th>
<th>95% CI</th>
<th>No. of Cases</th>
<th>Total No.</th>
<th>ORb</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;85</td>
<td>137</td>
<td>249</td>
<td>1.6</td>
<td>1.1, 2.4</td>
<td>47</td>
<td>87</td>
<td>1.2</td>
<td>0.6, 2.4</td>
</tr>
<tr>
<td>85–94.9</td>
<td>925</td>
<td>1,932</td>
<td>1.1</td>
<td>0.9, 1.3</td>
<td>299</td>
<td>578</td>
<td>1.2</td>
<td>0.9, 1.7</td>
</tr>
<tr>
<td>95–104.9</td>
<td>1,972</td>
<td>4,323</td>
<td>1.0</td>
<td>Reference</td>
<td>641</td>
<td>1,398</td>
<td>1.0</td>
<td>Reference</td>
</tr>
<tr>
<td>105–114.9</td>
<td>853</td>
<td>1,949</td>
<td>1.1</td>
<td>0.9, 1.3</td>
<td>224</td>
<td>577</td>
<td>0.9</td>
<td>0.6, 1.2</td>
</tr>
<tr>
<td>≥115</td>
<td>90</td>
<td>254</td>
<td>1.1</td>
<td>0.7, 1.7</td>
<td>26</td>
<td>86</td>
<td>0.6</td>
<td>0.3, 1.3</td>
</tr>
</tbody>
</table>

*P*-trend<sup>c</sup> 0.11 <0.001

Abbreviations: CI, confidence interval; OR, odds ratio.
* Ratio (%) of a singleton boy’s birth weight to the mean birth weight of all singleton brothers in his family. A ratio below 100 represents a birth weight that was lighter than the mean.
* Estimated by conditional logistic regression (mother was the identifier) and adjusted for gestational age at birth, mother’s parity, and calendar year of birth.
* *P* value estimate from regression trend test of the birth weight ratio modeled as a continuous variable.

**Table 2.** Odds Ratios for Cryptorchidism in 3,939 Families and Odds Ratios for Hypospadias in 1,221 Families According to Family Birth Weight Ratio<sup>a</sup> Among Singleton Brothers Born at Term (≥37 Weeks), Denmark, 1980–2008

**Figure 3.** Hazard ratios (HR) for cryptorchidism (top) and hypospadias (bottom) in singletons (solid line) and twins (dashed line) according to gestational age (left) and birth weight (right), Denmark, 1980–2008. The reference group was the highest category of singletons in each graph. Vertical lines represent 95% confidence intervals. *P* values tested the null-hypothesis of no overall difference between singletons and twins.
singleton brothers’ birth weights) had no reduced risk of cryptorchidism. This discrepancy may be due to the different risk patterns of the anomalies at high birth weights. Hypospadias showed a steady risk decrease with increasing birth weight, whereas cryptorchidism risk remained constant above 3,000 g (Table 1). Using family controls removes the between-family variation in fetal growth and birth weight, including a component of constitutional birth weight (29). The remaining within-family variation in birth weight might thus be a better measure of true fetal growth restriction (i.e., not attaining a target birth weight). Our analyses of twin and singleton brothers clearly showed that attaining a lower birth weight than one’s brother, indicating relative growth restriction, is associated with higher risk of urogenital anomalies.

Associations between anthropometric factors at birth (such as crown-heel length, head circumference, and abdominal circumference) and hypospadias have been reported (15, 24, 30–32). Symmetric reduction in all body dimensions has shown particularly strong associations (15). Some authors have suggested that symmetric growth restriction begins in the first trimester and hence spans a relevant time window for urogenital anomalies (15, 16). This use of symmetry to indicate early growth restriction has been questioned (17–19). We studied whether body proportions had explanatory value when assessed independently of birth weight. That is, do a long and skinny boy and a short and fat boy with identical birth weights face the same risks of urogenital anomaly? Our data showed no association between body proportions (independent of birth weight) and urogenital anomalies. It thus seems that, when studying urogenital anomalies, newborns’ body dimensions are merely proxy measures of the birth weight and hence might not contribute further to our understanding of the etiology of these anomalies.

Shared causes of fetal growth restriction and urogenital anomalies have been hypothesized (3, 9), and we provide evidence supporting this. Twins are generally born earlier and with lower birth weight than singletons (33, 34), often because of uterine crowding by 2 healthy fetuses (35). Twins in our study had higher urogenital anomaly risk than singletons, but when results were adjusted for birth weight (or gestational age), twinning became “protective.” Twins had a lower urogenital anomaly risk than singletons at most low birth weights (Figure 3), indicating that the causes of singleton growth restriction may also be stronger risk factors for urogenital anomalies than twinning. Other data have supported this (3, 8, 36), and within the conceptual framework of causal graphs, this indicates collider bias or intermediate-outcome confounding (37). This suggests that shared (and perhaps unknown) factors may cause both low birth weight (by fetal growth restriction) and urogenital anomalies. This might also be the case with early delivery and urogenital anomalies. A similar argument has been made to suggest shared causes of preterm birth and cerebral palsy (38). The existence of shared factors is further supported by a higher co-occurrence of urogenital anomalies among preterm boys and boys with low weight for gestational age (Table 3). Differential reporting of co-occurrence by prematurity or low birth weight seems unlikely.

Placental dysfunction and androgen deficiency in early pregnancy may be candidate shared factors due to their association with fetal growth and androgens’ importance for masculinization (13, 32, 39–41). Any such shared factors might also be shared by other male reproductive conditions associated with low birth weight, including testicular cancer and poor semen quality (42–46). Data on low birth weight and semen quality are as yet inconclusive (42–45), but testicular cancer has shown an association with low birth weight (46). As with cryptorchidism and hypospadias, twins had higher testicular cancer risk than singletons when findings were unadjusted for birth weight (46, 47). However, we were unable to identify data evaluating whether twinning becomes “protective” after birth weight adjustment (47, 48), which would indicate shared causes of fetal growth restriction, cryptorchidism, hypospadias, and testicular cancer.

We used administrative health data from Danish registries covering all boys born between 1980 and 2008. As a consequence, there was no selection in establishing the cohort, and loss to follow-up was minimal. Midwives routinely recorded newborns’ anthropometric characteristics and basic maternal characteristics. Any measurement error, including errors in gestational age, weight, length, and circumference measures, would most likely have attenuated associations. The presumably greater error in length and circumference measures than in birth weight might have attenuated associations with disproportionalia. The register-based endpoint of cryptorchidism was verified by orchiopexy to exclude transient cases (spontaneously

<table>
<thead>
<tr>
<th>Percentile of Weight for Gestational Age</th>
<th>No. of Boys With Co-Occurrence</th>
<th>Total No.</th>
<th>Co-occurrence Ratio</th>
<th>All Births</th>
<th>Preterm Births</th>
<th>Term Births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>819,111</td>
<td>1.8 1.5, 2.3</td>
<td>3.2 2.0, 5.1</td>
<td>1.6 1.3, 2.1</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>38</td>
<td>156,430</td>
<td>2.4 1.8, 3.4</td>
<td>2.7 1.5, 4.9</td>
<td>2.0 1.4, 3.0</td>
<td></td>
</tr>
<tr>
<td>20–39.9</td>
<td>16</td>
<td>162,335</td>
<td>1.8 1.1, 2.9</td>
<td>2.9 0.9, 9.5</td>
<td>1.6 0.9, 2.8</td>
<td></td>
</tr>
<tr>
<td>40–59.9</td>
<td>11</td>
<td>170,435</td>
<td>1.2 0.7, 2.2</td>
<td>2.7 0.6, 11.1</td>
<td>1.1 0.6, 2.1</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>19</td>
<td>329,911</td>
<td>1.5 0.9, 2.3</td>
<td>1.1 0.2, 7.9</td>
<td>1.5 0.9, 2.4</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

a Term birth, ≥37 weeks; preterm birth, <37 weeks.

b A ratio above 1 indicates higher co-occurrence than would be expected from the marginal distributions of cryptorchidism and hypospadias within each group.
descending testicles) caused by prematurity. A review of medical records from 43 hypospadias cases from the register confirmed 40 (93%) of the diagnoses (49). Lack of diagnostic specificity would tend to attenuate associations.

We conclude that cryptorchidism and hypospadias are associated with indicators of fetal growth restriction. Estimated relative growth restriction based on comparisons of brothers’ birth weights supported this. Newborns’ body proportions assessed independently of birth weight were not associated with urogenital anomalies. Previous speculations about shared factors’ causing fetal growth restriction, low birth weight, and urogenital anomalies were strongly supported by our data. Identifying shared causal factors might reveal new insights into the biology and etiology of urogenital malformations.

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REFERENCES


