The Missing Siblings of Infants Born Preterm

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BACKGROUND: Parents of very or extremely low birth weight infants have fewer subsequent children after preterm birth. Whether this applies to parents of less preterm infants is unknown.

METHODS: In this nationwide cohort study, we identified all 230 308 traceable (>99%) singletons (9983 preterm, 4.3%) live born in Finland between January 1, 1987, and September 30, 1990, and their parents. Quantitative contribution of gestational age of child to the birth of parental subsequent children was assessed by multivariate Cox regression models, stratifying by the number of previous children. The impact of gestational age on sibling count was estimated at individual and population level.

RESULTS: Mothers of extremely preterm (23–27 completed weeks) infants were, compared with mothers of term infants (39–41 weeks), less likely to have a subsequent live-born child (adjusted hazard ratio [HR]: 0.74; 95% confidence interval: 0.63–0.86). Corresponding HRs and confidence intervals were as follows: 28 to 31 weeks: 0.72 (0.65–0.80), 32 to 33 weeks: 0.82 (0.74–0.90), and 34 to 36 weeks: 0.90 (0.87–0.93). These HRs were consistent with those of fathers and couples. The cohort included 8002 firstborn preterm children, of whom 356 (4.4%) died in infancy. The 8002 children had a total of 13 826 subsequent siblings (1138 less than expected); per 1000 preterm births, this translates to the death of 44 preterm infants and 142 missing subsequent siblings.

CONCLUSIONS: Families with a preterm singleton child have fewer subsequent children. In a high-income country, the main population effect of preterm birth is caused by these “missing siblings,” whose number exceeds the number of those preterm infants who die.

WHAT’S KNOWN ON THIS SUBJECT: Parents of very or extremely low birth weight infants are less likely to have subsequent children after preterm birth. Whether this phenomenon extends over the whole range of prematurity has remained unassessed.

WHAT THIS STUDY ADDS: Having a preterm child, regardless of the degree of prematurity, reduces the final number of maternal, paternal, and parental children. In a high-income country, the preterm birth’s main population effect is caused by these “missing siblings,” rather than by infant mortality.


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Worldwide, ∼1 in 10 births is preterm (<37 full gestational weeks). This proportion tends to increase, yet there is considerable regional and etiological diversity. Preterm infants, regardless of the cause of prematurity, experience unfavorable pre- and postnatal conditions that differ greatly from the normal intrauterine environment and have lifelong consequences for the infant. In addition, preterm birth may have a negative emotional and psychosocial effect on the family, which could affect parental reproductive behavior by reducing their propensity to have more children and result in “missing siblings” within these families.

Factors affecting the timing and the likelihood of first or higher-order births are numerous and have been studied from various viewpoints. The population-wide effects of preterm birth on the parents’ further reproduction are, however, poorly known. The few prospective studies involve only extremely low birth weight (ELBW) (<1000 g) or very low birth weight (VLBW) (<1500 g) infants, and they reveal that parents of these infants are less likely to have subsequent children after preterm birth. We assessed the impact of preterm birth across all gestational ages (GAs) on the number of subsequent children, and we took into account various potential factors that could also affect parental reproductive behavior after preterm birth by linking population-wide data from comprehensive Finnish registries.

### METHODS

#### Data Sources

The data came from 5 national administrative registers: (1) the Finnish Medical Birth Register (MBR), (2) the Central Population Register (CPR), (3) the Education Register, (4) the Register of Congenital Malformations, and (5) the Finnish Care Register for Health Care, formerly the Hospital Discharge Register. These registers, including the validity of the data, are described in Supplemental Information.

The Finnish Ministry of Health and Social Affairs, relevant register authorities, and local ethics committees approved the study.

#### Cohort Members

We first identified from the MBR 235,622 infants (referred to as “index children”) with a valid personal identification number (99.8% of all live-born children) who were born in Finland between January 1, 1987, and September 30, 1990. Dates of births for the index children’s previous and subsequent siblings were available up to April 2012 and were obtained from the CPR, which also provided data on sibships that shared a biological or adoptive mother and/or father with the index child. These data from the CPR, parental educational data from Statistics Finland (updated through December 2012), and data from the Register of Congenital Malformations (January 2015) and Finnish Care Register for Health Care (December 2012) were linked to the population-wide data from the MBR and the CPR.

## FIGURE 1

Design of the study.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Extremely Preterm</th>
<th>Very Preterm</th>
<th>Moderately Preterm</th>
<th>Late Preterm</th>
<th>Early Term</th>
<th>Term</th>
<th>Postterm</th>
<th>Total Cohort</th>
</tr>
</thead>
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<tr>
<td><strong>Index children, n</strong></td>
<td>401</td>
<td>758</td>
<td>944</td>
<td>7058</td>
<td>38290</td>
<td>186991</td>
<td>9173</td>
<td>223615</td>
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<tr>
<td><strong>Length of gestation, wk, mean (SD)</strong></td>
<td>25.8 (1.4)</td>
<td>30.2 (1.1)</td>
<td>33.0 (0.6)</td>
<td>35.9 (0.8)</td>
<td>38.2 (0.5)</td>
<td>40.3 (0.8)</td>
<td>42.2 (0.2)</td>
<td>39.8 (1.7)</td>
</tr>
<tr>
<td><strong>Boy, n (%)</strong></td>
<td>215 (53.6)</td>
<td>443 (58.4)</td>
<td>527 (53.8)</td>
<td>3881 (55.1)</td>
<td>20234 (2.8)</td>
<td>84409 (30.6)</td>
<td>4726 (31.5)</td>
<td>114445 (51.2)</td>
</tr>
<tr>
<td><strong>Birth weight; g, mean (SD)</strong></td>
<td>829 (198)</td>
<td>1416 (332)</td>
<td>2003 (399)</td>
<td>2751 (479)</td>
<td>3349 (470)</td>
<td>3684 (458)</td>
<td>3589 (485)</td>
<td>3584 (542)</td>
</tr>
<tr>
<td><strong>Birth weight SD score, mean (SD)</strong></td>
<td>0.07 (1.4)</td>
<td>−0.30 (1.52)</td>
<td>−0.34 (1.52)</td>
<td>−0.20 (1.31)</td>
<td>0.00 (1.15)</td>
<td>0.03 (1.02)</td>
<td>−0.03 (1.01)</td>
<td>0.01 (1.06)</td>
</tr>
<tr>
<td><strong>SGA, n (%)</strong></td>
<td>32 (8.0)</td>
<td>125 (16.5)</td>
<td>140 (14.8)</td>
<td>615 (8.7)</td>
<td>3232 (1.9)</td>
<td>7862 (4.7)</td>
<td>894 (6.7)</td>
<td>11329 (5.1)</td>
</tr>
<tr>
<td><strong>Severe infant morbidity, n (%)</strong></td>
<td>127 (31.7)</td>
<td>194 (25.6)</td>
<td>163 (17.3)</td>
<td>564 (8.0)</td>
<td>297 (0.2)</td>
<td>472 (0.7)</td>
<td>14 (0.9)</td>
<td>813 (0.4)</td>
</tr>
<tr>
<td><strong>Died before first birthday, n (%)</strong></td>
<td>203 (50.8)</td>
<td>95 (12.5)</td>
<td>36 (3.8)</td>
<td>70 (1.0)</td>
<td>98 (0.3)</td>
<td>297 (0.2)</td>
<td>14 (0.9)</td>
<td>813 (0.4)</td>
</tr>
<tr>
<td><strong>Mothers, n (%)</strong></td>
<td>398</td>
<td>757</td>
<td>941</td>
<td>7044</td>
<td>39270</td>
<td>186878</td>
<td>9170</td>
<td>223458</td>
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<tr>
<td><strong>Age; y, mean (SD)</strong></td>
<td>29.4 (5.6)</td>
<td>29.0 (5.8)</td>
<td>29.3 (6.1)</td>
<td>28.7 (5.7)</td>
<td>28.3 (5.4)</td>
<td>284 (5.1)</td>
<td>27.8 (4.9)</td>
<td>28.5 (5.2)</td>
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<tr>
<td><strong>Upper-secondary Education level, n (%)</strong></td>
<td>179 (45.0)</td>
<td>340 (44.9)</td>
<td>424 (45.1)</td>
<td>3263 (46.3)</td>
<td>17019 (44.9)</td>
<td>75762 (45.4)</td>
<td>4234 (46.2)</td>
<td>101221 (45.3)</td>
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<td><strong>Postsecondary Education level</strong></td>
<td>88 (22.1)</td>
<td>160 (21.1)</td>
<td>171 (18.2)</td>
<td>1347 (19.1)</td>
<td>8088 (21.1)</td>
<td>36638 (22.0)</td>
<td>1832 (21.1)</td>
<td>48424 (21.7)</td>
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<tr>
<td><strong>Lower tertiary Education level</strong></td>
<td>23 (5.8)</td>
<td>65 (8.6)</td>
<td>67 (7.1)</td>
<td>560 (8.0)</td>
<td>3475 (9.1)</td>
<td>15534 (9.3)</td>
<td>818 (8.6)</td>
<td>20540 (9.2)</td>
</tr>
<tr>
<td><strong>Upper-tertiary or more Education level</strong></td>
<td>40 (10.0)</td>
<td>62 (8.2)</td>
<td>80 (8.5)</td>
<td>666 (9.5)</td>
<td>3657 (10.1)</td>
<td>17353 (10.4)</td>
<td>555 (10.4)</td>
<td>25013 (10.3)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>68 (17.1)</td>
<td>130 (17.2)</td>
<td>199 (21.1)</td>
<td>1206 (17.1)</td>
<td>5831 (15.2)</td>
<td>21991 (12.9)</td>
<td>1253 (13.4)</td>
<td>30260 (13.9)</td>
</tr>
<tr>
<td><strong>Unmarried, n (%)</strong></td>
<td>106 (28.0)</td>
<td>232 (31.1)</td>
<td>265 (28.3)</td>
<td>1783 (25.6)</td>
<td>7943 (20.8)</td>
<td>34432 (20.7)</td>
<td>2328 (25.5)</td>
<td>47099 (21.2)</td>
</tr>
<tr>
<td><strong>Smoked during pregnancy, n (%)</strong></td>
<td>85 (23.4)</td>
<td>143 (19.5)</td>
<td>197 (21.5)</td>
<td>1314 (19.0)</td>
<td>6051 (16.1)</td>
<td>24161 (14.8)</td>
<td>1487 (16.5)</td>
<td>33438 (15.3)</td>
</tr>
<tr>
<td><strong>Pregnancy disorder, n (%)</strong></td>
<td>50 (12.9)</td>
<td>218 (28.8)</td>
<td>257 (27.3)</td>
<td>1466 (20.8)</td>
<td>6255 (18.3)</td>
<td>13093 (7.8)</td>
<td>429 (4.7)</td>
<td>21786 (0.7)</td>
</tr>
<tr>
<td><strong>Severe maternal clinical course, n (%)</strong></td>
<td>50 (12.6)</td>
<td>32 (4.2)</td>
<td>22 (2.3)</td>
<td>193 (2.7)</td>
<td>806 (2.1)</td>
<td>3593 (2.2)</td>
<td>232 (2.5)</td>
<td>4928 (2.2)</td>
</tr>
<tr>
<td><strong>1 previous child, n (%)</strong></td>
<td>124 (51.2)</td>
<td>229 (30.3)</td>
<td>261 (27.2)</td>
<td>2048 (29.1)</td>
<td>12351 (33.8)</td>
<td>59288 (59.9)</td>
<td>2588 (29.2)</td>
<td>78107 (55.0)</td>
</tr>
<tr>
<td><strong>2 or more previous children, n (%)</strong></td>
<td>108 (27.1)</td>
<td>236 (25.1)</td>
<td>165 (21.8)</td>
<td>1807 (25.9)</td>
<td>10576 (27.6)</td>
<td>41370 (24.8)</td>
<td>1687 (18.4)</td>
<td>55829 (25.0)</td>
</tr>
<tr>
<td><strong>History of 2 or more miscarriages, n (%)</strong></td>
<td>51 (15.3)</td>
<td>66 (7.5)</td>
<td>63 (7.7)</td>
<td>325 (4.6)</td>
<td>1538 (4.0)</td>
<td>5493 (3.3)</td>
<td>255 (2.8)</td>
<td>7779 (3.5)</td>
</tr>
<tr>
<td><strong>History of stillbirths, n (%)</strong></td>
<td>14 (3.7)</td>
<td>29 (3.9)</td>
<td>29 (3.1)</td>
<td>134 (1.9)</td>
<td>530 (1.4)</td>
<td>1378 (0.8)</td>
<td>37 (0.4)</td>
<td>2151 (1.0)</td>
</tr>
<tr>
<td><strong>History of induced abortions, n (%)</strong></td>
<td>69 (19.3)</td>
<td>134 (19.1)</td>
<td>138 (15.9)</td>
<td>958 (14.2)</td>
<td>4664 (12.7)</td>
<td>18926 (11.8)</td>
<td>1051 (12.0)</td>
<td>25939 (12.1)</td>
</tr>
<tr>
<td><strong>Previous IBI length &lt;60 mo, n (%)</strong></td>
<td>142 (61.7)</td>
<td>257 (65.2)</td>
<td>309 (62.2)</td>
<td>2448 (65.6)</td>
<td>16919 (72.0)</td>
<td>74375 (73.5)</td>
<td>2974 (68.6)</td>
<td>97477 (72.8)</td>
</tr>
<tr>
<td><strong>Subsequent IBI length; mo, mean (SD)</strong></td>
<td>33.0 (27.4)</td>
<td>40.5 (29.2)</td>
<td>46.1 (34.8)</td>
<td>43.7 (32.7)</td>
<td>44.0 (32.2)</td>
<td>44.0 (31.8)</td>
<td>43.2 (32.1)</td>
<td>43.9 (31.9)</td>
</tr>
</tbody>
</table>
then linked to MBR data by encrypted personal identification numbers.

Figure 1 illustrates the design of the cohort. We included only singleton index children \( (n = 230,308) \), of whom 3377 (1.5%) had missing or seemingly incoherent data on GA, or had a GA >43 or <23 full weeks. Current national birth weight standards are available between 23 and 43 weeks’ gestation. We excluded 433 preterm index children whose birth weight for GA SD score was more than +3.0 SD (0.2% of total sample, 4.1% of all preterm infants); we also excluded 38 (0.02%) index children whose birth weight SD score was <−6.0 or missing because they were likely to represent reporting errors or exceptional medical conditions. Finally, we excluded 2845 (1.3%) index children (of whom 361, 12.7%, were preterm) with any major congenital anomaly. The total number of index children excluded was 6693 (2.9% of all singletons). Of those 3316 who were excluded with appropriate data on GA, 796 (24.0%) were reported to be preterm.

**Statistical Analyses**

**Exposure**

The exposure was the best clinical estimate of the length of gestation at birth, which at that time was based on ultrasound or last menstrual period. GA was categorized into 7 subgroups: extremely preterm: 23 to 27 full weeks, very preterm: 28 to 31 weeks, moderately preterm: 32 to 33 weeks, late preterm: 34 to 36 weeks, early term: 37 to 41 weeks (reference), and term: 42 weeks.1,14,15

**Outcomes and Data Analysis**

As the main outcome, any live birth of a subsequent biological child to the mother after the birth of the index child was assessed by using a Cox regression model,16 which estimated the hazard ratios (HRs) with 95% confidence intervals (CIs) for the GA categories. The mothers were followed up from 6 months after the birth of the index child until they gave birth to a subsequent child or to the end of the follow-up (April 30, 2012). Mothers who died (4893, 2.2%), migrated (1735, 0.8%), underwent a hysterectomy (25,892, 11.6%) or reached the age of 50 (146,712, 65.7%), or reached the end of the follow-up without a subsequent biological child (96,600, 43.2%), whichever occurred first, were censored. The follow-up was rounded up to the closest 30 days and varied from 0.0 years to 24.8 years (mean: 18.7 years; sum: 4.2 million person years). In subanalyses, any subsequent live birth of a biological child to a nonadoptive father (referred to as a “father”) or to a couple served as the outcome. Analysis among couples reflects the situation in which the index child and the subsequent child share the same biological parents. Because a total of 32,989 (14.8%) mothers had more than 1 index child within the cohort and because we, in our primary analysis, assumed no intramother correlation, a sensitivity analysis was restricted to first index child of each mother within the cohort. In addition, we considered a long interbirth interval (IBI) before the birth of an index child as a proxy for possible maternal subfertility, and we conducted a sensitivity analysis by excluding mothers whose IBI exceeded 60 months.17,18

The effect of the GA of the index child on the maternal final number of subsequent live-born biological children served as a second outcome and was analyzed with multinomial regression models. We also assessed whether the low GA of the index child is associated with any absolute reduction of mothers’ final total child count within the population.

**Covariates**

All analyses were stratified by the number of live-born children (biological or adoptive) before the birth of the index child. In Cox
regression analyses, an eventual death of the index child was first taken into account; for details, see our Results. Parental ages were then added to the models as continuous variables after testing for the linearity by using squared age variables that left all HR estimates unaffected. A series of models were then fitted by adding variables in clusters. Variables covered information on the sex of the index child, parental highest ever attained level of education, maternal marital status at the birth of the index child, maternal smoking during pregnancy, previous stillbirths (yes/no), induced abortions (yes/no), miscarriages (none or 1/2 or more), gestational hypertensive disorders, gestational diabetes, intrahepatic cholestasis of pregnancy, the index child’s smallness for GA, maternal severe clinical course, mode of delivery, bronchopulmonary dysplasia, apysxia, retinopathy of prematurity, and other severe infant morbidities. A detailed description of the covariates is presented in the Supplemental Information, including Supplemental Tables 5 and 6. The analyses were conducted with SPSS version 22 (IBM SPSS Statistics; IBM Corporation).

RESULTS

Characteristics

Table 1 and Supplemental Table 7 present the characteristics of the study population in relation to GA. Among mothers with a subsequent child, the mean time between the births of the index child and the subsequent child, that is, the subsequent IBI, was shortest in the extremely preterm group at 33.0 months (SD: 27.4 months). The majority of unfavorable characteristics, such as maternal smoking, during pregnancy and a history of stillbirths appeared to be accumulated among mothers of preterm infants.

GA and Later Childbirth, Follow-Up of the Mothers

The results of unadjusted Cox regression analyses revealed that the most extreme category of prematurity was associated with higher HRs for having a subsequent sibling (Fig 2, Supplemental Table 8). Because high mortality is a key characteristic within this category (Table 1), we further explored the effect of the death of the index child on maternal reproductive behavior. Of mothers whose index child died in infancy (before 1 year of age), 79.1% gave birth to a subsequent child, compared with 56.8% of mothers whose child survived (Supplemental Fig 3). For index children who died in infancy, the majority (53.6%) of siblings were born during the first 2 years after the death of the index child (Supplemental Fig 3B). Therefore, we adjusted our main analysis for the death of each index child by using a time-dependent variable (index child alive/index child’s death within 2 years/index child’s death more than 2 years ago). Adding this time-dependent variable to the model (Model 1b) revealed that extremely preterm birth was also associated with a lower hazard of subsequent child birth (Fig 2). Univariate associations of the covariates with maternal subsequent childbirth are presented in Supplemental Table 9. Adjustment (Models 2–7) for these covariates had only a small joint influence on GAs association with maternal propensity for subsequent children (Supplemental Table 8).

Sensitivity Analyses

We performed sensitivity analyses restricted to each mother’s first index child within the cohort. In addition, to take into account...
possible maternal subfertility, we also conducted sensitivity analyses after excluding mothers whose previous IBI exceeded 60 months. Neither of these 2 modifications had any major impact on the results (Supplemental Tables 10 and 11). A subanalysis in which we excluded index children (810, 0.4%) who died in infancy showed a clear decreasing trend of HRs according to declining GA (Supplemental Table 12), which is consistent with the results of the main analysis described above.

G and Later childbirth, Follow-up of Fathers and of Couples
Cox regression analyses among fathers (omitting covariates of maternal origin from the models) and couples (Supplemental Figs 4 and 5, Supplemental Tables 13 and 14) illustrate similar associations between GA and sibling birth, as compared with mothers. The effect of infant mortality on further reproductive behavior was also nearly identical (Supplemental Figs 6 and 7).

To explore the effect of the GA of the index child on the number of subsequent live-born children, we stratified the mothers according to their previous child count and calculated the percentages of mothers with no subsequent child or 1, 2, or more subsequent children by GA category at the end of the follow-up. This is shown in Table 2.

### Table 2: Percentages of Mothers With Children Subsequent to Index Child by No. of Previous Live-born Children and the GA of the Index Child

<table>
<thead>
<tr>
<th>No. of Previous Live-born Children</th>
<th>No. of Subsequent Live-born Children</th>
<th>Extremely Preterm</th>
<th>Very Preterm</th>
<th>Moderately Preterm</th>
<th>Late Preterm</th>
<th>Early Term</th>
<th>Term</th>
<th>Postterm</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>n = 398</td>
<td>n = 757</td>
<td>n = 941</td>
<td>n = 7044</td>
<td>n = 38270</td>
<td>n = 168878</td>
<td>n = 9170</td>
<td>n = 223458</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>28.5</td>
<td>37.2</td>
<td>30.7</td>
<td>23.9</td>
<td>20.3</td>
<td>18.0</td>
<td>18.1</td>
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<td>1</td>
<td>29.5</td>
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<td>33.8</td>
<td>&lt;.001</td>
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<td>&lt;.001</td>
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<td>&lt;.001</td>
<td>43.1</td>
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<tr>
<td>≥2</td>
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<td>28.9</td>
<td>&lt;.001</td>
<td>28.4</td>
<td>&lt;.001</td>
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<td>13.3</td>
<td></td>
<td>12.4</td>
<td></td>
<td>14.4</td>
</tr>
</tbody>
</table>

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*Completed weeks' gestation.

bP values within GA category comparisons, term group as a reference. Adjusted for maternal and paternal ages at the birth of the index child and for the sex of the index child.
infant (elevating this percentage from 29.5% to 47.0%). According to a multinomial logistic regression analyses, adjusted for parental ages and the sex of the index child, the above-mentioned differences within GA categories were significant. Please note the relatively small cell frequencies in the most extreme subgroups (Supplemental Tables 15 and 16).

To further illustrate the impact of preterm birth on sibling count at the population level, we investigated the effect of the GA of the index child on sibling birth among mothers. As Table 4 shows, preterm birth clearly reduces the final number of children. For each 1000 children born preterm, 44 die in infancy and 142 subsequent siblings remain unborn. This phenomenon is seen even among mothers without previous live-born children (Supplemental Table 17).

In our nationwide study of 223,615 children, we followed up the families virtually until the end of their reproductive period. Our results indicate that the more preterm the index child was, the fewer subsequent siblings were born. This trend was also present when those born early term were compared with those born at 39 to 41 completed gestational weeks. The only exception to this trend was caused by infant mortality, which is most common in the lowest GA groups; when an index child died, a sibling was more likely to be born. The associations between the increasing degree of prematurity and fewer subsequent siblings were essentially similar among the mothers or the fathers independently, or among the couples. Similarities in subsequent child birth trends, however, may predominantly reflect maternally driven associations between preterm birth and the number of children.
Ethnically diverse populations. Due to the small sample size of these subgroups, it is likely to be smaller than in more ethnically homogeneous populations. Only 0.8% had parents with migrant background.

The population of Finland, in 1990, was ethnically homogeneous; only 0.8% had parents with migrant background. Accordingly, the possible variation in reproductive behavior within our study population is likely to be smaller than in more ethnically diverse populations.

Some potential limitations in our study exist. We had no data on whether other children in the family were preterm. Furthermore, although we were able to adjust for maternal miscarriages, induced abortions, and fetal deaths before the birth of the index child, such data after that birth were unavailable, which may have led to underestimation of the number of subsequent pregnancies. Lack of comprehensive data over infertility and related treatments led to an inability to assess to what extent the lower number of subsequent children within the lower GA groups was caused by personal or family choices and to what extent it was caused by subfertility. Register data on infertility treatments, however, would only have reflected a part of the phenomenon, because not all subfertile couples seek medical attention. In a sensitivity analysis, the previous maternal (before the birth of the index child) IBI exceeding 60 months served as a proxy for any levels of subfertility or infertility; exclusion of these mothers left patterns in subsequent child birth trends virtually unchanged, suggesting that our findings are not wholly explained by maternal subfertility. In addition, we had no data on whether the GA of the index child was based on maternal last menstrual period or on fetal ultrasound, which, in 1987–1990, was quickly being introduced in clinical practice in Finland. In Northern Finland in 1985 to 1986, ∼40% of newborns had already undergone ultrasound before 24 weeks’ gestation. Although we excluded individuals with unlikely GAs, GA distribution may have shifted to the right, causing an overestimation of GA and consequently decreased rates of preterm births. Such inaccuracies in GA estimates, together with an overrepresentation of preterm index children within excluded study subjects, may have had a minor, mainly precision-reductive impact on our results.

Numerous studies on factors affecting parental reproductive behavior exist. The focus has ranged from human life-history theories, including kin conflict and kin selection, economics, employment trends and welfare programs, and parental personality and partners’
relationship-related factors, to maternal health issues, including subfertility, assisted reproduction, and the mode of delivery. However, the impact of preterm birth on parental reproductive behavior has been mostly neglected in the literature. The authors of one study have suggested that ELBW infants were less likely to have subsequent siblings than normal birth weight infants. However, this was caused by the higher morbidity among ELBW infants. The results of another study indicated that parents of VLBW infants expressed a stronger desire for more children than families with a term infant, who, however, were more likely to give birth again. In these 2 studies conducted in Canada, which at that time had fertility rates similar to those of Finland, ~60% to 70% of families of ELBW and VLBW infants remained without subsequent children. In our study, the corresponding rate for the mothers within the most extreme group (<28 weeks) was 63% if the Index child survived infancy. In contrast to previous literature, severe infant disease had, in our study, only a minor effect on parental reproductive behavior. A maternal severe clinical course during the delivery and puerperal period or the mode of delivery could also affect the propensity for becoming pregnant; however, their impact was almost nonexistent. A part of the associations among extremely or very preterm infants were explained by the history of previous miscarriages, induced abortions, and stillbirths, which might reflect difficulties in sustaining a viable pregnancy. For some parents, the risk for recurrence of preterm delivery serves as a rational reason for not desiring a subsequent child. Conversely, an increased parental propensity for having a subsequent child after the death of an infant may be explained by both the absence or truncation of lactation and conscious replacement.

The negative impact of prematurity is not restricted only to the individual or family level but has even broader societal consequences. In our study, we show that the legacy of preterm birth for birth rate even at the population level might be substantial: 44 of 1000 preterm infants die during infancy and 173 fewer subsequent siblings than expected are born per 1000 preterm births, resulting in a total loss of 217 children for every 1000 preterm births. Such a loss of children is only partially compensated for by a higher parental propensity for having subsequent children after the death of an infant, because a total loss of children caused by prematurity is 142 for every 1000 preterm singleton live births or 6 for any 1000 singleton live births. Overall, in developed regions with a mean preterm birth incidence of 8.6% worldwide, this would translate to a loss of over 1220 subsequent children per any 100,000 live births.

CONCLUSIONS

With these data, we show that preterm birth has substantial consequences on the further reproductive behavior of both parents and reduces the final number of children in the family. This finding adds a novel viewpoint to the discussion on the impacts of preterm birth. Even late preterm or early term infants have fewer subsequent siblings compared with those born at term. The main population effect of preterm birth in a high-income country is thus caused by these missing siblings, whose number is more than three-fold higher than that of preterm infants who die.

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ABBREVIATIONS

CPR: Central Population Register
CI: confidence interval
ELBW: extremely low birth weight
GA: gestational age
HR: hazard ratio
IBI: interbirth interval
MBR: Finnish Medical Birth Register
VLBW: very low birth weight

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REFERENCES


28. Vikat A. Women’s labor force attachment and childbearing in Finland. *Demogr Res*. 2004;Special Collection 3:177–212


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