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Association of Preterm Birth With Long-term Survival, Reproduction, and Next-Generation Preterm Birth

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PRETERM BIRTH, DEFINED AS BIRTH prior to 37 weeks of gestation, is the leading cause of infant mortality in the industrialized world after congenital anomalies. Both mortality and significant long-term sequelae are disproportionately more prevalent among infants born very early.¹⁻⁶ Disability occurs in 60% of survivors born at 26 weeks and in 30% of those born at 31 weeks.³ Several studies have investigated long-term disabilities among survivors of preterm birth, including chronic lung disease, visual and hearing loss, and neurodevelopmental handicaps.^{2,4-6} However, most of these studies have evaluated small to moderately sized samples and have focused primarily on health during childhood. In addition, studies of long-term survival have been limited to the childhood period and have used low birth weight as a predictor rather than preterm birth.⁷⁻⁹ Furthermore, studies that have examined long-term outcomes into adolescence and early adulthood have also analyzed survivors of low birth weight and have been limited to relatively small case-control studies.¹⁰⁻¹³ Little is known about the long-term risk of mortality and overall health among persons born preterm.

We hypothesize that preterm birth is associated with not only fetal, infant, and childhood morbidity and mor-

Context Preterm birth is a major cause of infant morbidity and mortality. Less is known about long-term health among persons born preterm.

Objective To determine the long-term effects of preterm birth on survival, reproduction, and next-generation preterm birth.

Design, Setting, and Participants Population-based, observational, longitudinal study using registry data from 1 167 506 singleton births in the Medical Birth Registry of Norway in 1967-1988. The cohort was followed up through 2002 for survival. The cohort was truncated to births from 1967-1976 for assessment of educational achievement and reproductive outcomes through 2004.

Main Outcome Measures In relation to sex and gestational age at birth, absolute mortality, risk of fetal, infant, child, and adolescent mortality, and incidence and risk of reproduction and next-generation preterm birth. Singleton term (37-42 weeks) fetal deaths and live births, stratified by sex, served as the reference group for all analyses.

Results The percentage who were born preterm was higher among boys (5.6%) than among girls (4.7%). Preterm participants had an increased risk of mortality throughout childhood. For boys born at 22 to 27 weeks, mortality rates were 1.33% and 1.01% for early and late childhood death, with relative risks (RRs) of 5.3 (95% confidence interval [CI], 2.0-14.2) and 7.0 (95% CI, 2.3-22.0), respectively. The mortality rate for girls born at 22 to 27 weeks was 1.71% for early childhood death, with an RR of 9.7 (95% CI, 4.0-23.7); there were no late childhood deaths. For 28 to 32 weeks, the early and late childhood mortality rates among boys were 0.73% and 0.37%, with RRs of 2.5 (95% CI, 1.6-3.7) and 2.3 (95% CI, 1.3-4.1), respectively. Girls born at 28 to 32 weeks did not have a significantly increased risk of childhood mortality. Reproduction was diminished for index participants born preterm. For men and women born at 22 to 27 weeks, absolute reproduction was 13.9% and 25%, with RRs of 0.24 (95% CI, 0.17-0.32) and 0.33 (95% CI, 0.26-0.42), respectively. For 28 to 32 weeks, absolute reproduction was 38.6% and 59.2% for men and women, with RRs of 0.7 (95% CI, 0.66-0.74) and 0.81 (95% CI, 0.78-0.85), respectively. Preterm women but not men were at increased risk of having preterm offspring.

Conclusion In persons born in Norway in 1967-1988, preterm birth was associated with diminished long-term survival and reproduction.

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tality but also with adverse outcomes that persist throughout adulthood. Using a national population-based registry containing birth and death data for more than 1 million men and women, our objective was to determine how preterm birth affects long-term survival, subsequent reproduction, and next-generation preterm birth. Such infor-

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See also p 1477 and Patient Page.

mation may be useful to practitioners caring for families with survivors of preterm birth as well as parents of preterm infants.

METHODS

Population-Based Data

This study is based on analyses of the Medical Birth Registry of Norway (MBRN), a population-based, mandatory registry of all fetal deaths and live births in Norway since 1967 (more than 2.2 million births by 2004). To assess long-term survival, singleton fetal deaths and live births from 1967 through 1988 occurring at or after 22 weeks of gestation or weighing at least 500 g were selected as the index cohort. Among these 1 234 796 individuals, gestational age was missing for 5.3%, leaving 1 169 702.

Gestational age estimates were based on reported last menstrual period and clinical evaluation at birth until 1999, when ultrasound findings were officially recorded within the MBRN and incorporated into gestational age estimation. Errors in reporting of gestational age were controlled for by applying current birth weight-for-gestational age standards for Norway as described by Skjaerven et al.¹⁴ Using a *z* score above 6 as the cut point for exclusion of improbable values between 22 and 32 weeks of gestation, an additional 0.19% of the index cohort (2196 participants) was excluded.

The final data set used for analysis consisted of 1 167 506 participants (600 093 male and 567 413 female individuals). Using the unique 11-digit personal identification number assigned to each individual born in Norway, data from the MBRN were linked to the Registry of Level of Education and the National Cause of Death Registry, both in Statistics Norway. The cohort was followed up through 2002 for survival. To allow for adequate assessment of educational achievement and reproductive outcomes, the index cohort was truncated to births occurring in 1967-1976. Reproduction, defined as any fetal stillbirth or live birth, was assessed through 2004. Based on the data

available within the MBRN, induced abortions could not be included as reproductive events. Use and analysis of the data were approved by the Norwegian Data Protectorate with exemption status obtained from the Duke University Medical Center Institutional Review Board. Index participants were grouped by sex and gestational age: extremely preterm (22-27 weeks), very preterm (28-32 weeks), preterm (33-36 weeks), term (37-42 weeks), and post-term (≥ 43 weeks).

Statistical Analysis

Singleton term fetal deaths and live births, stratified by sex, served as the reference group for all analyses. We determined mortality rates for the fetal, infant (<1 year), early childhood (1-5.9 years), late childhood (6-12.9 years), and adolescent (13-17.9 years) periods. Mortality rates were calculated by excluding earlier losses, ie, the proportion of participants who died during a specific age range among the total number of participants who were living at the beginning of that range. For the truncated cohort, educational achievement was assessed as the proportion of those achieving less than a high school education and those receiving postcollege graduate education. Reproduction and reproductive outcomes among the offspring of these participants were examined, including subsequent preterm birth, fetal mortality, and infant mortality.

Absolute risks (ARs) and relative risks (RRs) with corresponding 95% confidence intervals (CIs) were calculated, adjusting for year of birth (1967-1971, 1972-1976, 1977-1981, and 1982-1988), maternal age (<20 years, 20-24 years, 25-29 years, 30-34 years, and ≥ 35 years), and maternal education (less than high school, high school completed, graduate school). We used RR modeling (log link) as available in Stata's generalized linear models for the binomial family. Statistical analyses were performed using SPSS, version 14.0 (SPSS Inc, Chicago, Illinois) and Stata SE, version 9.0 (Stata Corp, College Station, Texas).

RESULTS

Parental Sociodemographic and Clinical Characteristics

The overall percentage born preterm in the entire index cohort was 5.2% (60 354/1 167 506). The percentage born preterm was higher among boys (5.6%) than among girls (4.7%), which is consistent with the male-dominated sex ratio of all births, regardless of gestational age.¹⁵ TABLE 1 describes the characteristics of the parents of the index participants at the time of birth of the index participants, by sex. There was no association between maternal or paternal age and preterm birth. As previous studies have shown, preterm births as well as postterm births were more likely to occur among mothers with lower education and among those who were unmarried. Diabetes and preeclampsia were more common among mothers who delivered preterm than among their term counterparts.

Mortality According to Gestational Age at Birth

Relative mortality by gestational age at birth for live births from the index cohort, adjusted for year of birth, maternal age, education, and infant sex, is shown in FIGURE 1. In this figure, the infant and early childhood periods were further subdivided to illustrate the rapid decline in mortality during this period as well as the relative stabilization in mortality for all gestational age categories at the end of this period. As expected, infant mortality was extremely high for individuals born preterm, particularly for those born at very early gestations (22-27 weeks). Increased relative mortality persisted into childhood for all preterm gestational age categories.

Detailed results from covariate-adjusted RR modeling for mortality by gestational age at birth and sex are shown in TABLE 2. While the absolute mortality after the first year of life is low overall, there are significant differences with regard to sex and gestational age. For girls, the risk of mortality in early childhood was elevated for most preterm births. Among girls,

for early childhood death the mortality rate was 1.71%, the AR was 1.52%, and the adjusted RR was 9.7 (95% CI, 4.0-23.7) for those born at 22 to 27 weeks and the mortality rate was 0.31%, the AR was 0.12%, and the adjusted RR was 1.6 (95% CI, 1.2-2.0) for those born at 33 to 36 weeks. These risk values were closely mirrored by early childhood deaths among boys, with the additional finding of increased mortality risk in the 28- to 32-week period. Boys of this gestational age had a mortality rate of 0.73%, an AR of 0.45%, and an adjusted RR of 2.5 (95% CI, 1.6-3.7). For female survivors of preterm birth, there were no statistically significant differences in mortality rates in late childhood or adolescence. However, among boys, for late childhood death the mortality rate was 1.01%, the AR was 0.85%, and the adjusted RR was 7.0 (95% CI, 2.3-22.0) for those born at 22 to 27 weeks and the mortality rate was 0.37%, the AR was 0.21%, and the adjusted RR was 2.3 (95% CI, 1.3-4.1) for those born at 28 to 32 weeks. For boys, there was no statistically significant increased adolescent mortality associated with preterm birth.

We also compared postterm and term births regarding risk of mortality. Infant mortality rates were higher among index participants born postterm, with a mortality rate of 0.66%, an AR of 0.19%, and an RR of 1.4 (95% CI, 1.2-1.6) for girls and a mortality rate of 0.73%, an AR of 0.13%, and an RR of 1.2 (95% CI, 1.03-1.4) for boys. Girls born postterm had no further increased risk of mortality later in life. However, this increased risk of death was again detected for postterm boys in the late childhood period, with a mortality rate of 0.23%, an AR of 0.07%, and an RR of 1.4 (95% CI, 1.1-1.8).

Educational and Reproductive Outcomes According to Gestational Age at Birth

With truncation of the cohort and follow-up through 2004, 283 457 female and 297 375 male survivors remained in the cohort. FIGURE 2 contrasts the covariate-adjusted RR for subsequent

Table 1. Index Participant Characteristics by Sex and Gestational Age

| Characteristics | Gestational Age, wk | | | | |
|---|---------------------|------------|------------|------------|------------|
| | 22-27 | 28-32 | 33-36 | 37-42 | ≥43 |
| Girls (n = 567 413), No. | 2068 | 4047 | 20 485 | 513 962 | 26 851 |
| Maternal age, mean (SD), y | 26.6 (6.0) | 26.2 (5.9) | 26.6 (5.8) | 26.7 (5.2) | 25.6 (5.0) |
| Paternal age, mean (SD), y | 30.4 (6.7) | 29.9 (6.7) | 29.9 (6.6) | 29.9 (5.9) | 29.0 (5.8) |
| Maternal education less than high school, % | 26.9 | 27.2 | 25.2 | 20.9 | 24.0 |
| Maternal unmarried status, % | 15.3 | 15.8 | 13.8 | 9.4 | 13.3 |
| Maternal preeclampsia, % | 3.1 | 8.8 | 6.8 | 2.1 | 1.8 |
| Maternal diabetes, rate per 1000 live and stillbirths | 4.3 | 9.4 | 15.8 | 1.3 | 0.3 |
| Maternal gestational diabetes, rate per 1000 live and stillbirths | 1.0 | 0.9 | 1.9 | 0.5 | 0.5 |
| Boys (n = 600 093), No. | 2534 | 5357 | 25 863 | 539 808 | 26 531 |
| Maternal age, mean (SD), y | 26.6 (6.0) | 26.2 (5.9) | 26.6 (5.8) | 26.7 (5.2) | 25.6 (5.0) |
| Paternal age, mean (SD), y | 30.2 (6.7) | 29.6 (6.6) | 29.9 (6.5) | 29.9 (6.0) | 29.0 (5.8) |
| Maternal education less than high school, % | 27.2 | 27.5 | 25.7 | 21.0 | 23.5 |
| Maternal unmarried status, % | 16.4 | 16.7 | 13.1 | 9.5 | 13.3 |
| Maternal preeclampsia, % | 1.7 | 7.1 | 6.3 | 2.3 | 2.0 |
| Maternal diabetes, rate per 1000 live and stillbirths | 2.8 | 8.0 | 13.1 | 1.2 | 0.6 |
| Maternal gestational diabetes, rate per 1000 live and stillbirths | 0.8 | 0.9 | 2.2 | 0.4 | 0.3 |

reproduction (any fetal death or live birth) among surviving men and women by gestational age. For both men and women, reproduction appeared to be considerably lower for those born preterm compared with those born at term and appeared to directly increase with increasing gestational age at birth until about 35 weeks of gestation. Men had noticeably lower rates of reproduction than women across all preterm gestational age groups, with significantly lower rates in the early preterm groups.

Detailed results from covariate-adjusted RR modeling for educational and reproductive outcomes by gestational age at birth and sex are shown in TABLE 3. The lower the gestational age of the index participant, the greater the risk of having less than a high school education and the lower the risk of having graduate education. With regard to reproduction, only 25.0% of women who had been born at 22 to 27 weeks had subsequently reproduced in contrast to approximately 68% of women born at term.

Similar findings were noted for index men, with reproductive rates of 13.9% and 50.4% for men who had been born at 22 to 27 weeks and at term, respectively. Female but not male index participants had an increased risk of recurrent preterm birth following a dose-response pattern such that increasing severity of prematurity was associated with an increasing risk of adverse outcomes among their offspring. Compared with 6.4% of index women born at term having preterm offspring, the incidence of having preterm offspring was 14.0% among women who had been born at 22 to 27 weeks (AR, 7.6%; RR, 2.4 [95% CI, 1.4-4.2]), 9.2% for those born at 28 to 32 weeks (AR, 2.8%; RR, 1.5 [95% CI, 1.4-4.2]), and 8.8% for those born at 33 to 36 weeks (AR, 2.4%; RR, 1.4 [95% CI, 1.3-1.5]). A similar pattern was seen for both fetal stillbirth and infant mortality among the offspring of index women born preterm. For fetal stillbirth, term index women had a subsequent fetal stillbirth rate of 7.6 per 1000 births compared with a rate

of 20.8 for those born at 22 to 27 weeks, 14.8 for those born at 28 to 32 weeks, and 8.9 for those born at 33 to 36 weeks. Despite such a pattern, the risk of stillbirth among offspring was only statistically significantly increased for women born at 28 to 32 weeks (14.8 per 1000 births; AR, 3.6; RR, 1.8 [95%CI, 1.2-2.7]). The incidence of infant mortality among offspring also increased with decreasing gestational age of index women but, similarly, was only statistically significant among those born at 28 to 32 weeks (7.5 per 1000 births; AR, 3.6; RR, 1.8 [95% CI, 1.1-3.1]).

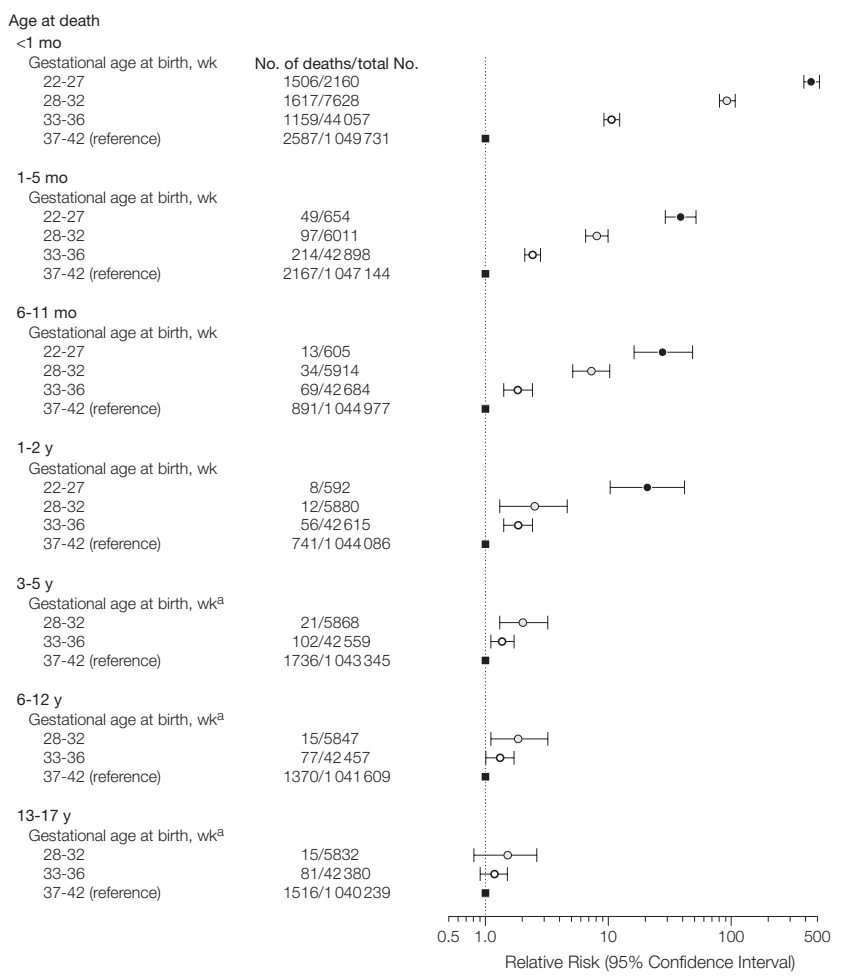
COMMENT

In persons born in Norway in 1967-1988, preterm birth was associated with increased perinatal and infant mortality and diminished long-term survival. Women and men born extremely preterm and very preterm have particularly high RRs of mortality into childhood. Similar registry or cohort studies have investigated long-term mortality and its association with birth weight rather than gestational age. Using the same Norwegian registry data except with mortality data only through 1991, Samuelsen et al⁹ found that low birth weight (<2500 g) was associ-

ated with increased mortality up to 10 years of age. In a case-control study of approximately 37 000 births in the state of Washington between 1968 and 1996, Li et al⁸ found that infants weighing less than 3000 g had a higher risk of mortality up to 14 years of age. However, using a population-based cohort of births in Jerusalem in 1967-1976, Friedlander et al⁷ did not find an association between low birth weight and mortality among participants aged 1 to 14 years. Although birth weight is a more accurate measure, gestational age may be a stronger predictor of postnatal maturity and, therefore, both short- and long-term survival. By dichotomizing birth weight, these earlier studies did not address the disproportionate contribution of very low birth weight or very preterm births to mortality risk at any time during childhood.

Mortality rates for boys are higher than rates for girls for every age group of children and youth, with the most dramatic difference among adolescent boys and girls.¹⁶ Regardless of category of gestational age at birth or age at death, we have demonstrated that boys generally have higher absolute mortality rates than their female counterparts. While it is generally accepted that male teenagers have higher mortality than their female counterparts because of high-risk behaviors,¹⁷ it is unclear why childhood mortality follows the same pattern. A known difference between boys and girls is the higher incidence of congenital anomalies,^{18,19} which, in previous analyses of the MBRN, has been associated with overall diminished long-term survival.^{20,21} Furthermore, the incidence of congenital anomalies is higher in preterm than in term births.^{22,23} These analyses, however, did not evaluate the relationship between gestational age and mortality. Previous studies of low birth weight and mortality have evaluated causes of death but were not sex-specific.^{8,9} We stratified our analysis by sex due to the differences in survival, clinical outcomes, and social behaviors between boys and girls.^{15,24,25} Analysis of sex-specific causes of mortality is cur-

Figure 1. Survival by Gestational Age at Birth for Singleton Live Births, 1967-1988, Followed Up Through 2002



Age at death is categorized by completed months or years. Error bars indicate 95% confidence intervals. ^aData for 22-27 weeks not shown because number of deaths was 1/584, 3/583, and 0/580 for 3-5 years, 6-12 years, and 13-17 years, respectively.

rently ongoing and may elucidate why preterm birth is associated with a higher risk of childhood mortality among boys than girls.

In addition to the association of preterm birth with long-term survival, we were also interested in the long-term consequences on quality of life among survivors of preterm birth. A recent co-

hort study by Ekholm et al²⁶ showed that women born with very low birth weight had reduced reproduction. Women born preterm did not have a statistically significant reduction in rate of reproduction, possibly because of a smaller overall cohort size and a smaller number of preterm births (6080/148 281). Men were excluded from

their cohort. Hack et al¹¹ studied women and men with very low birth weight and found lower pregnancy rates for women but not men; however, their case-control investigation was very likely limited by small sample size. We have shown among a large population cohort that both men and women born preterm have much lower rates of re-

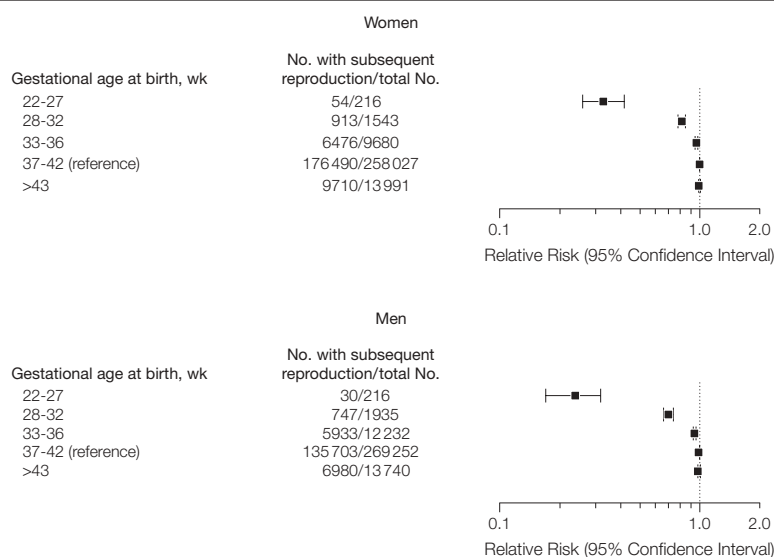
Table 2. Short- and Long-term Mortality of Index Participants by Sex and Gestational Age

| Age at Death | Gestational Age, wk | | | | |
|-----------------------------------|---------------------|------------------|------------------|---------------|------------------|
| | 22-27 | 28-32 | 33-36 | 37-42 | ≥43 |
| Girls (n = 567 413) | n = 2068 | n = 4047 | n = 20 485 | n = 513 962 | n = 26 851 |
| Fetal stillbirth | | | | | |
| Mortality, No. (%) ^a | 1109 (53.6) | 791 (19.6) | 1053 (5.1) | 1956 (0.38) | 143 (0.52) |
| RR (95% CI) | 141 (133-150) | 51 (48-55) | 13.5 (12.5-14.5) | 1 [Reference] | 1.37 (1.15-1.63) |
| Adjusted RR (95% CI) ^b | 133 (125-141) | 51 (48-56) | 13.5 (12.5-14.6) | 1 [Reference] | 1.4 (1.2-1.7) |
| Infancy (age <1 y) | | | | | |
| Mortality, No. (%) ^a | 667 (70.0) | 647 (19.9) | 582 (3.0) | 2427 (0.47) | 177 (0.66) |
| RR (95% CI) | 147 (139-156) | 43 (39-46) | 6.3 (5.8-6.9) | 1 [Reference] | 1.41 (1.21-1.64) |
| Adjusted RR (95% CI) ^b | 144 (136-153) | 42 (39-45) | 6.3 (5.7-6.9) | 1 [Reference] | 1.4 (1.2-1.6) |
| Early childhood (age 1-5.9 y) | | | | | |
| Mortality, No. (%) ^a | 5 (1.71) | 9 (0.34) | 58 (0.31) | 977 (0.19) | 64 (0.24) |
| RR (95% CI) | 9.1 (3.7-22.0) | 1.8 (0.92-3.5) | 1.61 (1.23-2.1) | 1 [Reference] | 1.26 (0.98-1.62) |
| Adjusted RR (95% CI) ^b | 9.7 (4.0-23.7) | 1.8 (0.93-3.5) | 1.6 (1.2-2.0) | 1 [Reference] | 1.2 (0.32-1.6) |
| Late childhood (age 6-12.9 y) | | | | | |
| Mortality, No. (%) ^a | 0 | 3 (.09) | 31 (.15) | 512 (.10) | 28 (.11) |
| RR (95% CI) | | 1.17 (0.38-3.64) | 1.56 (1.08-2.28) | 1 [Reference] | 1.07 (0.73-1.57) |
| Adjusted RR (95% CI) ^b | | 0.94 (0.3-2.9) | 1.5 (1.0-2.1) | 1 [Reference] | 1.1 (0.73-1.6) |
| Adolescence (age 13-17.9 y) | | | | | |
| Mortality, No. (%) ^a | 0 | 4 (0.16) | 25 (0.14) | 474 (0.11) | 28 (0.13) |
| RR (95% CI) | | 0.59 (0.22-1.57) | 1.04 (0.79-1.38) | 1 [Reference] | 1.14 (0.91-1.43) |
| Adjusted RR (95% CI) ^b | | 1.4 (0.5-3.8) | 1.3 (0.87-1.9) | 1 [Reference] | 1.2 (0.78-1.7) |
| Boys (n = 600 093) | n = 2534 | n = 5357 | n = 25 863 | n = 539 808 | n = 26 531 |
| Fetal stillbirth | | | | | |
| Mortality, No. (%) ^a | 1333 (52.6) | 985 (18.4) | 1238 (4.8) | 2083 (0.39) | 159 (0.60) |
| RR (95% CI) | 136 (129-144) | 48 (44-51) | 12.4 (11.6-13.3) | 1 [Reference] | 1.55 (1.32-1.82) |
| Adjusted RR (95% CI) ^b | 126 (119-134) | 47 (44-50) | 12.3 (11.5-13.2) | 1 [Reference] | 1.6 (1.3-1.9) |
| Infancy (age <1 y) | | | | | |
| Mortality, No. (%) ^a | 901 (75.0) | 1101 (25.2) | 860 (3.5) | 3227 (0.60) | 193 (0.73) |
| RR (95% CI) | 126 (120-132) | 42 (40-45) | 5.8 (5.4-6.3) | 1 [Reference] | 1.21 (1.05-1.40) |
| Adjusted RR (95% CI) ^b | 118 (112-123) | 41 (39-44) | 5.7 (5.3-6.2) | 1 [Reference] | 1.2 (1.03-1.4) |
| Early childhood (age 1-5.9 y) | | | | | |
| Mortality, No. (%) ^a | 4 (1.33) | 24 (0.73) | 100 (0.42) | 1500 (0.28) | 84 (0.32) |
| RR (95% CI) | 4.8 (1.8-12.9) | 2.6 (1.8-3.9) | 1.50 (1.23-1.84) | 1 [Reference] | 1.14 (0.92-1.86) |
| Adjusted RR (95% CI) ^b | 5.3 (2.0-14.2) | 2.5 (1.6-3.7) | 1.5 (1.2-1.8) | 1 [Reference] | 1.1 (0.90-1.4) |
| Late childhood (age 6-12.9 y) | | | | | |
| Mortality, No. (%) ^a | 3 (1.01) | 12 (0.37) | 46 (0.19) | 858 (0.16) | 60 (0.23) |
| RR (95% CI) | 6.4 (2.0-19.8) | 2.3 (1.3-4.1) | 1.21 (0.90-1.63) | 1 [Reference] | 1.43 (1.10-1.86) |
| Adjusted RR (95% CI) ^b | 7.0 (2.3-22.0) | 2.3 (1.3-4.1) | 1.2 (0.89-1.6) | 1 [Reference] | 1.4 (1.1-1.8) |
| Adolescence (age 13-17.9 y) | | | | | |
| Mortality, No. (%) ^a | 0 | 11 (0.34) | 50 (0.21) | 1042 (0.20) | 65 (0.25) |
| RR (95% CI) | | 1.33 (0.95-1.86) | 1.05 (0.91-1.21) | 1 [Reference] | 1.27 (1.12-1.44) |
| Adjusted RR (95% CI) ^b | | 1.6 (0.83-2.9) | 1.0 (0.78-1.4) | 1 [Reference] | 1.2 (0.97-1.6) |

Abbreviations: CI, confidence interval; RR, relative risk.

^aNumber of individuals who died within the specific age period for each gestational age category.

^bRelative risk models are adjusted for year of birth, maternal age, and maternal education, with all factors treated as categorical predictors.

Figure 2. Reproduction by Gestational Age at Birth for Women and Men Born in 1967-1976

Error bars indicate 95% confidence intervals.

production compared with those born at term. In addition to biological factors, psychosocial and economic factors also affect ability to reproduce. It is possible that survivors of preterm birth experience more difficulty finding a mate because of medical problems or diminished cognitive ability. Phillips et al²⁷ demonstrated that low birth weight in men was associated with lower social class, income, and rate of marriage. About 20% of men weighing less than 2500 g at birth had never married compared with about 10% of men with normal birth weight. Vågerö et al²⁸ found similar results for men but found no difference in marriage rates among women. Saigal et al¹³ evaluated men and women with very low birth weight in Canada and found no difference in marital status or parenthood, but, similar to the study by Hack et al,¹¹ they likely did not have the power to detect such differences in their small case-control study. We used educational achievement as a measure of social factors involved in subsequent reproduction. As anticipated, both male and female survivors of preterm birth were much more likely to have low educational achievement than survivors of term birth. However, it is unclear

whether this is a result of being born preterm or of being born into a high-risk social setting with poor parental education and a high rate of unmarried parents. In addition to functioning as a risk factor for preterm birth, our findings show that poor educational attainment is likely to function as an outcome or consequence of preterm birth. While biological factors may be at the root of the problem, interrelated social and economic stressors likely also diminish reproductive ability.

Advances in pharmacologic interventions and medical technology have dramatically improved survival after preterm birth.²⁹ Use of antenatal corticosteroids, antibiotic prophylaxis, surfactant therapy, and high-frequency ventilation was not widespread until the early to mid 1990s.²⁹ Based on the singleton births within the MBRN linked to the Cause of Death Registry, infant mortality rates after preterm birth in Norway have decreased from 10% in 1967 to 2% in 2002. However, improved survival possibly comes at the expense of diminished overall health and quality of life. Stoelhorst et al³⁰ compared 2 unique Dutch cohorts of births occurring prior to 32 weeks of gestation, one from the 1980s and one from the 1990s. In-

hospital mortality decreased from 30% to 11%, with an even greater decline in mortality among extremely preterm infants, from 76% to 33%. Mortality due to respiratory distress syndrome, the most common medical complication of prematurity, decreased from 29% to 6%; however, the incidence of bronchopulmonary dysplasia—a condition that results from respiratory distress syndrome and can lead to chronic lung disease—increased from 6% to 19%. Among surviving infants, overall health was described as abnormal in 14% in the 1980s cohort compared with 34% in the 1990s cohort. Given that all index participants in our study cohort were born before 1990, it is possible that those who survived preterm birth are healthier than those who have survived preterm birth in more recent years. If true, future studies should find continually improving survival among extremely and very preterm births but further diminishing reproduction in these groups due to increasing morbidity and long-term sequelae.

Strengths of our study include its evaluation of long-term survival related to preterm birth, comparison of women and men, and its examination of subsequent reproduction. We used a comprehensive, detailed, and highly accurate birth registry of national scope. All Norwegian births after 16 weeks of gestation, whether live births or stillbirths, are to be entered into the Medical Birth Registry by law. We were able to link information from the birth registry to both educational and mortality data for more than 35 years of follow-up. Furthermore, linkage of the index cohort to subsequent offspring (ie, across generations) was performed within the birth registry and is extremely accurate given the use of the unique and “transcription error-resistant” Norwegian personal identification number.³¹ Given the relatively low rate of emigration from Norway, the potential for differential loss to follow-up is extremely low.³² Moreover, use of such a large, detailed cohort of births allowed us to empirically evaluate associations of gestational age at birth with survival and reproductive

outcomes through RR modeling, controlling for potential confounders. Our analysis revealed an interesting dose-response relationship between gestational age and both outcomes. Al-

though we did perform multiple analyses using the same cohort of births, we have not adjusted for multiple comparisons because this would most likely obscure this interesting pattern in the results.

Our analyses required gestational-age correction. There are inherent errors in clinical estimation of gestational age due mostly to inaccurate menstrual history or improper fetal

Table 3. Educational and Reproductive Outcomes for Index Participants Born in 1967-1976 by Sex and Gestational Age

| Outcomes | Gestational Age, wk | | | | |
|--|---------------------|------------------|------------------|---------------|------------------|
| | 22-27 | 28-32 | 33-36 | 37-42 | ≥43 |
| Women (n = 283 457) | n = 216 | n = 1543 | n = 9680 | n = 258 027 | n = 13 991 |
| Less than high school education, % | 33.3 | 32.2 | 29.9 | 24.7 | 28.4 |
| RR (95% CI) | 1.34 (1.00-1.79) | 1.29 (1.19-1.40) | 1.21 (1.17-1.25) | 1 [Reference] | 1.15 (1.12-1.18) |
| Adjusted RR (95% CI) ^a | 1.28 (.96-1.7) | 1.19 (1.1-1.29) | 1.13 (1.1-1.17) | 1 [Reference] | 1.10 (1.07-1.14) |
| Graduate education, % | 36.6 | 37.1 | 37.7 | 43.4 | 39.4 |
| RR (95% CI) | 0.84 (0.64-1.10) | 0.86 (0.80-0.92) | 0.87 (0.85-0.89) | 1 [Reference] | 0.91 (0.89-0.93) |
| Adjusted RR (95% CI) ^a | 0.86 (0.67-1.1) | 0.94 (0.88-0.99) | 0.93 (0.91-0.95) | 1 [Reference] | 0.95 (0.93-0.97) |
| Individuals who reproduced, % | 25.0 | 59.2 | 66.9 | 68.4 | 69.4 |
| RR (95% CI) | 0.36 (0.29-0.46) | 0.85 (0.81-0.89) | 0.98 (0.96-0.99) | 1 | 1.01 (1.00-1.03) |
| Adjusted RR (95% CI) ^a | 0.33 (0.26-0.42) | 0.81 (0.78-0.85) | 0.97 (0.95-0.98) | 1 [Reference] | 1.0 (0.99-1.01) |
| Age when first child was born, mean (SD), y | 25.4 (4.1) | 24.4 (4.0) | 24.5 (4.1) | 24.7 (4.0) | 24.4 (4.1) |
| Preterm birth among offspring, % | 14.0 | 9.2 | 8.8 | 6.4 | 5.7 |
| RR (95% CI) | 2.1 (1.1-4.0) | 1.52 (1.29-1.80) | 1.42 (1.33-1.52) | 1 [Reference] | 0.90 (0.84-0.96) |
| Adjusted RR (95% CI) ^a | 2.4 (1.4-4.2) | 1.5 (1.4-4.2) | 1.4 (1.3-1.5) | 1 [Reference] | 0.87 (0.81-0.92) |
| Fetal stillbirth among offspring, rate per 1000 live and stillbirths | 20.8 | 14.8 | 8.9 | 7.6 | 7.7 |
| RR (95% CI) | 2.79 (0.69-11.3) | 1.96 (1.33-2.90) | 1.17 (0.97-1.42) | 1 [Reference] | 1.02 (0.86-1.22) |
| Adjusted RR (95% CI) ^a | 2.5 (0.62-10.2) | 1.8 (1.2-2.7) | 1.1 (0.95-1.4) | 1 [Reference] | 1.0 (0.87-1.2) |
| Infant mortality among offspring, rate per 1000 live births | 10.6 | 7.5 | 4.1 | 3.9 | 4.5 |
| RR (95% CI) | 2.72 (0.38-19.5) | 1.91 (1.10-3.30) | 1.03 (0.78-1.37) | 1 [Reference] | 1.18 (0.91-1.44) |
| Adjusted RR (95% CI) ^a | 2.5 (0.35-17.7) | 1.8 (1.1-3.1) | 1.1 (0.81-1.4) | 1 [Reference] | 1.2 (0.96-1.5) |
| Men (n = 297 375) | n = 216 | n = 1935 | n = 12 232 | n = 269 252 | n = 13 740 |
| Less than high school education, % | 35.6 | 34.7 | 28.9 | 25.3 | 29.1 |
| RR (95% CI) | 1.42 (1.09-1.86) | 1.36 (1.27-1.46) | 1.14 (1.11-1.17) | 1 [Reference] | 1.15 (1.12-1.18) |
| Adjusted RR (95% CI) ^a | 1.40 (1.09-1.8) | 1.27 (1.18-1.4) | 1.09 (1.06-1.12) | 1 [Reference] | 1.11 (1.07-1.14) |
| Graduate education, % | 20.8 | 26.2 | 28.8 | 32.6 | 29.2 |
| RR (95% CI) | 0.66 (.45-97) | 0.80 (0.74-0.87) | 0.88 (0.86-0.91) | 1 [Reference] | 0.90 (0.87-0.92) |
| Adjusted RR (95% CI) ^a | 0.70 (0.49-1.01) | 0.87 (0.80-0.94) | 0.95 (0.92-0.97) | 1 [Reference] | 0.95 (0.92-0.97) |
| Individuals who reproduced, % | 13.9 | 38.6 | 48.5 | 50.4 | 50.8 |
| RR (95% CI) | 0.26 (0.19-0.37) | 0.74 (0.70-0.78) | 0.96 (0.94-0.98) | 1 | 1.01 (0.99-1.03) |
| Adjusted RR (95% CI) ^a | 0.24 (0.17-0.32) | 0.70 (0.66-0.74) | 0.95 (0.93-0.96) | 1 [Reference] | 1.0 (0.98-1.01) |
| Age when first child was born, mean (SD), y | 26.9 (4.2) | 26.4 (3.6) | 26.5 (3.8) | 26.5 (3.7) | 26.3 (3.7) |
| Preterm birth among offspring, % | 14.0 | 6.7 | 6.9 | 6.1 | 6.4 |
| RR (95% CI) | 2.5 (1.1-5.6) | 1.1 (0.88-1.38) | 1.15 (1.06-1.24) | 1 [Reference] | 1.05 (0.97-1.14) |
| Adjusted RR (95% CI) ^a | 2.5 (0.35-17) | 1.8 (1.1-3.1) | 1.1 (0.81-1.4) | 1 [Reference] | 1.2 (0.96-1.5) |
| Fetal stillbirth among offspring, rate per 1000 live and stillbirths | 0 | 5.6 | 6.2 | 6.4 | 7.6 |
| RR (95% CI) | | 0.87 (0.41-1.84) | 0.96 (0.75-1.25) | 1 [Reference] | 1.2 (0.96-1.49) |
| Adjusted RR (95% CI) ^a | | 0.99 (0.49-2.0) | 0.96 (0.74-1.2) | 1 [Reference] | 1.3 (1.02-1.6) |
| Infant mortality among offspring, rate per 1000 live births | 0 | 2.4 | 4.5 | 3.2 | 3.8 |
| RR (95% CI) | | 0.75 (0.38-19.5) | 1.39 (0.24-2.32) | 1 [Reference] | 1.18 (0.87-1.61) |
| Adjusted RR (95% CI) ^a | | 0.71 (0.22-2.2) | 1.4 (1.1-1.9) | 1 [Reference] | 1.2 (0.91-1.7) |

Abbreviations: CI, confidence interval; RR, relative risk.

^aRelative risk models are adjusted for year of birth, maternal age, maternal education, and infant sex, with all factors treated as categorical predictors and additional adjustment for maternal education in index participants for next-generation/offspring birth outcomes.

growth. We used a conservative approach by including index participants born as early as 22 weeks of gestation but then corrected for potential misclassification for gestation through exclusion of participants for whom the birth weight was either too small or too large for the recorded gestational age. In recent years, errors in estimation of gestational age have been significantly reduced because of use of obstetrical ultrasound for antenatal estimation of gestational age.³³⁻³⁵ For our index cohort, ultrasound was not in widespread use in 1967-1988. Official recording of ultrasound findings within the registry began in 1999. Another limitation is that our follow-up of subsequent reproduction among the index cohort is incomplete such that participants who were born in later years may not have had the opportunity or desire to repro-

duce. While this is currently a drawback, the nature of this ongoing registry cohort allows us to perform follow-up analyses with additional long-term outcome data in the future. Another drawback to our study is that it may not be generalizable for other countries that have more racially and ethnically heterogeneous populations than does Norway. Finally, although our power to evaluate survival or mortality among the very preterm subgroups was limited by the small sample size in this subgroup, other studies that have evaluated the same topic have the same drawback and have not had nearly the number of participants as our investigation does.

In this study population, preterm birth was negatively associated with both long-term survival and reproduction. As the preterm birth survi-

vorship continues to grow, further studies will show whether improvements in obstetric and neonatal care affect survival as well as reproductive capacity and long-term quality of life. Continued research aimed at elucidating causal pathways and better therapeutic approaches are imperative for successful strategies to prevent preterm birth.

Author Contributions: Dr Skjærven had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Swamy, Østbye, Skjærven.

Acquisition of data: Skjærven.

Analysis and interpretation of data: Swamy, Østbye, Skjærven.

Drafting of the manuscript: Swamy.

Critical revision of the manuscript for important intellectual content: Swamy, Østbye, Skjærven.

Statistical analysis: Skjærven.

Administrative, technical, or material support: Østbye, Skjærven.

Study supervision: Swamy, Østbye, Skjærven.

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called into play in consanguineous populations to protect against cancer.

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In Reply: Dr Denic and colleagues extrapolate our findings, which deal with germline homozygosity and low-penetrance susceptibility to common solid tumors, to inbred populations. They then suggest that homozygotes for cancer alleles die prematurely and so it would not be likely to see homozygous cancer alleles.

We assume they are referring to traditional high-penetrance cancer susceptibility alleles, such as RB, TP53, and *BRCA1/2*, where null murine models are embryonic lethal. Although Rb^{-/-} murine models had been believed to be embryonic lethal in mice, their embryonic lethality is due only to a placental effect.¹ When the extra-embryonic tissues (including placenta) were rescued, Rb^{-/-} mice were shown to be born and viable.¹

Nonetheless, our data are most germane to low-penetrance susceptibility to common cancers in general populations as we studied unrelated white patients of northern and western European ancestry. The most homozygous hotspots did not correspond to regions harboring known high-penetrance cancer susceptibility genes, but instead to regions where some of the already identified low-penetrance single-nucleotide polymorphisms associated with these common cancers reside.

Furthermore, our observations have now been independently replicated by another group of investigators studying patients with another solid tumor, colorectal carcinoma.² These investigators found a high frequency of autozygous regions in white individuals with colorectal cancer compared with white individuals without cancer (but with macular degeneration or who belong to the Framingham Heart Study control group). In that study, patients with colorectal cancer and Jewish ancestry were

found to have more frequent autozygosity compared with other white individuals with the same cancer. The prevalence of cancers was higher among inbred populations and those with a high rate of consanguinity compared with noninbred populations. The authors postulate that this might be explained by particularly high frequencies of autozygosity involving regions that might harbor low-penetrance colorectal cancer susceptibility genes,² a conclusion similar to our results for different solid tumors and for noninbred populations.

It is very plausible that regions of homozygosity (or autozygosity) can harbor either low-penetrance disease-susceptibility genes or low-penetrance disease-protection genes. Because of the way we defined phenotype and the generally poor long-term follow-up of true-normal controls, it was easier to uncover disease-susceptibility genes compared with disease-protection genes. However, depending on the study design and populations used, finding both low-penetrance disease-susceptibility genes and disease-protection genes should be possible.

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CORRECTIONS

Incorrect Numbers in Table: In the Original Contribution entitled "Effect of Homocysteine Lowering on Mortality and Vascular Disease in Advanced Chronic Kidney Disease and End-stage Renal Disease: A Randomized Controlled Trial" published in the September 12, 2007, issue of *JAMA* (2007;298[10]:1163-1170), a row of data was erroneously calculated in Table 4. For the secondary outcome of thrombosis in hemodialysis patients (final row of the table), the denominator should have been (n=1208), which reflects only those patients who received hemodialysis in the study (618 in the vitamin group and 590 in the placebo group). The corresponding hazard ratio should have been 1.00 (95% confidence interval, 0.80-1.24; P=.96). The effect of treatment remained nonsignificant.

Incorrect Word: In the Editorial entitled "Improving Hypertension Control Rates: Technology, People, or Systems?" published in the June 25, 2008, issue of *JAMA* (2008;299[24]:2896-2898), a number was incorrectly reported as million. On page 2896, in the second sentence, the sentence should read "By 2025, it is predicted that more than 1.5 billion individuals worldwide will have hypertension, accounting for up to 50% of heart disease risk and 75% of stroke risk."¹² This article was corrected online for typographical errors on June 24, 2008.

Incorrect Data Analysis: In the Original Contribution entitled "Association of Preterm Birth With Long-term Survival, Reproduction, and Next-Generation Preterm Birth" published in the March 26, 2008, issue of *JAMA* (2008;299[12]:1429-1436), an error occurred in the statistical programming syntax of the analysis of reproduction. A subgroup of individuals who did not survive to age 18 years had been included in the denominator when calculating the propor-

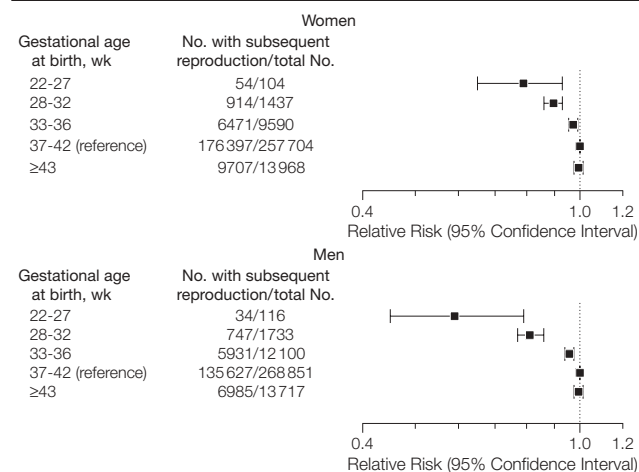
tions who reproduced. Therefore, the reported values for the percentages who reproduced and the associated unadjusted and adjusted relative risks and confidence intervals for the 22- to 27-week and 28- to 32-week gestational age categories were incorrect. The corrected analysis does not alter the statistically significant findings of reduced reproduction among women and men born preterm.

In the Results section of the abstract on page 1429, the eighth sentence should have read as follows: "For men and women born at 22 to 27 weeks, absolute reproduction was 29.3% and 51.9%, with RRs of 0.59 (95% CI, 0.45-0.79) and 0.78 (95% CI, 0.65-0.93), respectively. For 28 to 32 weeks, absolute reproduction was 43.1% and 63.6% for men and women, with RRs of 0.81 (95% CI, 0.77-0.86) and 0.89 (95% CI, 0.86-0.93), respectively."

In addition, the first sentence of the first paragraph of the section entitled "Educational and Reproductive Outcomes According to Gestational Age at Birth" on page 1431 should have read as follows: "With truncation of the cohort and follow-up through 2004, 282 803 female and 296 517 male survivors remained in the cohort." The third and fourth sentences of the second paragraph should have read as follows: "With regard to reproduction, only 51.9% of women who had been born at 22 to 27 weeks had subsequently reproduced in contrast to approximately 68% of women born at term. Similar findings were noted for index men, with reproductive rates of 29.3% and 50.4% for men who had been born at 22 to 27 weeks and at term, respectively."

The corrected **FIGURE 2** and the corrected relevant data from **TABLE 3** appear here.

Figure 2. Reproduction by Gestational Age at Birth for Women and Men Born in 1967-1976



Error bars indicate 95% confidence intervals.

Table 3. Educational and Reproductive Outcomes for Index Participants Born in 1967-1976 by Sex and Gestational Age

| Outcomes | Gestational Age, wk | | | | |
|-----------------------------------|---------------------|------------------|------------------|---------------|------------------|
| | 22-27 | 28-32 | 33-36 | 37-42 | ≥43 |
| Women (n = 282 803) | n = 104 | n = 1437 | n = 9590 | n = 257 704 | n = 13 968 |
| Individuals who reproduced, % | 51.9 | 63.6 | 67.5 | 68.4 | 69.5 |
| RR (95% CI) | 0.76 (0.63-0.91) | 0.92 (0.88-0.95) | 0.98 (0.97-0.99) | 1 [Reference] | 1.02 (1.00-1.03) |
| Adjusted RR (95% CI) ^a | 0.78 (0.65-0.93) | 0.89 (0.86-0.93) | 0.98 (0.96-0.99) | 1 [Reference] | 1.00 (0.99-1.01) |
| Men (n = 296 517) | n = 116 | n = 1733 | n = 12 100 | n = 268 851 | n = 13 717 |
| Individuals who reproduced, % | 29.3 | 43.1 | 49.0 | 50.4 | 50.9 |
| RR (95% CI) | 0.57 (0.43-0.77) | 0.83 (0.78-0.88) | 0.97 (0.95-0.99) | 1 [Reference] | 1.01 (0.99-1.03) |
| Adjusted RR (95% CI) ^a | 0.59 (0.45-0.79) | 0.81 (0.77-0.86) | 0.96 (0.94-0.97) | 1 [Reference] | 0.99 (0.98-1.01) |

Abbreviations: CI, confidence interval; RR, relative risk.

^aRelative risk models are adjusted for year of birth, maternal age, maternal education, and infant sex, with all factors treated as categorical predictors and additional adjustment for maternal education in index participants for next-generation/offspring birth outcomes.