Premature Adult Death in Individuals Born Preterm: A Sibling Comparison in a Prospective Nationwide Follow-Up Study

Kari R. Risnes1,2*, Kristine Pape3, Johan H. Bjørngaard2,3, Dag Moster4,5,6, Michael B. Bracken7, Pal R. Romundstad2

1 Department of Pediatrics, St Olav Hospital, University Hospital, Trondheim, Norway, 2 Institute of Public Health and General Practice, NTNU, Norwegian University of Science and Technology, Trondheim, Norway, 3 Forensic Department and Research Centre Brøset St. Olav’s University Hospital, Trondheim, Norway, 4 Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway, 5 Department of Pediatrics, Haukeland University Hospital, Bergen, Norway, 6 Norwegian Institute of Public Health, Oslo, Norway, 7 Schools of Public Health and Medicine, Yale University, New Haven, Connecticut, United States of America

* Kari.Risnes@ntnu.no

Abstract

Background
Close to one in ten individuals worldwide is born preterm, and it is important to understand patterns of long-term health and mortality in this group. This study assesses the relationship between gestational age at birth and early adult mortality both in a nationwide population and within sibships. The study adds to existing knowledge by addressing selected causes of death and by assessing the role of genetic and environmental factors shared by siblings.

Methods
Study population was all Norwegian men and women born from 1967 to 1997 followed using nation-wide registry linkage for mortality through 2011 when they were between 15 and 45 years of age. Analyses were performed within maternal sibships to reduce variation in unobserved genetic and environmental factors shared by siblings. Specific outcomes were all-cause mortality and mortality from cardiovascular diseases, cancer and external causes including accidents, suicides and drug abuse/overdoses.

Results
Compared with a sibling born in week 37–41, preterm siblings born before 34 weeks gestation had 50% increased mortality from all causes (adjusted Hazard Ratio (aHR) 1.54, 95% confidence interval (CI) 1.17, 2.03). The corresponding estimate for the entire population was 1.27 (95% CI 1.09, 1.47). The majority of deaths (65%) were from external causes and the corresponding risk estimates for these deaths were 1.52 (95% CI 1.08, 2.14) in the sibships and 1.20 (95% CI 1.01, 1.43) in the population.
Conclusion
Preterm birth before week 34 was associated with increased mortality between 15 and 45 years of age. The results suggest that increased premature adult mortality in this group is related to external causes of death and that the increased risks are unlikely to be explained by factors shared by siblings.

Background
Modern neonatal intensive care and prenatal maternal corticosteroids were introduced in the late 1960s and considerably improved neonatal survival of preterm infants [1, 2]. Survivors of early neonatal intensive care are now reaching middle age and may be at risk for chronic disease and premature death.

Preterm birth has been consistently associated with reduced long-term cognitive function, as well as poor psychiatric[3, 4] and social well-being [2, 5]. Studies have reported adverse cardiovascular risk patterns in individuals born preterm, but increased cardiovascular disease has not been well documented[6–9]. Higher cancer risk after preterm birth has been indicated in some studies[10, 11] and preterm birth has been associated with increased all-cause mortality in young adulthood in a large Swedish population based study [12]. A weakness with many studies assessing long-term outcomes related to preterm birth has been a lack of data that can disentangle possible confounding by maternal and socioeconomic factors related to both risk of preterm birth and unfavourable adult social and health-related outcomes[2, 6, 12].

The main objective of this study was to study the association between preterm gestational age at birth and all-cause and cause-specific mortality in young adulthood, specifically mortality from external causes, cardiovascular diseases and cancer. We address potential residual confounding by comparing associations in the population cohort with associations within maternal sibships. We hypothesized that the associations between gestational age and mortality would remain when assessed within sibships, to indicate that genetic and environmental factors shared by siblings are unlikely to explain observed associations.

Methods
Study cohorts
Norwegian men and women born between 1967 and 1997 were followed for all-cause and cause specific mortality through 2011 when they were between 15 and 45 years of age. Only individuals with information on gestational age, with a gestational age recorded at 23 weeks through 44 weeks, and who were alive and residing in Norway at the age of 15 years were eligible. Eligible individuals were identified through the Medical Birth Registry of Norway (MBRN) which comprises compulsory registration of all births in the country from 1967.

Linkage to the Cause of Death Registry at Statistics Norway (CDRN), was ascertained by the 11-digit identification number allocated to all Norwegian residents. Linkage between siblings with the same mother was performed using the mother’s identification number. We identified two cohorts for analysis: 1) the population cohort consisted of the population as a whole, and 2) a sibling cohort consisting of all individuals identified in a family having at least two maternal siblings at least one of whom having died during follow-up.
Variables

The exposure of interest was completed weeks of gestation according to the first day of the mother’s last menstrual period, as in previous publications from the cohort[2, 13]. Gestational age was assessed by a continuous measure (completed weeks) and grouped as: very preterm (23 to 33 weeks + 6 days), late preterm (34 to 36 weeks + 6 days), term (37 to 41 weeks + 6 days) and post-term (42 to 44 weeks + 6 days). An extremely preterm group (23 to 27 weeks + 6 days) was further identified. The choice of gestational age <34 weeks as a main exposure category was based on several considerations: infants born <34 weeks share factors related to biologic vulnerability including susceptibility to infections and preterm lung disease. Moreover, this group particularly benefited from antenatal corticosteroids introduced in the early 70s [14] that substantially reduced neonatal mortality[2, 15]. Survival of extreme preterms (<28 weeks) was very low until the late 70s[2] and the present study included too few individuals in the extreme preterm group to reach robust conclusions. Information about the mother at time of birth was abstracted from MBRN and categorized: maternal age (<24, 25–29, 30–35, >35 years), parity (0, 1, 2, >3), length of education at child’s birth (0–2, 3–5, 6–8 years of education after high school). Offspring’s sex, multiple versus singleton birth and birth cohort (1967–1976, 1977–1986, and 1987–1997) were evaluated. Gestational age and sex-specific birth weight SD-scores were calculated as an indicator of gestational age related birth weight and as a proxy indicator of intrauterine growth. SD scores were created by subtracting the reference mean value of birth weight within each sex and gestational week stratum from the observed value [16], divided by the stratum specific standard deviation. Individuals with birth weight more than 6 SD below or above the mean birth weight for gestational age were excluded from the analyses.

Information on congenital malformations in the offspring was abstracted from the MBRN, and classified according to International Classification of Diseases, Eighth and Tenth Editions (ICD8and 10) as 740–759 (ICD8) and Q00-99 (ICD10).

Mortality Outcomes in Adults

Individuals alive and living in the country by 15 years of age were individually linked to mortality and emigration information from the CDRN. Cause of death is determined by the doctor who examined the individual after death usually supported by previous patient history or autopsy. To ensure completeness, CDRN is cross linked to updated vital status recorded by the National Population Register. Follow-up for mortality started January 1981 at a minimum of 15 years of age and ended December 31st 2011, at a maximum of 45 years of age. Cause of death was classified according to the International Classification of Disease (ICD), 8th through 10th editions: External Causes includes accidents/violence, suicide and substance-abuse/overdose (ICD 8/9: E800-999, ICD 10: V01-Y98), Cancer (including all neoplasms, 140–239, C00-D48) and Diseases of the Circulatory System (CVD, 390–459, I00-I99). Specific external causes of death studied were: accidents excluding poisonings (E800-E929, V01-X39, X50-59), suicide/intentional self-harm (E950-E959, X60-X84 Y87.0), accidental poisoning/substance abuse/overdose (303–305, F10-F19 X40-49). The study was approved by the Regional Committee for Medical Research Ethics in Southern and Eastern Norway (2012/188).

Statistical methods

We used the Cox proportional hazards model to calculate hazard ratios (HR) for all cause and cause specific mortality according to gestational age. The proportional hazards assumption was tested graphically and by the use of Schoenfeld residuals. Basic models were age-adjusted using attained age as the time variable. Adjusted models included maternal age, parity, length of
education, offspring sex, plurality and birth cohort. Potential confounding by intrauterine
growth was addressed by adjusting for the SD score of birth weight for gestational age in a sepa-
rate model and by sensitivity analyses excluding individuals with an SD score < three SD. Pos-
sible effects of congenital malformations or multiple pregnancy were evaluated by excluding
individuals with these conditions in separate sensitivity analyses. In supplementary analyses,
we explored a possible dose-response effect of the degree of preterm birth by further categori-
zation of the <34 preterm group into extremely preterm (23 to 27 weeks + 6days) and very pre-
term (28 to 33 weeks + 6days). We evaluated potential effect modification owed to sex and
birth order by including a product term between gestational age and sex/birth order, tested by
a likelihood ratio test. Estimates precision was assessed by 95% confidence intervals (CI). In
regression models, with weeks of gestation as a continuous variable, we calculated two-sided P-
values from trend tests for the linear effects of gestational age; non-linear associations were
tested by adding a quadratic term in the regression model and using a likelihood ratio test. To
account for non-linear effects, we used restricted cubic splines with three knots in the graphical
presentations of the associations. For the graphical presentations the estimates for predictions
were calculated relative to gestational age 40 weeks (reference value with HR = 1.00). The sib-
ling analyses estimated associations within maternal sibships in stratified cox models with
mother's identification number defining each stratum. Analyses were adjusted for maternal
age, parity, offspring sex, plurality and birth cohort. These analyses use information only from
sibships discordant for outcome status (death) and exposure (gestational age). Sibling analyses
take advantage of the fact that siblings share many background factors that could potentially
confound the associations between gestational age and mortality. Performing analyses within
sibships is one approach to handling residual confounding from unobserved family-level con-
founders, including shared genetic and environmental factors[17] [18].

All statistical analyses and graphs were conducted using Stata for Windows (Version 12/13
StataCorp LP, 1985–2007).

Results
Cohort analysis
Among 1,727,494 individuals born in Norway from 1967 through 1996, 22,004 died before
their 15th birthday and another 15,841 were not registered as residents of Norway at the begin-
ning of follow-up at 15 years of age. After excluding individuals with missing information
1,562,647 were included in the population cohort (S1 Fig). Among 1,245,318 individuals (80%)
registered with at least one maternal sibling, we identified 29,536 individuals who belonged to
one of 11,316 maternal sibling groups in which at least one sibling died. Characteristics of the
population and sibling cohorts are presented in Table 1. The sibling cohort included a larger
proportion of males and a larger proportion of participants born in the earliest birth cohorts
compared to the population cohort.

Mortality
At follow-up 14,919 individuals had died (11,570 in the sibling cohort) and nearly two thirds
were from External Causes. Associations for all-cause mortality and for mortality from three
main causes of death (External Causes, Cancer and CVD) are shown in Table 2 and illustrated
in Fig 1. All-cause mortality was increased in individuals born before week 34 in the population
cohort (adjusted Hazard Ratio (aHR) 1.27, 95% confidence interval (CI) 1.09, 1.47). Findings
in the sibling cohort were similar. Thus, compared with a sibling born at term, preterm siblings
born in week 23 through 33 had 54% increased risk of mortality from all causes (aHR 1.54 95%
There was not strong evidence for increased mortality for the late preterm group (week 34 through 36).

The group born before 34 weeks’ gestation was at increased risk of death from External Causes in the population cohort (aHR 1.20, 95% CI 1.01, 1.43) and in the sibling cohort (aHR 1.52, 95% CI 1.08, 2.14). For death from neoplasms, there were few cases to yield precise estimates, although the effect estimates for the most preterm group were comparable to those for all-cause mortality. Mortality from CVD accounted for only 6% of all deaths and the analyses included a relatively low number of cases. We observed an inverse linear association between gestational age and CVD mortality in the population cohort, but these findings were not supported in the sibling cohort.

Associations between gestational age and specific groups of external causes (accidents/violence, suicide, and substance abuse/overdose) are shown in Table 3, and although some results lack power for robust conclusions, they indicate that shorter gestational age is associated with higher mortality from these three causes of death. In the sibling cohort, we found a two-fold increased risk of death due to accidents and violence for gestational age less than 34 weeks compared to term births. The corresponding result for suicide was similar, but a lower number of cases yielded a less precise estimate. The estimates for substance abuse related deaths were attenuated in the sibling analyses and do not support any association.

Table 1. Baseline characteristics of a nationwide population cohort and a sibling based study born in Norway 1967–1997.

| Category                        | Population a, N = 1,562,647 | Siblings b, N = 29,536 |
|---------------------------------|-------------------------------|------------------------|
| Categories of gestation         | 23–33 w+6d                   | 34-36w+6d              |
| Number of participants (%)      | 19,597 (1)                   | 350 (1)                |
| Length of gestation, weeks (SD) | 31(2)                        | 31 (2)                 |
| Birth weight, g (SD)            | 1,850 (689)                  | 2,012 (730)            |
| Female sex (%)                  | 8,914 (45)                   | 37 (39)                |
| Non-singleton births (%)        | 2,335 (12)                   | 39 (11)                |
| Born 1967–76 (%)                | 6,097 (1)                    | 172 (11)               |
| Born 1977–86 (%)                | 5,242 (1)                    | 115 (1)                |
| Born 1987–97 (%)                | 8,258 (2)                    | 63 (1)                 |
| Maternal age, no (%)            |                               |                        |
| <24y                            | 7,460 (38)                   | 153 (44)               |
| 25-29y                          | 6,109 (31)                   | 84 (24)                |
| 30-35y                          | 3,973 (20)                   | 79 (22)                |
| ≥35y                           | 2,055 (11)                   | 34 (10)                |
| Maternal education, no (%)      |                               |                        |
| 0-2y                            | 13,164 (67)                  | 218 (62)               |
| 3–5 y                           | 5,612 (29)                   | 118 (34)               |
| ≥6 y                            | 821 (4)                      | 14 (4)                 |
| Maternal parity, no (%)         |                               |                        |
| 0                               | 9,749 (50)                   | 118 (34)               |
| 1                               | 5,454 (28)                   | 106 (30)               |
| ≥3                              | 2,794 (14)                   | 69 (20)                |

a Norwegians born 1967–1997 who were living in the country and alive at 15 years of age and could be followed for mortality

b Maternal siblings belonging to a sibling group in which at least one member died during follow-up

Percentages may not sum to 100 after rounding to nearest whole number

doi:10.1371/journal.pone.0165051.t001
Table 2. Mortality and gestational age by cause of death. Nation-wide cohort born in Norway 1967–1997.

| Cause of death\(^a\) / Length of gestation Weeks (w)+days (d) | Population\(^a\) N = 1,562,647 | Siblings\(^b\) N = 29,536 |
|-------------------------------------------------------------|---------------------------------|---------------------------|
|                                                             | Deaths (N) HR \(^c\) 95% CI \(^c\) P trend | Deaths (N) HR \(^b\) 95% CI \(^b\) P trend |
| All causes of death                                          |                                 |                           |
| 22–33 w+6d                                                  | 213 1.27 1.09, 1.47             | 158 1.54 1.17, 2.03       |
| 34–36 w+6d                                                  | 635 1.11 1.02, 1.20             | 488 1.00 0.86, 1.16       |
| 37–41 w+6d                                                  | 11,866 Ref                      | 9,187 Ref                 |
| > = 42 w+0d                                                 | 2,205 1.08 1.03, 1.13           | 1,737 1.08 1.00, 1.18     |
| P trend-linear \(^d\) /quadratic \(^e\)                     | 14,919 0.04/<0.001              | 11,570 0.2/0.001          |
| External causes of death\(^f\)                              |                                 |                           |
| 22–33 w+6d                                                  | 135 1.20 1.01, 1.43             | 98 1.52 1.08, 2.14        |
| 34–36 w+6d                                                  | 417 1.09 0.99, 1.21             | 320 0.94 0.78, 1.13       |
| 37–41 w+6d                                                  | 7,793 Ref                       | 6,119 Ref                 |
| > = 42 w+0d                                                 | 1,456 1.08 1.03, 1.14           | 1,154 1.03 0.93, 1.15     |
| P trend-linear \(^e\) /quadratic \(^e\)                     | 9,744 0.7/<0.001                | 7,691 0.2/0.07            |
| Cancer\(^f\)                                                |                                 |                           |
| 22–33 w+6d                                                  | 25 1.30 0.97, 1.93              | 22 1.52 0.64, 3.67        |
| 34–36 w+6d                                                  | 58 0.86 0.66, 1.13              | 43 0.77 0.47, 1.27        |
| 37–41 w+6d                                                  | 1,472 Ref                       | 1,113 Ref                 |
| > = 42 w+0d                                                 | 282 1.12 0.98, 1.27             | 217 1.13 0.88, 1.43       |
| P trend-linear \(^e\) /quadratic \(^e\)                     | 1,837 0.2/0.4                   | 1,373 0.3/0.2             |
| Cardiovascular Diseases\(^f\)                               |                                 |                           |
| 22–33 w+6d                                                  | 15 1.58 0.94, 2.64              | 8 1.01 0.29, 3.55         |
| 33–36 w+6d                                                  | 39 1.18 0.85, 1.64              | 29 1.31 0.68, 2.52        |
| 37–41 w+6d                                                  | 674 Ref                         | 499 Ref                   |
| > = 42 w+0d                                                 | 105 0.90 0.73, 1.11             | 79 1.01 0.70, 1.46        |
| P trend-linear \(^e\) /quadratic \(^e\)                     | 833 0.01/1.01                   | 615 0.8/0.9               |

HR: Hazard ratio, CI: Confidence Interval

\(^a\) Norwegians born 1967–1997 who were living in the country and alive at 15 years of age and could be followed for mortality

\(^b\) Maternal siblings belonging to a sibling group in which at least one member died during follow-up

\(^c\) Adjusted for sex, birth cohort (1967–1976, 1977–1986, and 1987–1997), maternal age (<24, 25–29, 30–35, ≥35 years), maternal parity (0, 1, 2, ≥3), maternal education (0–2, 3–5, 6–8 years of education after high school), singleton born (y/n)

\(^d\) P linear: value for linear association across weeks of completed gestational age.

\(^e\) P quadratic: non-linear associations, tested by using a likelihood ratio test, by adding a quadratic term in the regression model.

\(^f\) Cause of death (ICD10 and ICD9 codes): External causes (V01-Y89 and E800-E999, included drug/alcohol-related deaths F10-19, 303–305); Cancer (C00-D48, 140–239); Cardiovascular Diseases (I00-I99, 390–459)

doi:10.1371/journal.pone.0165051.t002

Supplementary analyses

Exclusion of individuals born after a multiple pregnancy, with a neonatal diagnosis of congenital malformations, a SD score for birthweight higher than three, or adjustment for birth weight for gestational age (data not shown), did not meaningfully alter the estimates. Since we found limited evidence for effect modification by sex (p-value 0.3), we performed combined analyses of men and women, and included sex as a co-variable in the regression analyses. There was weak evidence of effect modification by birth order (p-value 0.1). An observed tendency of non-proportional hazards for gestational age and mortality was accounted for by performing separate analyses stratified by age during follow-up (Table 4). There was some evidence that risk estimates for overall mortality and mortality from external causes increased by increasing age at death. The adjusted HR for all-cause mortality after 35 years of age for the group with
gestational age 33 weeks or less, compared to those born at term, was 1.60 (95% CI 1.18, 2.17) in the population cohort. The corresponding estimate for External Causes of death was 2.22 (95% CI 1.50, 3.29). Supplementary analyses indicated a dose-response relationship with higher estimates for the lowest category (<28 weeks) (Table A in S1 File and Table B in S1 File), but these analyses lack power for any robust conclusions.

Discussion

In this complete nation-wide follow-up of 1.5 million adults, shorter length of gestation was associated with higher mortality in early adulthood and the risk estimate was particularly high for external causes of deaths after 35 years of age. The main findings were robust in sibship analyses that control for environmental and genetic factors shared between siblings with same mother.

Comparison with other studies

Mortality. Many historical cohort studies have reported that lower birth weight is associated with increased adult mortality[19]. However, birth weight is strongly related to both gestational age at birth, as well as maternal genetic and socioeconomic factors that may affect intrauterine growth. The separate roles of gestational age and family factors were only partly disentangled in previous mortality studies[19]. However, a recent sibling analyses on Swedish data concluded that shared family factors could not explain increased mortality in individuals born with lower birth weights [20]. A recent study assessed mortality related to small for gestational age status and concluded that individuals born SGA were at increased mortality risk in childhood, but not after 30 years of age[21]. Thus, these two studies may support a conclusion
that neither family factors nor intrauterine growth restriction can explain increased long-term mortality in individuals born small.

Some recent studies [13, 18, 22] report an increased long-term mortality risk related to preterm birth, but in less detail on mortality causes and with shorter follow-up than the present study.

Using data from The Swedish Medical Birth Registry, Crump and co-workers [22] showed that increased overall mortality related to preterm birth was strong in childhood, tended to disappear in adolescents (13–17 years) and reappeared in young adulthood (18–36 years). The same Swedish data was recently re-analysed [18], and the sibling analyses showed no attenuation of the inverse association between gestational age and overall mortality between 1 and 36 years of age. Although childhood mortality was the main contributor to overall mortality in that study, the conclusion supports our finding that the association between gestational age and long-term all-cause mortality is robust to confounders shared by siblings.

Mental illness, social function and cognition. Susceptibility to mental illness, including attention problems and factors related to cognitive skills and social well-being, could possibly explain some of the observed increased risk of deaths from external causes of death in the present study. Large Scandinavian register-based data analyses have found associations between

---

Table 3. Mortality and gestational age by external cause of death. Nation-wide cohort born in Norway 1967–1997.

| Cause of death / Length of gestation (w)+days (d) | Population ^aN = 1,562,647 | Siblings ^bN = 29,536 |
|-------------------------------------------------|-----------------------------|------------------------|
|                                                 | Deaths (N) HR ^c 95% CI ^c P trend | Deaths (N) HR ^c 95% CI ^c P trend |
|-------|---------------------------------|-----------------|-----------------|
| Accidents and violence ^f | | | |
| 22–33 w+6d | 56 | 1.20 | 0.92, 1.57 | 43 | 1.87 | 1.12, 3.10 |
| 34–36 w+6d | 161 | 1.02 | 0.87, 1.19 | 146 | 1.03 | 0.77, 1.38 |
| 37–41 w+6d | 3,204 | Ref | | 2,538 | Ref | |
| = 42 w+0d | 554 | 1.00 | 0.92, 1.10 | 443 | 0.90 | 0.77, 1.07 |
| P trend-linear ^d /quadratic ^e | 3,975 | 0.70/0.08 | 3,154 | 0.007/0.04 |
| Suicide ^f | | | |
| 22–33 w+6d | 42 | 1.16 | 0.85, 1.57 | 28 | 1.96 | 0.97, 3.98 |
| 34–36 w+6d | 142 | 1.14 | 0.96, 1.35 | 112 | 1.08 | 0.78, 1.49 |
| 37–41 w+6d | 2,587 | Ref | | 2,054 | Ref | |
| = 42 w+0d | 503 | 1.14 | 1.04, 1.26 | 397 | 1.05 | 0.88, 1.26 |
| P trend-linear ^d /quadratic ^e | 3,274 | 1.0/ 0.006 | 2,591 | 0.5/0.002 |
| Substance abuse/overdose ^f | | | |
| 22–33 w+6d | 31 | 1.22 | 0.87, 1.75 | 24 | 1.07 | 0.55, 2.01 |
| 34–36 w+6d | 104 | 1.21 | 0.99, 1.48 | 69 | 0.65 | 0.44, 0.97 |
| 37–41 w+6d | 1,745 | Ref | | 1,322 | Ref | |
| = 42 w+0d | 347 | 1.13 | 1.00, 1.26 | 278 | 1.15 | 0.92, 1.44 |
| P trend-linear ^d /quadratic ^e | 2,227 | 0.6/0.3 | 1,693 | 0.3/ 0.6 |

HR: Hazard ratio, CI: Confidence Interval
^a Norwegians born 1967–1997 who were living in the country and alive at 15 years of age and could be followed for mortality
^b Maternal siblings belonging to a sibling group in which at least one member died during follow-up
^c Adjusted for sex, birth cohort (1967–1976, 1977–1986, and 1987–1997), maternal age (<24, 25–29, 30–35, ≥35 years), maternal parity (0, 1, 2, ≥3), maternal education (0–2, 3–5, 6–8 years of education after high school), singleton born (y/n)
^d P linear: value for linear association across weeks of completed gestational age
^e P quadratic: non-linear associations, tested by using a likelihood ratio test, by adding a quadratic term in the regression model
^f Cause of death (ICD10 and ICD9 codes): Accidents and violence (V01-X39, X50-59, Y85-86, E800-E929), Suicide (X60-X84, Y87.0, E950-E959), Substance abuse/overdoses (F10-F19 X40-49, 303–305)

doi:10.1371/journal.pone.0165051.003
preterm birth and a wide range of educational, social, cognitive and mental health outcomes in adolescence and young adulthood [2–4, 18, 23–27]. However, a causal relationship between preterm birth and cognition was recently questioned in a Swedish analysis which showed that the effect of preterm birth (<30 weeks) on low school grades attenuated in sibling analyses [28].

Overall, outcomes related to mental and social well-being have been well described in adolescents born preterm, but is less well documented in adults. Some studies suggest increasing risk of psychopathology and cognitive problems as children born preterm reach middle-age [29–31], supporting our findings of particularly high risk in the 35–45 year group. In the present analyses, we observed a tendency of increased suicide risk in individuals born preterm and a causal relationship may be supported by the observed high risk estimates for suicide in the preterm group in the sibling comparison. In contrast to this finding, sibling analyses on preterm birth and suicide attempts in Swedish data did not support a causal relationship [18]. An explanation for this discrepancy might be that our analyses included only completed suicides and other mechanisms may apply to suicide attempts.

Cardiovascular risk and disease. Our results do not support a robust association between preterm gestational age and early adult cardiovascular mortality, although increased risk estimates for CVD death was observed for deaths after 20 years of age. However, firm conclusions are hampered by low number of cardiovascular deaths, possibly explained by the still relatively

---

Table 4. Mortality and gestational age by cause of death. Nation-wide cohort born in Norway 1967–1997. Analyses stratified by age at death.

| Cause of death | Age 15–25 | Age 25–35 | Age 35–45 |
|----------------|-----------|-----------|-----------|
| All causes     | HR a population | HR a siblings b | HR a population | HR a siblings b | HR a population | HR a siblings b |
| 22–33 weeks+6days | 1.13 (0.91, 1.39) | 1.45 (0.99, 2.13) | 1.32 (1.05, 1.65) | 1.58 (1.01, 2.45) | 1.60 (1.18, 2.17) | 1.99 (0.81, 4.93) |
| 34–36 weeks+6days | 1.08 (0.95, 1.21) | 1.02 (0.83, 1.25) | 1.05 (0.92, 1.21) | 0.99 (0.77, 1.28) | 1.32 (1.10, 1.58) | 0.94 (0.62, 1.43) |
| 37–41 weeks+6days | > = 42 weeks | 1.09 (1.02, 1.17) | 1.06 (0.95, 1.19) | 1.10 (1.02, 1.19) | 1.16 (1.01, 1.33) | 1.00 (0.89, 1.12) | 0.99 (0.75, 1.29) |
| Cancer         | HR a population | HR a siblings b | HR a population | HR a siblings b | HR a population | HR a siblings b |
| 22–33 weeks+6days | 0.98 (0.44, 2.21) | 2.74 (0.58, 12.90) | 1.55 (0.85, 2.83) | 1.35 (0.40, 4.59) | 1.33 (0.66, 2.45) | 0.46 (0.04, 5.76) |
| 34–36 weeks+6days | 1.12 (0.73, 1.70) | 1.37 (0.61, 3.05) | 0.69 (0.42, 1.12) | 0.40 (0.17, 0.99) | 0.83 (0.52, 1.33) | 1.04 (0.32, 3.40) |
| 37–41 weeks+6days | > = 42 weeks | 1.01 (0.80, 1.29) | 1.03 (0.69, 1.52) | 1.24 (1.01, 1.52) | 1.22 (0.82, 1.81) | 1.08 (0.86, 1.35) | 1.15 (0.68, 1.94) |
| External Causes | HR a population | HR a siblings b | HR a population | HR a siblings b | HR a population | HR a siblings b |
| 22–33 weeks+6days | 1.07 (0.83, 1.37) | 1.29 (0.81, 2.03) | 1.11 (0.82, 1.49) | 1.51 (0.86, 2.67) | 1.33 (0.66, 2.45) | 0.46 (0.04, 5.76) |
| 34–36 weeks+6days | 1.01 (0.88, 1.17) | 0.91 (0.71, 1.16) | 1.04 (0.88, 1.22) | 1.08 (0.78, 1.50) | 1.66 (1.29, 2.12) | 0.75 (0.41, 1.34) |
| 37–41 weeks+6days | > = 42 weeks | 1.11 (1.02, 1.20) | 1.03 (0.90, 1.18) | 1.06 (0.97, 1.16) | 1.06 (0.89, 1.27) | 1.08 (0.91, 1.29) | 0.92 (0.59, 1.45) |
| Cardiovascular (833) | HR a population | HR a siblings b | HR a population | HR a siblings b | HR a population | HR a siblings b |
| 22–33 weeks+6days | 0.37 (0.05, 2.66) | 2.93 (1.50, 5.72) | 2.47 (0.46, 13.15) | 1.31 (0.54, 3.18) | 3.10 (0.14, 70.32) | 0.87 (0.56, 1.36) |
| 34–36 weeks+6days | 1.05 (0.53, 2.07) | 1.34 (0.27, 6.62) | 1.56 (0.95, 2.56) | 1.39 (0.49, 3.93) | 0.95 (0.54, 1.66) | 1.30 (0.33, 5.08) |
| 37–41 weeks+6days | > = 42 weeks | 0.90 (0.59, 1.36) | 0.95 (0.51, 1.77) | 1.06 (0.76, 1.46) | 1.56 (0.86, 2.84) | 0.77 (0.54, 1.09) | 0.65 (0.28, 1.52) |

HR: Hazard ratio, CI: Confidence Interval

a Maternal siblings belonging to a sibling group in which at least one member died during follow-up
b Adjusted for sex, birth cohort (3), maternal age (<24, 25–29, 30–35, ≥35 years), maternal parity (0, 1, 2, ≥3), maternal education (0–2, 3–5, 6–8 years of education after high school), singleton (y/n)
c Cause of death (ICD10 and ICD9 codes): Accidents and violence (V01-X39, X50-59, Y85-86, E800-E929), Suicide (X60-X84, Y87.0, E950-E959), Substance abuse/overdoses (F10-F19 X40-49, 303–305)

doi:10.1371/journal.pone.0165051.t004
young age of this cohort. Our findings of a possible attenuation of risk estimates for CVD deaths in the sibling study compared to in the population cohort could indicate that increased CVD risk after preterm birth is confounded by family factors. This interpretation may be supported by a Swedish follow-up study[32] that reported that mothers who had previously given preterm birth themselves had increased CVD mortality later in life, suggestive of genetic factors linked to preterm labour and later CVD. Cardiovascular and metabolic long-term outcomes after preterm birth have been extensively studied and debated. In a recent meta-analysis [8] the authors concluded that preterm birth was not associated with unfavourable metabolic outcomes in adulthood (mean 20–30 years) although the analysis reported higher blood pressure in adults born preterm. In contrast, a Finnish follow-up study found preterm birth associated with higher fat percentage and risk of metabolic syndrome in young adults[33]. Previous studies did not indicate robust associations of preterm birth with ischemic heart disease in historic cohorts that were limited by low precision in gestational age assessments[34–37]. More recent cohorts support these findings[9, 38], although studies are limited by a low number of cases of ischemic heart disease at these relatively young adult ages. For adult cerebrovascular diseases, studies indicate an increased risk in adults born preterm[9, 34, 35]. In our study, there were too few cardiovascular deaths to robustly evaluate deaths due to specific cardiovascular diagnoses.

**Weaknesses and strengths**

The present results were based on a large population based study with almost complete follow-up. De-identified information on exposure, outcome and cofactors were abstracted and linked by high quality Norwegian national registries (NMBR: https://www.fhi.no/en/op/data-access-from-health-registries-health-studies-and-biobanks/medical-birth-registry-and-registry-of-pregnancy-termination/core-artic les and CDRN: https://www.fhi.no/en/hn/health-registries/cause-of-death-registry/)

Another important strength is that we could assess mortality within many sibships. We accounted for unobserved factors, shared between siblings, which could influence the risk of being born preterm and for premature mortality, such as educational and socioeconomic factors of the household and genetic variability. Although comparing differentially exposed siblings would take into account shared confounding, non-shared confounding and random measurement error can still bias the results of sibling analyses [39]. Furthermore, we cannot exclude the possibility that comparisons within families may be vulnerable to time-dependent factors that could influence preterm birth risk and the family environment. Differential effects on siblings (such as parental death or illness, divorce, unemployment, foster care, domestic violence) may have occurred at different stages of the siblings’ lives. The risk estimates from our analyses were typically higher in the sibling comparisons compared to the population sample. This could be due to the fact that the sibling comparisons may provide a better adjustment for rather subtle but potentially important factors for which information is usually not available. The within sibling analyses were restricted to sibships with discordant exposure, which might be vulnerable to selection bias and measurement error[20]. We would rather expect reduced estimates in case of non-differential measurement error, but we cannot rule out the possibility of selection bias from non-shared factors due to restriction on discordant exposure status. Sensitivity analyses limiting the sample to one-child families yielded similar estimates to those in families with more than one child and could therefore not explain the higher estimates in the sibling sample. Other studies have also shown higher magnitudes of estimates in sibling comparisons[20, 40].

The study included a high number of cases that makes chance an unlikely explanation for our main findings. However, the cohort is still relatively young and few have reached an age
when death from chronic diseases is prevalent. It is a shortcoming that we cannot draw strong conclusions for more specific categories of cause-specific adult deaths. In the present study we could only include a relatively low number of individuals born extremely preterm (gestational age <28 weeks) and our results do not allow specific conclusions for this group. Neonatal treatment and survival for individuals born preterm differs by time and place of birth\[2, 41\], and long-term outcomes may therefore be dependent on these factors. Our data did not permit studying possible birth cohort effects on long-term mortality. A longer follow-up time is needed to study adult mortality for the increasing number of survivors after extreme preterm birth, born in the post-surfactant era. Preterm birth rates in Norway increased by 25% from 1980–98\[42\], but are still low at 6.1% for 2015.\[2, 41\] Generalizability of long-term risk to other countries with higher prevalence of preterm births or different perinatal care may therefore be limited.

Specific causes of death, particularly the distinction between accidents and suicide, may be underreported. This would only bias our results if the underreporting was associated with gestational age at birth. The prospective design of the study makes such bias unlikely. It is a weakness that gestational age is assessed by last menstrual period and so may be more prone to misclassification than modern standards using ultrasound. However, sensitivity analyses that excluded extreme birth weights for gestational ages and analyses that adjusted for birth weight did not affect the results. Misclassification of gestational age is most likely to have led to a non-differential bias that would tend to attenuate associations.

Relevance

Distribution of causes of death in adolescents and young adults in the present study corresponds well with global data showing that injuries and self-harm are the main contributors to loss of life years in this age group\[43, 44\]. Thus, increased mortality risk from external causes in individuals born preterm has public health interest. The present findings should be interpreted with caution. Recent cohorts of preterm infants have higher neonatal survival and are exposed to changing medical treatments that may cause different long-term risk profiles from cohorts born three to four decades ago. We only included early adult deaths, and changing patterns of morbidity and mortality by age may produce different results with longer follow-up. Nevertheless, the results warrant close attention to risk assessment in young adults born preterm and to the importance of following cohorts of individuals born preterm as they age.

Supporting Information

S1 Fig. Establishment of cohort. Nation-wide cohort born in Norway 1967–1997. (TIF)

S1 File. Table A. Mortality and gestational age by cause of death. Nation-wide cohort born in Norway 1967–1997. Table B. Mortality and gestational age by external cause of death Nation-wide cohort born in Norway 1967–1997. (DOCX)

Author Contributions

Conceptualization: KR PRR MBB.

Formal analysis: KRR KP JHB.

Funding acquisition: KRR KP.
Investigation: KRR PRR.
Methodology: KR KP JHH PRR.
Project administration: KRR.
Validation: KRR KP.
Visualization: KRR KP.
Writing – original draft: KRR KP.
Writing – review & editing: KRR KP JHB MBB DM PRR.

References

1. Horwood SP, Boyle MH, Torrance GW, Sinclair JC. Mortality and morbidity of 500- to 1,499-gram birth weight infants live-born to residents of a defined geographic region before and after neonatal intensive care. Pediatrics. 1982; 69(5):613–20. PMID: 7079020
2. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. N Engl J Med. 2008; 359(3):262–73. doi: 10.1056/NEJMoa0706475 PMID: 18635431
3. Lindstrom K, Lindblad F, Hjern A. Preterm birth and attention-deficit/hyperactivity disorder in school-children. Pediatrics. 2011; 127(5):856–65. doi: 10.1542/peds.2010-1279 PMID: 21502231
4. Lindstrom K, Lindblad F, Hjern A. Psychiatric morbidity in adolescents and young adults born preterm: a Swedish national cohort study. Pediatrics. 2009; 123(1):e47–53. doi: 10.1542/peds.2008-1654 PMID: 19117846
5. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 2009; 124(2):717–28. doi: 10.1542/peds.2008-2816 PMID: 19651588
6. Hack M. Adult outcomes of preterm children. J Dev Behav Pediatr. 2009; 30(5):460–70. doi: 10.1097/DBP.0b013e3181ba0fba PMID: 19823140
7. Kajantie E, Hovi P. Is very preterm birth a risk factor for adult cardiometabolic disease? Seminars in fetal & neonatal medicine. 2014; 19(2):112–7. doi: 10.1016/j.siny.2013.11.006 PMID: 24332842
8. Parkinson JR, Hyde MJ, Gale C, Santhakumar S, Modi N. Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis. Pediatrics. 2013; 131(4):e1240–63. doi: 10.1542/peds.2012-1777 PMID: 23929172
9. Ueda P, Cnattingius S, Stephansson O, Ingelsson E, Ludvigsson JF, Bonamy AK. Cerebrovascular and ischemic heart disease in young adults born preterm: a population-based Swedish cohort study. European journal of epidemiology. 2014; 29(4):253–60. doi: 10.1007/s10654-014-9892-5 PMID: 24687624
10. Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Olausson PO. Cancer risk in children and young adults conceived by in vitro fertilization. Pediatrics. 2010; 126(2):270–6. doi: 10.1542/peds.2009-3225 PMID: 20643723
11. Ekborn A, Erlandsson G, Hsieh C, Trichopoulos D, Adami HO, Cnattingius S. Risk of breast cancer in prematurely born women. J Natl Cancer Inst. 2000; 92(10):840–1. PMID: 10814680
12. Crump C, Sundquist K, Sundquist J, Winkley MA. Gestational age at birth and mortality in young adulthood. JAMA: the journal of the American Medical Association. 2011; 306(11):1233–40. doi: 10.1001/jama.2011.1331 PMID: 21934056
13. Swamy GK, Ostbye T, Skjaerven R. Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth. JAMA: the journal of the American Medical Association. 2008; 299(12):1429–36. doi: 10.1001/jama.2008.1041 PMID: 18364485
14. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics. 1972; 50(4):515–25. PMID: 4561295
15. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. The Cochrane database of systematic reviews. 2006;(3):CD000454. doi: 10.1002/14651858.CD000454.pub2 PMID: 16856047
16. Skjaerven R, Gjesing HK, Bakkeiteig LS. Birthweight by gestational age in Norway. Acta obstetricia et gynecologica Scandinavica. 2000; 79(6):440–9. PMID: 10857867
17. Bjorngaard JH, Bjerkedset O, Vatten L, Janszky I, Gunnell D, Romundstad P. Maternal age at child birth, birth order, and suicide at a young age: a sibling comparison. American journal of epidemiology. 2013; 177(7):638–44. doi: 10.1093/aje/kwt014 PMID: 23479347

18. D’Onofrio BM, Class QA, Rickert ME, Larsson H, Langstrom N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. JAMA psychiatry. 2013; 70 (11):1231–40. doi: 10.1001/jamapsychiatry.2013.2107 PMID: 24068297

19. Risnes KR, Vatten LJ, Baker JL, Jameson K, Sovio U, Kajantie E, et al. Birthweight and mortality in adulthood: a systematic review and meta-analysis. International journal of epidemiology. 2011; 40 (3):647–61. doi: 10.1093/ije/dyq267 PMID: 21324938

20. Class QA, Rickert ME, Lichtenstein P, D’Onofrio BM. Birth weight, physical morbidity, and mortality: a population-based sibling-comparison study. American journal of epidemiology. 2014; 179(5):550–8. doi: 10.1093/aje/kwt304 PMID: 24355331

21. Wennerstrom EC, Simonsen J, Melbye M. Long-Term Survival of Individuals Born Small and Large for Gestational Age. PLoS One. 2015; 10(9):e0138594. doi: 10.1371/journal.pone.0138594 PMID: 26390219

22. Crump C, Sundquist K, Winkleby MA, Sundquist J. Early-term birth (37–38 weeks) and mortality in young adulthood. Epidemiology (Cambridge, Mass). 2013; 24(2):270–6. doi: 10.1097/EDE.0b013e318280da9 PMID: 23337240

23. Crump C, Winkleby MA, Sundquist K, Sundquist J. Preterm birth and psychiatric medication prescription in young adulthood: a Swedish national cohort study. International journal of epidemiology. 2010; 39(6):1522–30. doi: 10.1093/ije/dyq103 PMID: 20570995

24. Eide MG, Oyen N, Skjærven R, Bjerkedal T. Associations of birth size, gestational age, and adult size with intellectual performance: evidence from a cohort of Norwegian men. Pediatric research. 2007; 62 (5):636–42. doi: 10.1203/PDR.0b013e3181558669 PMID: 17805203

25. Ekeus C, Lindstrom K, Lindblad F, Rasmussen F, Hjern A. Preterm birth, social disadvantage, and cognitive competence in Swedish 18- to 19-year-old men. Pediatrics. 2012; 125(1):e67–73. doi: 10.1542/peds.2008-0017 PMID: 19969613

26. Lindstrom K, Winblad B, Haglund B, Hjern A. Preterm infants as young adults: a Swedish national cohort study. Pediatrics. 2007; 120(1):70–7. doi: 10.1542/peds.2006-3260 PMID: 17606563

27. Nosarti C, Reichenberg A, Murray RM, Cnattingius S, Lambe MP, Yin L, et al. Preterm birth and psychiatric disorders in young adult life. Archives of general psychiatry. 2012; 69(6):E1–8. doi: 10.1001/archgenpsychiatry.2011.1374 PMID: 22660967

28. Ahlsson F, Kaijser M, Adami J, Lundgren M, Palme M. School performance after preterm birth. Epidemiology (Cambridge, Mass). 2015; 26(1):106–11. doi: 10.1097/ede.0000000000000171 PMID: 25215531

29. Saigal S. Functional outcomes of very premature infants into adulthood. Seminars in fetal & neonatal medicine. 2014; 19(2):125–30. doi: 10.1016/j.y隋py.2013.11.001 PMID: 24289905

30. Boyle MH, Miskovic V, Van Lieshout R, Duncan L, Schmidt LA, Houlit L, et al. Psychopathology in young adults born at extremely low birth weight: Psychosocial development. Psychosomatic medicine. 2011; 41(8):1763–74. doi: 10.1017/s0033291710002357 PMID: 21134317

31. Lund LK, Vik T, Skrane S, Lydersen S, Brubakk AM, Indredavik MS. Low birth weight and psychiatric morbidity; stability and change between adolescence and young adulthood. Early human development. 2012; 88(8):623–9. doi: 10.1016/j.eahumdev.2012.01.006 PMID: 22325843

32. Bonamy AK, Parikh NI, Cnattingius S, Ludvigsson JF, Ingelsson E. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. Circulation. 2011; 124(25):2839–46. doi: 10.1161/circulationaha.111.034884 PMID: 22124377

33. Sipola-Leppanen M, Vaarasmaki M, Tikanmaki M, Matinlinna HM, Miettola S, Hovi P, et al. Cardiometabolic risk factors in young adults who were born preterm. American journal of epidemiology. 2015; 181 (11):861–73. doi: 10.1093/aje/kwu243 PMID: 25947956

34. Koupil I, Leon DA, Lithell HO. Length of gestation is associated with mortality from cerebrovascular disease. J Epidemiol Community Health. 2005; 59(6):473–4. 59/6/473 [pii] doi: 10.1136/jech.2004.026518 PMID: 15911642

35. Lawlor DA, Ronalds G, Clark H, Smith GD, Leon DA. Birth weight is inversely associated with incident coronary heart disease and stroke among individuals born in the 1950s: findings from the Aberdeen Children of the 1950s prospective cohort study. Circulation. 2005; 112(10):1414–8. doi: 10.1161/CIRCULATIONAHA.104.528356 PMID: 16129799

36. Kaijser M, Bonamy AK, Akre O, Cnattingius S, Granath F, Norman M, et al. Perinatal risk factors for ischemic heart disease: disentangling the roles of birth weight and preterm birth. Circulation. 2008; 117 (3):405–10. doi: 10.1161/circulationaha.107.710715 PMID: 18172034
37. Kajantie E, Osmond C, Eriksson JG. Coronary Heart Disease and Stroke in Adults Born Preterm—The Helsinki Birth Cohort Study. Paediatric and perinatal epidemiology. 2015; 29(6):515–9. doi: 10.1111/ppe.12219 PMID: 26250056

38. Zoller B, Sundquist J, Sundquist K, Crump C. Perinatal risk factors for premature ischaemic heart disease in a Swedish national cohort. BMJ open. 2015; 5(6):e007308. doi: 10.1136/bmjopen-2014-007308 PMID: 26038357

39. Frisell T, Oberg S, Kuja-Halkola R, Sjolander A. Sibling comparison designs: bias from non-shared confounders and measurement error. Epidemiology (Cambridge, Mass). 2012; 23(5):713–20. doi: 10.1097/EDE.0b013e31825fa230 PMID: 22781362

40. Bergvall N, Iliadou A, Tuovemo T, Cnattingius S. Birth characteristics and risk of high systolic blood pressure in early adulthood: socioeconomic factors and familial effects. Epidemiology (Cambridge, Mass). 2005; 16(5):635–40.

41. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ (Clinical research ed). 2012; 345:e7976. doi: 10.1136/bmj.e7976 PMID: 22422811

42. Thompson JM, Irgens LM, Rasmussen S, Daleveit AK. Secular trends in socio-economic status and the implications for preterm birth. Paediatric and perinatal epidemiology. 2006; 20(3):182–7. doi: 10.1111/j.1365-3016.2006.00711.x PMID: 16629692

43. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380(9859):2095–128. doi: 10.1016/s0140-6736(12)61728-0 PMID: 23245604

44. Murray CJ, Barber RM, Foreman KJ, Ozgoren AA, Abd-Allah F, Ahera SF, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. Lancet. 2015. doi: 10.1016/s0140-6736(15)61940-x