



Critically Appraised Article

## **Extremely premature children have lower long term survival, educational achievements, reproductive capacity and a higher incidence of prematurity**

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## Extremely premature children have lower long term survival, educational achievements, reproductive capacity and a higher incidence of prematurity

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### Structured abstract:

**Objective:** to determine the long term effect of prematurity on survival, reproduction and premature births in the following generations.

**Design:** population based study / historical cohort.

**Location:** community study, based on the Medical Birth Registry of Norway for births and deaths during the years 1967-1988.

**Study population:** the final study population was 1.167.506 participants (600.063 males and 567.413 females) with a gestational age  $\geq$  22 weeks or with a birth weight  $\geq$  than 500 grams.

**Risk factor evaluation:** the estimations on gestational age were based on the date of the last menstrual period and on clinical evaluation (until 1999) or by echography (after 1999). The participants were grouped by gender and gestational age in: extremely premature (22-27 WG), very premature (28-32 WG), premature (33-36 WG), at term (37-42 WG), and postterm ( $\geq$  43 WG).

**Outcome measures:** mortality rates were determined for foetal deaths, infant (< 1 year), early childhood (1-5.9 years), late childhood (6-12 years), and adolescence (13-17.9). Educational achievement was assessed as the proportion of those achieving less than a high school education and those receiving postcollege graduate education. The reproductive outcomes among the offspring of the participants were evaluated by means of premature births, foetal mortality and infant mortality. Relative risks were calculated (RR) with a confidence interval of 95% (CI 95%) adjusted by year of birth (1967-1971, 1972-1976, 1977-1981 and 1982-1998), maternal age (< 20, 20-24, 25-29, 30-34 and 35 years) and maternal education (inferior to high school, high school completed, and graduate education).

**Main outcome measures:** the percentage of premature children in the study cohort was 5.2 % (5.6% males and 4.7 % females). No association was found between prematurity and maternal or paternal age, but lower education and those who were unmarried were associated.

Prematurity is associated with a statistically significant increase in foetal mortality and in those infants whose age was < than 1 year, in males and females; the greater mortality in early childhood (age 1-5.9 years), late childhood (age 6-12.9 years), and adolescence (age 13-17.9 years) was only statistically significant in premature males (table 1). Premature children (males and females) also had a statistically significant reduction

in reproductive capacity. Premature females (but not the males) had themselves an increased number of premature births (table 2). Association has also been found with prematurity and lower educational achievements in adult age (table 2). The majority of these differences are especially important in the extremely premature (22-27 WG) and very premature (28-32 WG).

**Conclusion:** in this study a negative association was found between prematurity and adverse events on the long run related to quality of life (survival, educational level, and reproduction).

**Conflict of interests:** none declared.

**Financial source:** none declared.

### Critical commentary:

**Justification:** prematurity is one of the principal causes of infantile mortality and morbidity in the industrialized world. The results on early and midtime morbi-mortality in premature children are well known as has been demonstrated in recent studies<sup>1,2</sup>. Fewer studies have investigated morbid-mortality at latter stages and those that exist are of small sample size and/or use low birth weight as a risk factor (instead of gestational age)<sup>3,4</sup>. Due to the therapeutical and technological advances in Neonatology, the survival of these children is progressively greater for the very premature children. This is a basic reason that pushed the authors to study the "survival pathology" not only in infancy, but also in adolescence and adulthood.

**Validity:** this is a well designed cohort study, with well defined question and objectives. It meets adequately the majority of the items of the STROBE declaration for observational studies<sup>5</sup>. The most interesting aspects are the long-term follow up, the comparison by gender and the follow up into reproductive ages; furthermore, the authors used a national registry, with a large population and with precise data (it is not probable that significant losses have occurred due to the fact that the emigration levels in Norway are very low). The potential limitations are: the necessity to establish corrections for gestational age (due to the inherent errors in the estimation used, especially in the first period in which echography was not available, in any case the authors have used a conservative limit, excluding children whose birth weight was either too small or too large for registered gestational age), the incomplete follow up in terms of reproductive capacity in younger members of the cohort, the difficulty in generalizing to other countries (in which

racial heterogeneity is greater) and the small sample size in the group of the very premature (this could limit the conclusions).

**Clinical relevance:** this study tries to answer a question that has been scarcely addressed or analyzed in a way not conclusive until now: the impact of prematurity in the adult ages in terms of quality of life. The data obtained imply prematurity as a cause of greater mortality in different stages in the different paediatric age groups, with a lower educational achievement in adult ages, with a lower fertility rate and a greater frequency of premature births in the descendants. These data imply that prematurity presents an important impact over the global concept of health and quality of life.

**Applicability in clinical practice:** in Spain 8 to 10 % of newborn live babies are born prematurely before 37 weeks of gestational age and approximately 1,5 % with a birth weight inferior to 1500 grams. These values tend to become greater with time due to the evident changes in the pattern of natality in our country (all of them due to the increase in the number of premature births): a greater number of adolescent mothers and aged mothers, an important increase of newborn children of immigrant mothers and the increase in pregnancies by means of assisted reproduction . It is known that the best treatment for prematurity is prevention (especially

extreme prematurity), due to the high early, and long term costs (social and medical) that it has.

#### Bibliography:

- 1.- Zeitlin J, Draper ES, Kollée L, Milligan D, Boerch K, Agostino R, et al; MOSAIC research group. Differences in rates and short-term outcome of live births before 32 weeks of gestation in Europe in 2003: results from the MOSAIC cohort. *Pediatrics*. 2008;121: e936-44.
- 2.- Larroque B, Ancel PY, Marret S, Marchand L, André M, Arnaud C, et al; EPIPAGE Study group. Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study. *Lancet*. 2008;371: 813-20.
- 3.- Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes in young adulthood for very-low-birth-weight infants. *N Engl J Med*. 2002;346:149-57.
- 4.- Saigal S, Stoskopf B, Streiner D, Boyle M, Pinelli J, Paneth N, et al. Transition of extremely low-birth-weight infants from adolescence to young adulthood: comparison with normal birth-weight controls. *JAMA*. 2006;295: 667-75.
- 5.- Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandembroucke JP, for the STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. *PLoS Medicine*. 2007;4: e296.

	<b>22-27 WG</b>	<b>28-32 WG</b>	<b>33-36 WG</b>	<b>37-42 WG</b>	<b>≥ 43 WG</b>
<b>Females (n= 567 413)</b>	(n= 2 068)	(n= 4 047)	(n= 20 485)	(n= 513 962)	(n= 26 851)
Fetal mortality	133 (125-141)	51 (48-56)	13.5 (12.5-14.6)	1 (reference)	1.4 (1.2-1.7)
Mortality < 1 year	144 (136-153)	42 (39-45)	6.3 (5.7-6.9)	1 (reference)	1.4 (1.2-1.6)
Mortality 1-5.9 years	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)
Mortality 6-12.9 years	-	0,94 (0.3-2.9)	1.5 (1.0-2.1)	1 (reference)	1.1 (0.73-1.6)
Mortality 13-17.9 years	-	1,4 (0.5-3.8)	1.3 (0.87-1.9)	1 (reference)	1.2 (0.78-1.7)
<b>Males (n= 600 093)</b>	(n= 2 534)	(n= 5 357)	(n= 25 863)	(n= 539 808)	(n= 26 531)
Fetal mortality	126 (119-134)	47 (44-50)	12.3 (11.5-13.2)	1 (reference)	1.6 (1.3-1.9)
Mortality < 1 year	118 (112-123)	41 (39-44)	5.7 (5.3-6.2)	1 (reference)	1.2 (1.03-1.4)
Mortality 1-5.9 years	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)
Mortality 6-12.9 years	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)
Mortalidad 13-17.9 years	-	1,6 (0.83-2.9)	1.0 (0.78-1.4)	1 (reference)	1.2 (0.97-1.6)

WG= weeks of gestation  
 \* Data calculated as relative risk adjusted by year of birth , maternal age and level of maternal education (95% confidence interval in parenthesis).  
 En sombreado se indican los resultados estadísticamente significativos  
 The statistically significant results are enhanced in grey.

<b>TABLE II: Reproductive capacity and educational level by gender and gestational age*</b>					
	<b>22-27 WG</b>	<b>28-32 WG</b>	<b>33-36 WG</b>	<b>37-42 WG</b>	<b>≥ 43 WG</b>
<b>Females (n= 283 457)</b>	(n= 216)	(n= 1 543)	(n= 9 680)	(n= 258 027)	(n= 13 991)
Reproductive capacity	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)
Premature births	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)
Education inferior to high school	1.28 (0.96-1.70)	1.19 (1.10-1.29)	1.13 (1.10-1.17)	1 (reference)	1.10 (1.07-1.14)
<b>Males (n= 297 375)</b>	(n= 216)	(n= 1 935)	(n= 12 232)	(n= 269 252)	(n= 13 740)
Reproductive capacity	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)
Premature births	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)
Education inferior to high school	1.42 (1.09-1.80)	1.27 (1.18-1.40)	1.09 (1.06-1.12)	1 (reference)	1.11 (1.07-1.14)

WG= weeks of gestation  
 \* Data registered as relative risk adjusted by year of birth, maternal age and level of education (95%confidence interval in paréntesis).  
 The statistically significant results are enhanced in grey.