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Long-term mortality in mothers with perinatal losses and risk modification by surviving children and attained education: a population-based cohort study

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ABSTRACT

Objective: To assess the association between perinatal losses and mother's long-term mortality and modification by surviving children and attained education.

Design: A population-based cohort study.

Setting: Norwegian national registries.

Participants: We followed 652 320 mothers with a first delivery from 1967 and completed reproduction before 2003, until 2010 or death. We excluded mothers with plural pregnancies, without information on education (0.3%) and women born outside Norway.

Main outcome measures: Main outcome measures were age-specific (40–69 years) cardiovascular and non-cardiovascular mortality. We calculated mortality in mothers with perinatal losses, compared with mothers without, and in mothers with one loss by number of surviving children in strata of mothers' attained education (<11 years (low), ≥11 years (high)).

Results: Mothers with perinatal losses had increased crude mortality compared with mothers without; total: HR 1.3 (95% CI 1.3 to 1.4), cardiovascular: HR 1.8 (1.5 to 2.1), non-cardiovascular: HR 1.3 (1.2 to 1.4). Childless mothers with one perinatal loss had increased mortality compared with mothers with one child and no loss; cardiovascular: low education HR 2.7 (1.7 to 4.3), high education HR 0.91 (0.13 to 6.5); non-cardiovascular: low education HR 1.6 (1.3 to 2.2), high education HR 1.8 (1.1 to 2.9). Mothers with one perinatal loss, surviving children and high education had no increased mortality, whereas corresponding mothers with low education had increased mortality; cardiovascular: two surviving children HR 1.7 (1.2 to 2.4), three or more surviving children HR 1.6 (1.1 to 2.4); non-cardiovascular: one surviving child HR 1.2 (1.0 to 1.5), two surviving children HR 1.2 (1.1 to 1.4).

Conclusions: Irrespective of education, we find excess mortality in childless mothers with a perinatal loss. Increased mortality in mothers with one perinatal loss and surviving children was limited to mothers with low education.

Strengths and limitations of this study

- A large population-based material from virtually complete registries.
- Long follow-up—median 52 years from birth of the mother until death or censoring.
- The study lack data on (cardiovascular risk factors) smoking, alcohol intake and Body Mass Index.
- The study does not include women without children. When studying mortality in childless mothers with a perinatal loss, women without children and perinatal losses would have been the optimal reference.
- Few maternal deaths among mothers with high education and perinatal losses introduce uncertainty.

INTRODUCTION

The long-term effects of perinatal losses on maternal mortality are unclear. A recent Danish population-based study found increased mortality in mothers with perinatal losses.[1] A body of studies indicates that grieving a lost child can induce poor physical and mental health and increase later-life mortality.[2–5] However, pre-existing risk factors, genetic and lifestyle induced, can represent shared pathways for a perinatal loss and excess mortality in later life.[6]

Of all perinatal losses, stillbirths account for more than 50%, and between 30% and 50% of the stillbirths remain unexplained.[7 8] Only 10% of stillbirths are associated with maternal medical conditions, predominantly hypertension and diabetes.[9] The most important risk factors for stillbirths in developed countries are nulliparity, obesity and advanced maternal age, obesity and smoking being the highest-ranking modifiable risk

factors.[10 11] In general, low educational attainment is highlighted as a major stressor affecting women during pregnancy and childbirth, increasing the likelihood of adverse outcomes like perinatal loss.[12]

The normal response to losing a child is to have a new child.[13 14] Studies on the effects of a replacement-child on the grieving process show diverging results. Morbid grief reactions[15] and severe anxiety[16 17] have been reported. On the other hand, replacing a loss with a subsequent child is found to alleviate the grief[18 19] and is associated with less depression.[20 21]

The aim of the study was to assess the association between perinatal losses and long-term maternal mortality and the modifying effects of surviving children and attained education.

MATERIALS AND METHODS

We conducted a population-based cohort study on long-term mortality of mothers with perinatal losses registered in the Medical Birth Registry of Norway from 1967 to 2003. Perinatal deaths were in this study defined as fetal losses from 16 weeks of gestation, stillbirths and neonatal deaths in the first week after birth. Surviving children were defined as children surviving the perinatal period. The Medical Birth Registry of Norway has recorded delivery data since 1967, with registration legally mandated for all births from 16 weeks of gestation. The Medical Birth Registry includes data on demographics, maternal diseases and detailed pregnancy and delivery information, as well as infant outcomes. The Medical Birth Registry of Norway is routinely matched with the Central Person Register, which provides every live-born infant in Norway with a unique national identification number. Mothers are registered with their unique identification numbers, which enables all births to a given mother to be linked in sibling files with the mother as the observation unit. Causes of death came from the Norwegian population-based Cause of Death Registry. Cardiovascular causes of death were defined as ischaemic heart diseases, I20–I25 (International Classification of Disease, 10th Revision (ICD-10)), 410–414 (ICD-8 and ICD-9) and cerebrovascular diseases (stroke), I60–I69 (ICD-10), 430–438 (ICD-8 and ICD-9). Non-cardiovascular causes of death were defined as all other than cardiovascular (ICD-8, ICD-9 and ICD-10). For information on maternal educational level, the data were linked to the National Education Database. The educational system in Norway is organised in primary school (7 years), lower secondary school (3 years), upper secondary school (3 years) and higher education. The first 10 years are mandatory.

All births in the Medical Birth Registry of Norway were included, of which 0.2% were late miscarriages (16–21 weeks). To analyse mothers with complete birth records, we included women with first births from 1 January 1967 and last births until 31 December 2002 (providing 7 years of follow-up to 31 December 2009—the end of observation for maternal deaths). About 97% of mothers have their second child within 7 years after their first birth if they chose to have another. We excluded women with plural pregnancies, women born outside Norway and mothers without information on education (0.3%).

Initially, we analysed crude mortality in mothers with perinatal losses compared with mothers without losses. We evaluated modifications on the crude mortality ratios by mothers' education, low or high, and by having or not having surviving children. Low education was defined as <11 years and high education as ≥11 years. Further stratification on education did not provide additional information.

In strata of education (low and high), we first assessed mortality in childless mothers with one perinatal loss relative to mothers with one child and no loss. Second, we estimated mortality in mothers with one perinatal loss by having surviving children, one to three or more. Here, we used mothers without losses and number of births corresponding to number of surviving children as strata-specific references. In repeated analyses, we included mothers with surviving children from zero to three or more, and used mothers without losses and two births as a common reference category.

Subanalyses: Irrespective of education, we evaluated the association between perinatal losses (one and two or more, separately) and maternal mortality in strata of number of births from one to five. Mothers without losses were used as strata-specific references. By low and high education for mothers with two or more births, we evaluated whether having a loss in the first or in the last birth affected mortality. Finally, we evaluated if mortality differed in mothers by having a loss in the last birth before the age of 30 years, compared with at 30 or more years.

In sensitivity analyses, we evaluated differences in the crude mortality estimates by the mothers' birth year (before 1950 and in 1950 or later). To control for potential bias, we repeated the main analyses excluding mothers who lost children aged 2 weeks to 7 years. We also evaluated the contribution of pre-eclampsia and preterm births on the association between perinatal losses and mortality.

We used Cox proportional hazard regression models (SPSS for Windows, V.22, http://www.spss.com) to calculate age-specific (40–69 years) HRs for total, cardiovascular and non-cardiovascular mortality. The underlying time variable in the Cox model was the mothers' birth year. In order to handle effect differences by calendar time, we adjusted for the mothers' birth year using a linear term. We further adjusted for the mothers' age at first birth. We applied a multiplicative model to evaluate interactions between perinatal losses and education for maternal mortality. To calculate rates (per 1000), in tables 2–4, we used a standard life-table approach.

RESULTS

Of the 652 320 mothers, 16 490 died during follow-up (table 1). The median follow-up time from birth of the mother to death or censoring was 52 years (IQR 45–59 years) and from first delivery 27 years (IQR 27 (19–35)). Overall occurrence of perinatal losses was 2.9%.

Mothers with low education, age at first birth <20 years or >34 years had the highest occurrence, 3.4%, 3.8% and 3.0%, respectively. Less than 6% of the mothers with a perinatal loss ended up childless. Occurrence of a perinatal loss increased with increasing number of births from 9 per 1000 in mothers with one or two births to 156 per 1000 in mothers with five or more births (table 2).

Of the mothers with losses and more than one birth, 50% had a loss in the first birth and only 14% had a loss in the last birth.

Crude mortality in mothers with a perinatal loss: modifications by education and surviving children

Mothers with a perinatal loss had higher mortality than mothers without losses; crude HRs (95% CIs), total: 1.3 (1.3 to 1.4), cardiovascular: 1.8 (1.5 to 2.1), non-cardiovascular: 1.3 (1.2 to 1.4) (table 3).

The crude results were significantly modified by the mothers' level of education. For mothers with low education, the HRs were similar to the crude estimates, but for mothers with high education, the associations almost disappeared. We found a significant interaction between perinatal loss and educational level for cardiovascular mortality (p=0027). There were not significant interactions for overall or non-cardiovascular mortality (p=0.084 and p=0.40, respectively). Modification by no or any surviving children also gave significant differences in mortality. Childless mothers with one perinatal loss had a doubled risk compared with mothers with one loss and surviving children (table 3).

Mortality in childless mothers with one perinatal loss

Figure 1A–D illustrates the increased mortality risk in childless mothers with one perinatal loss, compared with mothers without losses and two children. Having a perinatal loss as the only birth was 1.7 times more common and cardiovascular deaths in mothers were 10 times higher if maternal education was low rather than high (table 4).

Comparing cardiovascular mortality for childless mothers with a loss to mothers with only one birth and no loss gave a HR of 2.7 (1.7 to 4.3) for mothers with low education and 0.91 (0.13 to 6.5) for mothers with high education. The corresponding figures for non-cardiovascular mortality were: low education HR 1.6 (1.3 to 2.2) and high education HR 1.8 (1.1 to 2.9).

Mortality in mothers with surviving children and one perinatal loss

Mortality in mothers with high education, one perinatal loss and surviving children did not differ significantly from mothers without losses, although CIs were wide (table 5 and figure 1B,D). In contrast, for mothers with low education and one loss, we found significant differences in mortality risks (table 5 and figure 1A,C).

Cardiovascular mortality risk was increased in mothers with two and three or more surviving children (HR 1.7

Table 1 Baseline characteristics of the mothers by education in years

		Years of education		
Characteristic	**Total**	**Less than 11**	**11 or More**	**Less than 11:11 or more ratio**
Mothers: N, (% row)	652 320 (100)	311 374 (48)	340 946 (52)	0.9
Mothers with perinatal losses: n, (% of N)	18 636 (2.9)	10 586 (3.4)	8050 (2.4)	1.4
Mothers with one perinatal loss (% of n)	17 491 (94)	9883 (93)	7608 (95)	1.0
Mothers with two or more perinatal losses (% of n)	1145 (6.1)	703 (6.6)	442 (5.5)	1.2
Median year of birth (IQR)	1957 (1950–1964)	1954 (1948–1961)	1960 (1953–1966)	–
Median age at death (IQR)	52 (47–58)	53 (47–58)	52 (46–58)	–
Median age at first birth (IQR)	24 (21–27)	22 (20–25)	25 (22–28)	–
Total no. of deaths: X (% of N)*	16 490 (2.5)	11 703 (3.8)	4787 (1.4)	2.7
Total no. of deaths in mothers with perinatal losses (% of X)*	769 (4.7)	603 (5.2)	166 (3.4)	1.5
Cardiovascular deaths: x_1, (% of N)*†	1895 (0.3)	1499 (0.5)	396 (0.1)	5.0
Cardiovascular deaths in mothers with perinatal losses (% of x_1)*†	115 (6.1)	104 (6.9)	11 (2.8)	2.5
Non-cardiovascular deaths: x_2, (% of N)*‡	14 595 (2.2)	10 204 (3.3)	4391 (1.3)	2.5
Non-cardiovascular deaths in mothers with perinatal losses (% of x_2)*‡	654 (4.5)	499 (4.9)	155 (3.5)	1.4

*Data are presented for age-specific deaths, 40–69 years.
†Cardiovascular causes of death: ischaemic heart disease and cerebrovascular disease combined (see the Materials and methods section).
‡Non-cardiovascular causes of death: all other causes than cardiovascular causes (see the Materials and methods section).

Table 2 Mortality, ages 40–69, by number of births and number of perinatal losses, in 652 320 mothers

Mothers stratified by number of births, and then number of losses	Cardiovascular mortality			Non-cardiovascular mortality		
	N (per 1000)	Deaths (per 1000)	(HR 95% CI)*	N	Deaths (per 1000)	(HR 95% CI)*
One birth (18%)						
Total	115 603	550 (4.8)		117 123	3588 (31)	
No loss	114 595 (991)	531 (4.6)	1.0 (ref)	116 091	3513 (30)	1.0 (ref)
One loss	1008 (9)	19 (19)	2.5 (1.6 to 4.0)	1036	75 (72)	1.7 (1.4 to 2.2)
Two births (49%)						
Total	315 517	797 (2.5)		318 513	6789 (21)	
No loss	312 694 (991)	775 (2.5)	1.0 (ref)	315 629	6646 (21)	1.0 (ref)
One loss	2730 (9)	20 (7.0)	2.1 (1.4 to 3.3)	2788	135 (48)	1.7 (1.5 to 2.1)
Two losses	93 (0)	2 (22)	5.0 (1.2 to 20)	96	8 (82)	2.4 (1.2 to 4.9)
Three births (26%)						
Total	166 266	404 (2.4)		167 609	3091 (18)	
No loss	158 471 (953)	358 (2.3)	1.0 (ref)	159 760	2935 (18)	1.0 (ref)
One loss	7542 (45)	41 (5.4)	1.9 (1.3 to 2.6)	7593	144 (19)	1.4 (1.2 to 1.6)
Two or more losses	253 (1.5)	5 (20)	5.7 (2.3 to 14)	256	12 (47)	1.7 (0.97 to 3.0)
Four births (6%)						
Total	37 947	107 (2.8)		38 299	810 (21)	
No loss	33 064 (871)	88 (2.7)	1.0 (ref)	33 361	681 (20)	1.0 (ref)
One loss	4443 (117)	16 (3.6)	1.3 (0.75 to 2.2)	4487	104 (23)	1.1 (0.88 to 1.3)
Two or more losses	440 (12)	3 (7)	2.0 (0.63 to 6.4)	451	25 (55)	2.0 (1.4 to 3.0)
Five or more births (2%)						
Total	9711	37 (3.8)		9808	212 (22)	
No loss	7888 (812)	28 (3.5)	1.0 (ref)	7943	166 (21)	1.0 (ref)
One loss	1519 (156)	8 (5.3)	1.4 (0.65 to 3.1)	1530	37 (24)	1.1 (0.79 to 1.6)
Two or more losses	304 (31)	1 (3.3)	0.81 (0.11 to 5.9)	335	9 (27)	1.2 (0.64 to 2.4)

*HR with 95% CI, adjusted for the mothers' birth year and age at first birth.

Table 3 Mortality, ages 40–69, in mothers with one perinatal loss, compared with mothers without, and modifications by mothers' education and surviving children

		Years of education		Childless mothers		Mothers with children	
	HR (95% CI) Crude	Less than 11	11 or more	Deaths (per 1000)	HR (95% CI) N=1046	Deaths (per 1000)	HR (95% CI) N=16 445
Total	1.3 (1.3 to 1.4)	1.4 (1.2 to 1.5)	1.2 (0.99 to 1.3)	94 (90)	2.4 (2.0 to 3.0)	610 (37)	1.2 (1.1 to 1.3)
Cardiovascular	1.8 (1.5 to 2.1)	1.8 (1.5 to 2.3)	0.92 (0.50 to 1.7)	19 (19)	4.1 (2.6 to 6.4)	85 (5)	1.5 (1.2 to 1.9)
Non-cardiovascular	1.3 (1.2 to 1.4)	1.3 (1.2 to 1.4)	1.2 (1.0 to 1.4)	75 (72)	2.2 (1.7 to 2.7)	525 (32)	1.2 (1.1 to 1.3)

Table 4 Maternal mortality, ages 40–69, for mothers with one perinatal loss and no surviving child compared with mothers with one birth without perinatal losses

	One birth and no loss		One birth and loss		
Education	N	Deaths (per 1000)	N	Deaths (per 1000)	HR (95% CI)*
Cardiovascular mortality					
Low	56 198	417 (7.0)	634	18 (28)	2.7 (1.7 to 4.3)
High	58 382	114 (2.0)	374	1 (2.7)	0.91 (0.13 to 6.5)
Ratio low:high	1.0	3.5	1.7	10	3.0
Non-cardiovascular mortality					
Low	57 263	2547 (44)	655	59 (90)	1.6 (1.3 to 2.2)
High	58 823	966 (16)	381	16 (42)	1.8 (1.1 to 2.9)
Ratio low:high	1.0	2.8	1.7	2.1	0.9

Analyses stratified on low (<11 years) and high (≥11 years) education level.
*HR with 95% CI, adjusted for the mothers' birth year and age at first birth.

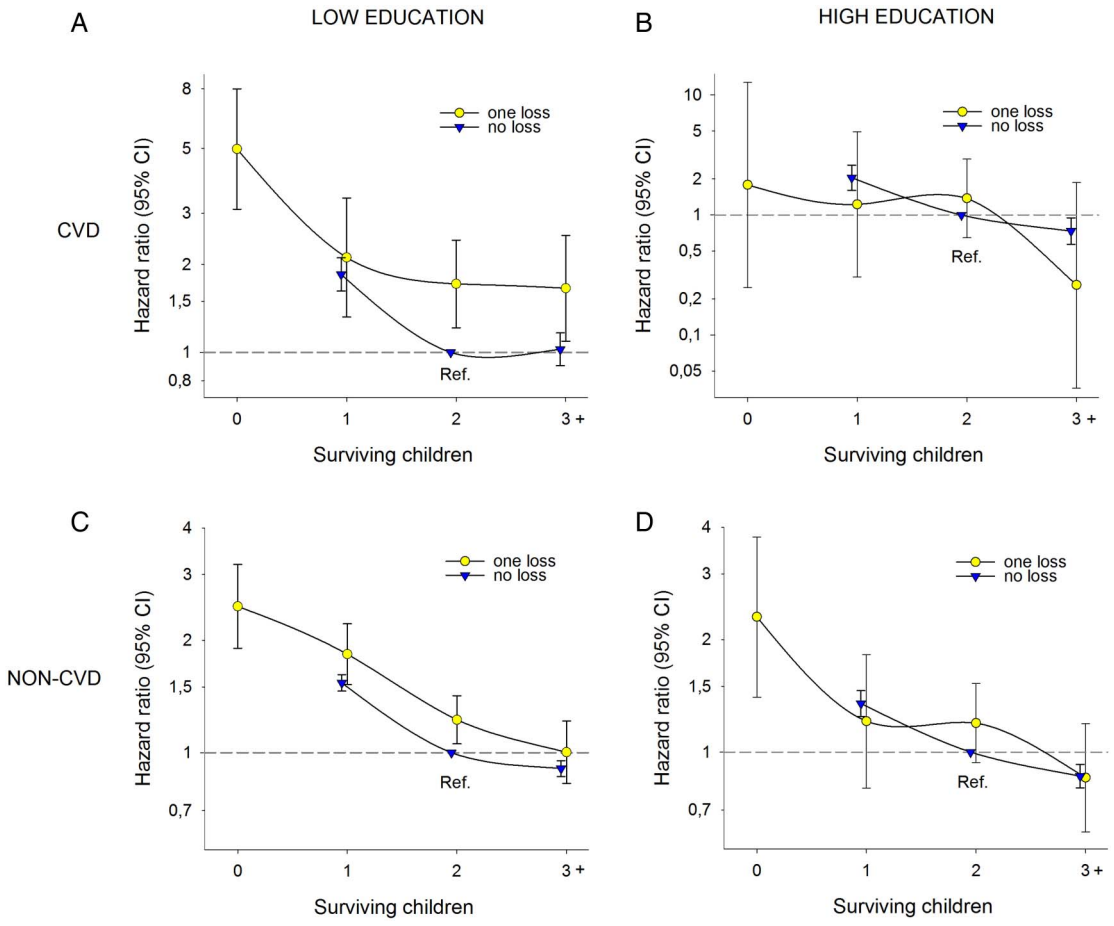

Figure 1 Age-specific, 40–69 years, mortality risk in mothers with one perinatal loss by surviving children from zero to three or more. Cardiovascular mortality: Low education (A) and high education (B). Non-cardiovascular mortality: Low education (C) and high education (D). Adjusted for the mothers' birth year and age at first delivery. CVD, cardiovascular disease; NON-CVD, non-cardiovascular disease; Ref, reference.

(1.2 to 2.4) and HR 1.6 (1.1 to 2.4), respectively) and non-cardiovascular mortality was increased in mothers with one or two surviving children (HR 1.2 (1.0 to 1.5) and HR 1.2 (1.1 to 1.4), respectively).

Subanalyses

A high number of births weakened the association between perinatal losses and maternal mortality (table 2). In mothers with one perinatal loss, the point estimates for cardiovascular mortality decreased from HR 2.5 (1.6 to 4.0) in mothers with one birth to HR 1.3 (0.75 to 2.2) in mothers with four births. The same pattern was seen for non-cardiovascular mortality (one birth HR 1.7 (1.4 to 2.2) and four births HR 1.1 (0.79 to 1.6)). Having two or more perinatal losses, relative to one loss, indicated excess mortality, but also here the association weakened with increasing number of births.

In mothers with one loss and surviving children, the increased mortality relative to mothers without losses did not differ significantly by having the loss in the first or the last birth (table 6).

Having a perinatal loss in the last birth before the age of 30 years compared with having a loss in the last birth at the age of 30 or more was associated with increased mortality; cardiovascular: HR 2.3 (1.2 to 4.5), non-cardiovascular: HR 1.6 (1.2 to 2.3).

Sensitivity analyses

The associations between crude maternal mortality and perinatal loss, compared with mothers without losses, by birth year of the mother gave small differences; cardiovascular: before 1950, HR 1.7 (1.4 to 2.2), 1950 or later, HR 1.4 (1.0 to 2.1); non-cardiovascular: before 1950, HR 1.2 (1.1 to 1.3), 1950 or later, HR 1.4 (1.3 to 1.6).

Repeating the main analyses, excluding mothers who lost children aged 2 weeks to 7 years or mothers with pre-eclampsia did not change the associations of mortality with perinatal loss. Mortality in mothers with a preterm loss did not differ from having a term loss.

DISCUSSION

Using linked data from the Medical Birth Registry of Norway, the Cause of Death Register and the National Education Database, we found that childless mothers with one perinatal loss had excess later-life non-cardiovascular mortality. For cardiovascular mortality, the association was only found in mothers with low

Table 5 Maternal mortality, ages 40–69, for mothers with one loss by total number of children surviving the perinatal period compared with mothers with no perinatal losses by number of births

	Mothers with no loss		Mothers with one loss		
Surviving children by education	**N**	**Deaths (per 1000)**	**N**	**Deaths (per 1000)**	**HR (95% CI)*†**
Cardiovascular mortality					
Low education					
1	56 198	417 (7)	1668	18 (11)	1.2 (0.73 to 1.9)
2	144 821	593 (4)	4137	34 (8)	1.7 (1.2 to 2.4)
≥3	94 916	385 (4)	3214	23 (7)	1.6 (1.1 to 2.4)
High education					
1	58 382	114 (2)	1062	2 (2)	0.59 (0.15 to 2.4)
2	167 873	182 (1)	3352	7 (2)	1.4 (0.65 to 2.9)
≥3	104 508	89 (0.9)	2748	1 (0.4)	0.36 (0.05 to 2.6)
Non-cardiovascular mortality					
Low education					
1	57 263	2547 (44)	1715	112 (65)	1.2 (1.0 to 1.5)
2	146 791	4534 (31)	4211	182 (43)	1.2 (1.1 to 1.4)
≥3	96 035	2624 (27)	3255	106 (33)	1.1 (0.90 to 1.3)
High education					
1	58 823	966 (16)	1073	23 (21)	0.89 (0.59 to 1.4)
2	168 838	2112 (13)	3382	67 (20)	1.2 (0.94 to 1.5)
≥3	105 042	1158 (11)	2765	35 (13)	0.99 (0.71 to 1.4)

Analyses stratified on low (<11 years) and high (≥11 years) education level.
*HR with 95% CI, adjusted for the mothers' birth year and age at first birth.
†Data are defined: Reference; mothers without losses, strata specific.

Table 6 Mortality, ages 40–69, for mothers with one perinatal loss in first or last birth, compared with mothers with two births and no loss

	Two births and no loss		Two or more births and loss in first			Two or more births and loss in last		
Education	**N**	**Deaths (per 1000)**	**N**	**Deaths (per 1000)**	**HR (95% CI)***	**N**	**Deaths (per 1000)**	**HR (95% CI)***
Cardiovascular mortality								
Low	144 821	593 (4.1)	4466	39 (8.7)	1.8 (1.3 to 2.4)	1250	15 (12)	2.6 (1.5 to 4.3)
High	167 873	182 (1.1)	3437	6 (1.7)	1.1 (0.50 to 2.5)	825	1 (1.2)	0.75 (0.11 to 5.4)
Low:high (rate ratio)	0.9	3.7	1.3	5.1	1.6	1.5	10	3.3
Non-cardiovascular mortality								
Low	146 791	4534 (31)	4563	234 (51)	1.4 (1.3 to 1.6)	1242	55 (44)	1.3 (0.97 to 1.7)
High	168 838	2112 (13)	3465	62 (18)	1.1 (0.82 to 1.4)	824	15 (18)	1.0 (0.61 to 1.7)
Low:high (rate ratio)	0.9	2.4	1.3	2.8	1.3	1.5	2.4	1.3

Analyses stratified on low (<11 years) and high (≥11 years) education level.
*HR with 95% CI, adjusted for the mothers' birth year and age at first birth (last line).

education. Increased long-term mortality in mothers with one perinatal loss and surviving children was limited to mothers with low education.

Little is known about the long-term consequences for mothers who experience perinatal losses. A Danish population-based study, with limited follow-up (15 years from first birth) and few deaths, reported that mothers with a perinatal loss had increased mortality, especially of cardiovascular causes.[1] The authors aimed at isolating the effect of bereavement by adjusting for cardiovascular disease at the time of delivery. A limitation of this study was the likely inadequate control for predisposing disease, which threatens the ability to isolate the effect of bereavement because manifest chronic disease is rare during the years of childbearing. Predisposing factors like obesity, smoking and familial disposition (genetic factors) were not accounted for[22] and nearly two-thirds of the women who suddenly die of cardiovascular disease have no previously recognised symptoms.[23] There may also have been inadequate control for social founding because they adjusted for educational level at the time of the first pregnancy and neglected that many mothers will complete their education after giving birth to their first child.

Crude mortality in mothers with a perinatal loss: modifications by education and surviving children

Crude mortality in mothers with a perinatal loss, compared with mothers without, corresponded with the

results of the Danish study. However, having high education or surviving children almost eliminated the excess risk (table 3). We have recently reported that a high number of births was associated with excess mortality in mothers with low education and reduced mortality in mothers with high education.[24] Perinatal losses were more frequent in mothers with low education relative to mothers with high education (ratio low: high 1.4, table 1) and the occurrence increased with number of births (table 2). Maternal deaths were clustered in mothers with low education and we found a significant interaction between perinatal losses and educational level for cardiovascular mortality. When assessing mortality in mothers with perinatal losses, stratification by educational level and number of surviving children should be applied to avoid bias.

Mortality in childless mothers with a perinatal loss

Childless mothers with a perinatal loss were more likely to have low education (ratio low: high 1.7, table 4) and excess cardiovascular risk was restricted to mothers with low education, indicating modification by social factors. However, non-cardiovascular mortality was increased irrespective of education. Of the non-cardiovascular deaths in mothers with low education, 41% died of cancer and 17% of these originated from the reproductive organs (breast, ovary, cervix and uterus). In mothers with high education, 50% died of cancer and here 63% were reproductive cancers. Non-cardiovascular causes of death, other than cancer, were in low-educated mothers, mainly lifestyle related, 69%, and half of these were alcohol or drug induced. In contrast, the proportion of lifestyle-related deaths in mothers with high education was only 13%. Here, the dominating causes of non-cardiovascular deaths, other than cancer, were traumatic injuries, 63%, and diseases not related to lifestyle, 25%. These contrasting patterns for causes of mortality for childless mothers with a loss, suggest that more mothers with high education relative to low experienced restricted fertility by biology (biological infertility). The causation between lifestyle-induced diseases and impaired fertility is relatively weak as reproduction takes place early in life when the alterations in the organs are minor compared to later in life. This implies that factors other than impaired biological fertility, like lack of resources, no partner or instability, may contribute to the reduced fertility to a larger extent in mothers with low compared with high education (social infertility).

Mortality in mothers with surviving children and a perinatal loss

Perinatal losses increase fertility.[25] In mothers with high education and a perinatal loss, surviving children neutralised the excess mortality risk associated with the loss. In mothers with low education and a perinatal loss, surviving children reduced the mortality risk, but not completely (table 5). A previous study on the association between pre-eclampsia and later-life cardiovascular mortality also demonstrated that number of births modified the association. Increased later-life cardiovascular mortality was concentrated in mothers with preterm pre-eclampsia and only one birth.[26] Of the mothers with one perinatal loss, 86% had a subsequent birth. A replacement-child prevents complicated grief, but can also indicate good health, stability and resources. Not replacing a perinatal loss at younger age, compared with higher age, significantly increased both cardiovascular and non-cardiovascular mortality. This suggests that younger mothers who fail to replace a loss are more likely to carry predisposing factors associated with reduced fertility and disease later in life.

Competing risk: biology or social factors

Subfertility is associated with underlying factors predisposing to cardiovascular disease.[27] We recently reported increased cardiovascular mortality in mothers with one birth, relative to mothers with two births.[24] Having a perinatal loss further increased the cardiovascular mortality in mothers with one birth, but only in mothers with low education (table 4). If a perinatal loss was a biological marker for later-life cardiovascular disease, the contribution to mortality risk should be similar or higher in mothers with fewer additional risk factors (high education mothers). In addition, with a reduced occurrence of perinatal loss in more recent years a condensation of risk would be expected, but we found an indication of reduction of cardiovascular risk over time. The differences in cardiovascular and non-cardiovascular mortality of mothers with perinatal loss between educational groups suggest that reduced fertility outweighs perinatal losses as a risk factor for later-life mortality. Negative lifestyle factors in disadvantaged mothers seem to be a shared pathway for perinatal losses and excess later-life mortality.

Strengths and limitations

The strengths of this study are the large population-based material and long follow-up. Registration of number of births, perinatal losses, education and deaths was prospective and virtually complete. The Medical Birth Registry of Norway is the only registry in Scandinavia with compulsory recording of losses from 16 weeks of gestation. Norwegian mothers with a low perinatal mortality rate constitute an ideal population to study the association between perinatal losses and maternal mortality. Modification of risk by education and surviving children should have external generalisability, especially in developed countries where selective fertility is strong. Weaknesses of the study are the lack of data on cardiovascular risk factors such as smoking, alcohol intake and Body Mass Index. The study does not include women without births. When evaluating mortality in childless mothers with a perinatal loss, women without births would have been the ideal reference group. Very few maternal deaths among mothers with high education and perinatal losses are a strong finding by itself, but introduce uncertainty reflected in wide CIs (especially for cardiovascular mortality).

Interpretation

Women with low education have increased risk for perinatal loss and excess long-term mortality. Irrespective of education, we find excess mortality in childless mothers with a perinatal loss. Increased mortality in mothers with one perinatal loss and surviving children was limited to mothers with low education. Our study suggests that lifestyle factors and subfertility outweigh perinatal loss as a risk factor for later-life maternal mortality. Experiencing a perinatal loss should not be used as an indicator for maternal long-term mortality alone.

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