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Preconception maternal bereavement and infant and childhood mortality: A Danish population-based study

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Abstract

Objectives—Preconception maternal bereavement may be associated with an increased risk for infant mortality, though these previously reported findings have not been replicated. We sought to examine if the association could be replicated and explore if risk extended into childhood.

Methods—Using a Danish population-based sample of offspring born 1979–2009 (N=1,865,454), we predicted neonatal (0–28 days), post-neonatal infant (29–364 days), and early childhood (1–5 years) mortality following maternal bereavement in the preconception (6–0 months before pregnancy) and prenatal (between conception and birth) periods. Maternal bereavement was defined as death of a first degree relative of the mother. Analyses were conducted using logistic and log-linear Poisson regression that were adjusted for offspring, mother, and father sociodemographic and health factors.

Results—We identified 6,541 (0.004%) neonates, 3,538 (0.002%) post-neonates, and 2,132 (0.001%) children between the ages of 1 to 5 years who died. After adjusting for covariates, bereavement during the preconception period was associated with an increased odds of neonatal (adjusted odds ratio [aOR] = 1.87, 95% CI: 1.53–2.30) and post-neonatal infant mortality (aOR=1.52, 95% CI: 1.15–2.02). Associations were timing-specific (6 months prior to pregnancy only) and consistent across sensitivity analyses. Bereavement during the prenatal period was not consistently associated with increased risk of offspring mortality, however this may reflect relatively low statistical power.

Conclusions—Results support and extend previous findings linking bereavement during the preconception period with increased odds of early offspring mortality. The period immediately

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prior to pregnancy may be a sensitive period with potential etiological implications and ramifications for offspring mortality.

Keywords

Bereavement; infant mortality; preconception; prenatal; stress

Although rates of early child mortality are improving, the etiology of this tragic occurrence is not fully understood (1,2). Identifying robust risk factors and vulnerable periods of development will improve our understanding of etiological mechanisms and inform effective global prevention programs (3). Previous research suggests that early maternal health factors, such as bereavement and stress in the preconception and prenatal periods, may influence offspring mortality rates (4–7).

A recent Swedish population-based study examining exposure to maternal bereavement found that increased risk for infant mortality, or death in the first year of postnatal life, was specific to preconception insult. The study identified no increased risk for infant mortality after prenatal maternal bereavement (5), however. A growing body of research also suggests that preconception maternal health, more generally, is associated with offspring mortality (8,9). Others have found that preconception and prenatal bereavement and stress increases offspring rates of stillbirth and spontaneous abortions, outcomes that may be etiologically related to infant mortality (6,7,10). It has additionally been suggested that maternal bereavement in both the preconception and prenatal periods increases the risk for childhood cancer (11), which may lead to childhood mortality. In sum, studies on early insult and offspring mortality are mixed and not yet able to identify if sensitive periods exist for these outcomes. Importantly, however, taking a translational epidemiological approach to examining sensitive periods has the power to highlight etiological mechanisms that may subsequently be explored.

Bereavement is frequently rated as the most significant life stressor (12). From a psychological perspective, cognitive stress theory, attachment theory, trauma theory, and social-functional emotion processing theory all contribute to an integrative understanding of the bereavement process (13). The survivor’s interpretation of the meaning, context, representation of the lost relationship, and ability to emotionally cope with the loss interact to shape the bereavement experience within the survivor’s cultural framework (13). From a physiological perspective, bereavement correlates with changes in stress- and health-related characteristics. For example, women experiencing complex bereavement show flattened diurnal cortisol patterns (14) and higher blood pressure as compared with women experiencing non-complicated grief (15). Therefore, bereavement may be considered a major life stressor from both a psychological and physiological perspective. From this, researchers often adopt the hypothesis that it is through changes in the maternal stress system that bereavement affects offspring development (5,6,16–18). For example, preconception bereavement may influence the mother’s biological preparedness for pregnancy (19), extend to affect early fetal organogenesis (20,21), and/or alter offspring neuronal morphology via epigenetic changes (22). Maternal bereavement during offspring prenatal development may directly affect the fetus through changes in the maternal/placental

stress-responsive hypothalamic-pituitary-adrenal (HPA) axis or immunological mechanisms (23–25).

We sought to test and extend previous associations between maternal bereavement before and during pregnancy with offspring mortality. We used the Danish Population Register to examine the association of bereavement and risk for neonatal, post-neonatal infant, and early childhood mortality. Preconception (4,5,8,9,26,27) and/or prenatal (1,16,18,28) maternal health factors may influence offspring mortality via adverse birth outcomes, such as preterm birth and low birth weight. Therefore, in addition to adjusting for individual, maternal, and paternal covariates, we examined the possible mediating role of gestational age at birth and low birth weight. Based on a recent publication using the Swedish population register (5), we hypothesized that preconception insult, and not insult during pregnancy, would moderately and robustly increase risk for offspring mortality across the neonatal, infant, and childhood ages.

Methods

Sample

We constructed a Danish population-based sample of all women who gave birth between January 1, 1979 and December 31, 2009 using the Medical Birth Registry (29). Years were limited by data availability and time needed for children to live through the risk period. Multiple births were not included because the rate of adverse birth outcomes for multiple births differs from that for singleton births (28). First degree relatives of the mother, in particular, her parents, siblings, and already born children, were identified using Civil Registration Numbers (30). We determined if and when these relatives died within the study period using The Danish Civil Registration System. The Danish Civil Registration System was also used to determine if and when the target offspring died and the cause of death was found in The Danish Cause of Death Register (31). The Danish National Patient Register provided information on maternal history of diabetes, hypertension, and cardiovascular or renal disease (32).

Measures

Bereavement included death of the mother’s father, mother, sibling, or already born child. Preconception exposure to bereavement included bereavement in the 18–13 months, 12-7 months, or 6 to 0 months prior to conception. Prenatal exposure to bereavement was classified by trimester: first (0–12 weeks gestation), second (13–24 weeks gestation), and third trimester (25 weeks gestation to birth). If multiple deaths were experienced, the date of the first event was used.

Offspring mortality outcomes included neonatal (0–28 days post birth), post-neonatal (29–364 days post birth), and childhood (1 to 5 years old) outcomes.

Adverse birth outcomes were used in sensitivity analyses. Gestational age was based on the last menstrual period, although it was often corrected by ultrasound measures, mainly for the most recent years (33). Birth weight was recorded in 10 g increments from 1979 until 1990 and 1 g increments from 1991 onwards. Due to a marked digit preference to the nearest 10,

50, and 100 g, it was assumed that birth weight was recorded in 100 g increments during the study period.

Analyses

We used logistic regression to predict neonatal and post-neonatal infant mortality via odds ratio (OR) estimates with 95% confidence intervals (CI). Log-linear Poisson regression with aggregated person-years (34) was used to predict childhood mortality. The first model was unadjusted. The second model controlled for infant sex, year of birth, parity, maternal age (<19, 20–24, 25–29, 30–34, or 35 or more years), paternal age (<19, 20–29, 30–34, 35–39, or 40 or more years), parental country of origin (categorized as Danish, non-Danish, or unknown), as well as maternal medical history (a binary indicator including type II diabetes mellitus, hypertension, cardiovascular disease, or renal disease during pregnancy). The third model additionally included gestational age (22–32, 33–36, 37–41, and 42 or more weeks) and birth weight (<1500 g, 1500–2500 g, >2500 g, and missing) as these factors are influenced by maternal bereavement (16,18) and predictive of infant mortality (28,35).

Sensitivity Analyses

Sensitivity analyses were used to rule out alternative hypotheses for the associations found and further explore the robustness of the findings. We first examined timing specificity of risk by expanding the preconception risk period. We then examined moderation by offspring sex, as it has been suggested that sex differentially influences mortality risk (28). We also limited the risk variable to include only death of the mother's parent or sibling rather than her already born children. Thus, we tested whether associations were independent of immediate-family mortality risk or due to cascading stress related to bereavement from a previous child's death. Finally, we expanded the childhood mortality age range from 1 to 5 years to 29 days to 5 years in order to obtain a larger sample size.

Results

We identified 1,865,454 live singleton births born between 1979 and 2009 with follow-up information until December 31, 2010.

Table 1 presents background participant information. We identified a total of 6,541 (0.004%) offspring who died as neonates, of whom 57.9% (n=3,790) were male. Post-neonatal deaths included 3,538 (0.002%) offspring, of whom 57.5% (n=2,028) were male. Childhood deaths included 2,132 (0.001%) offspring, of whom 55.3% (n=1,178) were male. The most common causes of death among offspring who died in the first year of life (neonatal and post-neonatal deaths), were congenital malformations for 2,139 (21.2%), Sudden Infant Death Syndrome (SIDS) for 1,386 (13.8%) and asphyxia for 205 (2.0%) deaths. We identified a total of 145 infants who died after exposure in the preconception period and 94 infants who died after exposure in the prenatal period.

As presented in Table 2, preconception bereavement in the 6 to 0 months immediately prior to pregnancy was associated with increased risk for neonatal mortality (OR = 2.48, 95% CI = 2.02–3.03) and post-neonatal infant mortality (OR = 1.95; 95% CI = 1.47–2.58) in unadjusted analyses. Model 2 showed that the magnitude of association remained robust to

the inclusion of measured covariates when examining neonatal (adjusted OR = 1.87, 95% CI = 1.53–2.30) and post-neonatal infant mortality (adjusted OR = 1.52; 95% CI = 1.15 – 2.02). After further adjusting for gestational age and birth weight in Model 3, the magnitude of association was further attenuated, though still elevated in magnitude, for neonatal (adjusted OR = 1.29; 95% CI = 1.01 – 1.64) and post-neonatal infant mortality (adjusted OR = 1.35; 95% CI = 1.01 – 1.81). For childhood mortality, no significant association was identified following preconception bereavement across models. However, we did identify a non-significant elevated magnitude of association that remained elevated in Model 3 for preconception bereavement (n = 26 exposed children, adjusted RR = 1.37; 95% CI = 0.93–2.02) and childhood mortality.

In contrast, prenatal bereavement was not associated with increased odds of neonatal, post-neonatal infant, or childhood mortality across trimester periods (Table 2). There were, however, elevated, non-significant magnitudes of association following bereavement in the first trimester and neonatal (adjusted OR = 1.16; 95% CI = 0.75 – 1.81) and childhood (adjusted RR = 1.72; 95% CI = 0.95 – 3.11) mortality, though the sample sizes were limited. To increase statistical power, we collapsed across trimesters. We did not find an increased risk for neonatal (adjusted OR = 0.98; 95% CI = 0.75 – 1.30), post-neonatal infant (adjusted OR = 1.04; 95% CI = 0.75 – 1.45), or childhood mortality (adjusted RR = 1.23; 95% CI = 0.92 – 1.64) following prenatal maternal bereavement across the entire prenatal period.

Sensitivity Analyses

We examined timing specificity in the preconception period by examining if increased mortality risk was conferred to the offspring following exposure in the 18 to 13 and 12 to 7 month preconception periods. When examining neonatal mortality, exposure in months 18 to 13 (n=53 exposed neonates; adjusted OR = 1.15; 95% CI = 0.85 – 1.55) and 12 to 7 (n=71 exposed neonates; adjusted OR = 1.15; 95% CI = 0.89 – 1.50) did not confer a statistically significant increased odds of mortality in Model 3 analyses. Similarly, when post-neonatal mortality was examined, exposure in months 18 to 13 (n=26 exposed infants; adjusted OR = 1.02; 95% CI = 0.69 – 1.51) and 12 to 7 (n=35 exposed infants; adjusted OR = 1.11; 95% CI = 0.80 – 1.56) did not confer an increased odds of mortality in Model 3. For childhood mortality, exposure in months 18 to 13 (n=4 exposed infants; adjusted RR = 0.51; 95% CI = 0.19 – 1.36) and 12 to 7 (n=5 exposed infants; adjusted RR = 0.83; 95% CI = 0.34 – 2.00) also did not confer an increased odds of mortality in Model 3, though the number of exposed infants was small.

Focusing on the 6 to 0 month preconception period, we then tested if offspring sex moderated the association. Across all mortality periods, confidence intervals between male and female offspring were overlapping and interaction terms were not significant (results upon request). Therefore, we cannot conclude that there are association differences between male and female offspring.

Though greatly attenuated and no longer statistically significant, the magnitudes of association remained elevated following preconception bereavement in months 6 to 0 due to the death of the mother’s parent or sibling only, not any first degree relative, for neonatal (n=46 exposed neonates; adjusted OR = 1.14; 95% CI = 0.86 – 1.53), post-neonatal infant

(n= 29 exposed infants; adjusted OR = 1.36; 95% CI = 0.94 – 1.96), and childhood mortality (n= 16 exposed infants; adjusted RR = 1.23; 95% CI = 0.75 – 2.01), but again, CI were wide due to limiting the sample size.

Finally, because the sample size of childhood mortality was small, we expanded the definition of this outcome to include post-neonatal deaths, as well as childhood deaths. The results were similar to those found in main analyses where childhood mortality was treated as death between years 1 and 5, though the association were now found to be statistically significant. More specifically, when examining mortality from 29 days to 5 years following maternal bereavement during the 6 months prior to conception, the magnitude of association was significantly elevated (adjusted RR = 1.49; 95% CI = 1.18 – 1.87). There was no statistical difference in association magnitude between males (adjusted RR = 1.64; 95% CI = 1.22 – 2.19) and females (adjusted RR = 1.30; 95% CI = 0.90 – 1.88), as confidence intervals were overlapping.

Discussion

Using a Danish population sample, we identified increased risk for neonatal (0–28 days post birth) and post-neonatal infant (29–364 days post birth) mortality following maternal bereavement in the six month period immediately before pregnancy. Rate of childhood (29 days to 5 years old) mortality were also elevated in offspring exposed to preconception bereavement in unadjusted analyses. Our findings replicate previous work using a Swedish population sample that similarly found increased risk for infant mortality following bereavement exposure in the 6 to 0 months prior to pregnancy (5).

We did not identify an association between prenatal bereavement and offspring mortality across any offspring age range (5), though the magnitude of risk appeared to decrease over the prenatal period for neonatal and childhood mortality. With a larger sample size, an independent effect of prenatal bereavement on offspring mortality may be detected.

We found that the association between preconception bereavement and mortality was specific to the 6 months immediately prior to pregnancy. Associations were attenuated after the inclusion of gestational age and birth weight. Therefore, in agreement with previous research (5), these adverse birth outcomes may partially mediate the association between preconception maternal bereavement and infant mortality. Preconception bereavement may induce stress in the mother and affect her psychological and physiological functioning for several months (12–15,20). Thus, preconception bereavement may extend to influence offspring development at the time of conception and the vulnerable process of early organogenesis (21). It has been shown that preconception bereavement increases rates of placental abruption (36), which affects fetal growth and development. Additionally, two of the leading causes of neonatal and post-neonatal infant mortality, congenital malformations and SIDS (28,35), may be more strongly influenced by preconception and early prenatal insults than by events later in pregnancy (37–39), supporting our timing-specific findings. One leading cause of death in childhood is cancer (11). A previous study found a non-timing specific link between preconception and prenatal maternal bereavement and increased risk for childhood cancers (11). Future research with larger mortality samples should investigate

if patterns of association differ by cause of infant mortality, as this information may shed light on the underlying mechanisms.

In the current study, sensitivity analyses were used to test alternative hypotheses and the robustness of the associations. We replicated findings (5) showing that the association was limited to the 6 months immediately prior to pregnancy. Future research should explore if risk gradually declines over the prenatal period. A similar decrease from preconception into the prenatal developmental period was identified between bereavement and risk for placental abruption (36). Power issues may have affected our ability to draw conclusions about sex differences. Previous research suggested that sex differences may exist (5), though sample size also limited their ability to draw conclusions. Magnitudes of association also suggested that risk was also present when the death included only the mother's parent or sibling (40), though associations were not statistically significant. This test was performed to begin to rule out the possible alternative explanation of an increased immediate family mortality risk or cascading stressors from a previous child's death. Finally, we also expanded our definition of childhood mortality to include post-neonatal infant deaths in order to increase the sample size. The magnitudes of association were similar with those identified when predicting childhood mortality defined as death in years 1 to 5 and confidence intervals were tighter.

The current replication and extension is an important step in moving the field forward. As the original Swedish finding had not been previously shown, our replication in a different population highlights the importance of investigating possible mechanisms that account for the association between preconception bereavement and early offspring death. Bereavement can influence the survivor's psychological, cognitive, behavioral, endocrine, physiological-somatic, and immunological functioning (12–15,20) and is considered a major life stressor (12,41). Preconception nutritional depletion due to bereavement may also play a role in maternal pregnancy preparedness (4,26). Maternal infection and/or disruption of the HPA axis have been suggested as mechanisms that can affect the maternal prenatal milieu and fetal development (23–25). There is great variability in bereavement processes, however. Therefore, it is difficult to hypothesize about mechanisms without follow-up studies that use different measures of risk in a variety of study designs.

The strengths of this work include a large, population-based sample spanning several decades. The comprehensiveness of the data allowed us to adjust for several measured covariates. We also tested for timing specificity, sex moderation, and family mortality or cascading stress. Future research, however, should address possible selection factors that contribute to both infant mortality and preconception bereavement exposure (42). Perhaps uncontrolled selection factors contributed to certain women becoming pregnant during a bereavement period. The life event may have also induced a spontaneous abortion or influenced the woman's likelihood of getting pregnant; therefore, our sample may be biased towards resilient fetuses (7,43). Future efforts should be made to examine the role of socioeconomic factors in these associations, as socioeconomic factors are associated with the occurrence of life events, adverse birth outcomes, and early childhood mortality. It is possible that the death of a first degree relative did not induce a substantial stressor in the mother. Similarly, for cases of long-term illness for example, the death may have reduced

the amount of stress in a mother's life (44). Therefore, other life events, daily stressors, and the appraisal of stressors should be examined to identify if converging evidence across study designs and measures are found. Finally, studying associations between rare risks and thankfully rare outcomes requires large sample sizes. To improve on our ability to examine timing and sex differences specifically, larger samples are needed in future research.

Underscoring the importance of future research on the preconception period, we found that maternal bereavement immediately prior to pregnancy may increase the risk for neonatal, post-neonatal infant, and childhood mortality until age 5 years. Our sample size did not allow for precise estimates of association between prenatal bereavement and offspring mortality, though the slightly elevated magnitudes of association suggest that these associations warrant further examination. Overall, our findings suggest that the 6 month period prior to pregnancy may be a sensitive developmental period with implications for early offspring mortality and should continue to be researched.

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Acronyms

CI	confidence interval
HPA	hypothalamic-pituitary-adrenal
OR	Odds ratio

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Table 1

Descriptive Characteristics of All Singleton Pregnancies in Denmark (1979–2009) With Live-Born Offspring by Maternal Bereavement Exposure Status (n=1,865,454)

	Exposure period, n(%)		
Descriptive characteristic	**Unexposed**	**6-0 months Preconception**	**Prenatal**
n	1,388,518	15,865	33,252
Male offspring	713,242(51.4)	8,075 (50.9)	17,142 (51.6)
Birth order			
1	677,121(48.8)	5,048 (31.8)	12,105 (36.4)
2	511,334(36.8)	6,470 (40.8)	12,957 (39.0)
3+	200,063 (14.4)	4,347 (27.4)	8,490 (25.5)
Maternal age			
<19	35,972(2.6)	282 (1.8)	579 (1.7)
20–24	273,493(19.7)	2,678 (16.9)	5,095 (15.3)
25–29	545,237(39.3)	5,561 (35.1)	11,329 (34.1)
30–34	395,566(28.5)	4,867 (30.7)	10,854 (32.6)
35+	138,250(10.0)	2,477 (15.6)	5,695 (17.1)
Paternal age			
<19	10,025 (0.7)	68 (0.4)	176 (0.5)
20–29	141,940 (10.2)	1,313 (8.3)	2,567 (16.2)
30–34	443,691(32.0)	4,356 (27.5)	8,798 (26.5)
35–39	473,390 (34.1)	5,408 (34.1)	11,432 (34.4)
40+	319,472 (23.0)	4,720 (29.8)	10,579 (31.8)
Maternal country of origin			
Denmark	1,342,047 (96.7)	15,022 (94.7)	32,006 (96.3)
Other	45,600 (3.3)	825 (5.2)	1,512 (4.5)
Unknown	871 (<0.1)	18 (0.1)	34 (0.1)
Paternal country of origin			
Denmark	1,297,176 (93.4)	14,518 (91.5)	30,797 (92.6)
Other	89,107 (6.4)	1,172 (7.4)	2,409 (7.2)
Unknown	2,235 (0.2)	175 (1.1)	346 (1.0)
Positive medical history	20,541 (1.5)	313 (2.0)	668 (2.0)
Smoking (from 1990)	223,552 (16.1)	2,762 (17.4)	6,290 (18.9)
Birth weight (g)			
<1500	7,584 (0.5)	162 (1.0)	289 (0.9)
1500–2500	43,664 (3.1)	659 (4.2)	1,315 (4.0)
>2500	1,332,423 (96.0)	14,969 (94.4)	31,830 (95.7)
Missing	4,847 (0.3)	75 (0.5)	118 (0.4)
Gestational age (weeks)			

	Exposure period, n(%)		
Descriptive characteristic	**Unexposed**	**6-0 months Preconception**	**Prenatal**
22–32	12,217 (0.9)	252 (1.6)	437 (1.3)
33–36	51,707 (3.7)	752 (4.7)	1,481 (4.5)
37–41	1,206,307 (86.9)	13,687 (86.3)	28,933 (87.0)
42+	118,287 (8.5)	1,174 (7.4)	2,701 (8.1)

Note: Medical history included diagnosis of any of the following during pregnancy: type II diabetes mellitus, hypertension, cardiovascular disease, and renal disease.

Table 2

Odds ratios and relative risks across statistical models of preconception and prenatal maternal bereavement predicting neonatal and post-neonatalinfant, and child mortality

		Model OR / RR (95% CI)		
	N exposed	**1. Unadjusted**	**2. Adjusted for family-level covariates[a]**	**3. Adjusted with gestational age and birth weight[b]**
Neonatal Mortality[c]				
Preconception				
6-0 months	96	2.48 (2.02–3.03)	1.87 (1.53–2.30)	1.29 (1.01–1.64)
Prenatal				
Trimester 1	25	1.76 (1.19–2.62)	1.33 (0.89–1.98)	1.16 (0.75–1.81)
Trimester 2	17	1.19 (0.74–1.91)	0.89 (0.55–1.43)	0.87 (0.51–1.48)
Trimester 3	16	0.86 (0.52–1.40)	0.68 (0.41–1.11)	0.87 (0.52–1.45)
Post-neonatal Infant Mortality[d]				
Preconception				
6-0 months	49	1.95 (1.47–2.58)	1.52 (1.15–2.02)	1.35 (1.01–1.81)
Prenatal				
Trimester 1	9	0.98 (0.51–1.88)	0.85 (0.44–1.64)	0.83 (0.43–1.60)
Trimester 2	13	1.40 (0.81–2.41)	1.24 (0.72–2.14)	1.19 (0.69–2.06)
Trimester 3	14	1.15 (0.68–1.95)	1.04 (0.62–1.77)	1.07 (0.63–1.82)
Child Mortality[e]				
Preconception				
6-0 months	26	1.60(1.08–2.35)	1.42(0.97–2.10)	1.37(0.93–2.02)
Prenatal				
Trimester 1	11	1.84(1.02–3.34)	1.74(0.96–3.16)	1.72(0.95–3.11)
Trimester 2	20	1.30(0.83–2.02)	1.19(0.76–1.76)	1.15(0.74–1.80)
Trimester 3	15	1.14(0.68–1.89)	1.06(0.64–1.76)	1.04(0.62–1.72)

Note: OR = Odds ratio;RR = relative risk;

[a] covariates included infant sex, year of birth, parity, maternal age, paternal age, parental country of origin, and maternal medical history;

[b] gestational age at birth and birth weight added to covariates included in Model 2;

[c] offspring died 0–28 days after birth;

[d] offspring died 29–364 days after birth;

[e] offspring died 1–5 years after birth.