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ORIGINAL ARTICLE

Maternal bereavement and the risk of preterm delivery: the importance of gestational age and of the precursor of preterm birth

K. D. László[1]*, J. Li[2], J. Olsen[2,3], M. Vestergaard[4,5], C. Obel[4,5,6] and S. Cnattingius[1]

[1] *Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden*
[2] *Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark*
[3] *Department of Epidemiology, School of Public Health, University of California, Los Angeles, CA, USA*
[4] *Research Unit for General Practice, Department of Public Health, Aarhus University, Aarhus, Denmark*
[5] *Section for General Practice, Department of Public Health, Aarhus University, Aarhus, Denmark*
[6] *Research Program for Mental Child Health, Department of Public Health and Knowhow, AU Center Knowledge of Welfare and Health, Aarhus University, Aarhus, Denmark*

Background. Maternal stress during pregnancy may increase the risk of preterm delivery (PD), but the associations between stress and subtypes of PD are not clear. We investigated maternal loss of a close relative and risks of very and moderately PD (<32 and 32–36 weeks, respectively) and spontaneous and medically indicated PD.

Method. We studied 4 940 764 live singleton births in Denmark (1978–2008) and Sweden (1973–2006). We retrieved information on death of women's family members (children, partner, siblings, parents), birth outcomes and maternal characteristics from nationwide registries.

Results. Overall, the death of a close family member the year before pregnancy or in the first 36 weeks of pregnancy was associated with a 7% increased risk of PD [95% confidence interval (CI) 1.04–1.10]. The highest hazard ratios (HR) for PD were found for death of an older child [HR (95% CI) 1.20 (1.10–1.31)] and for death of a partner [HR (95% CI) 1.31 (1.03–1.66)]. These losses were associated with higher risks of very preterm [HR (95% CI) 1.61 (1.29–2.01) and 2.07 (1.15–3.74), respectively] than of moderately preterm [HR (95% CI) 1.14 (1.03–1.26) and 1.22 (0.94–1.58), respectively] delivery. There were no substantial differences in the association between death of a child or partner and the risk of spontaneous *v.* medically indicated PD.

Conclusions. Death of a close family member the year before or during pregnancy was associated with an increased risk of PD, especially very PD. Possible mechanisms include both spontaneous and medically indicated preterm birth.

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Key words: Bereavement, medically indicated preterm delivery, moderately preterm delivery, preterm delivery, spontaneous preterm delivery, stress, very preterm delivery.

Introduction

Emerging (Copper *et al.* 1996; Hedegaard *et al.* 1996; Nordentoft *et al.* 1996; Rosenberg *et al.* 2002; Dole *et al.* 2003, 2004; Mustillo *et al.* 2004; Khashan *et al.* 2009; Class *et al.* 2011; Mendez *et al.* 2014), though not consistent (Krabbendam *et al.* 2005; Kramer *et al.* 2009; Niedhammer *et al.* 2009; Abeysena *et al.* 2010; Larsen *et al.* 2013; Mendez *et al.* 2014), evidence from prospective studies suggests that maternal psychological stress during pregnancy is associated with a modestly increased risk of preterm delivery (PD). Most investigations have focused on overall risk of PD, but PD is a heterogeneous condition and its association with stress could vary according to subtypes of PD (Wadhwa *et al.* 2011).

It has often been suggested that stress – studied generally in terms of stressful life events, perceived stress or racism – may primarily affect the risk of spontaneous PD. The suggested mechanisms include elevations in stress hormones, changes in health behavior, increased susceptibility to infections, pro-inflammatory changes, uteroplacental ischemia and impaired fetal growth (Wadhwa *et al.* 2011). Studies of the effect of stress on the risk of spontaneous preterm birth show mixed results (Berkowitz & Kasl, 1983; Copper *et al.* 1996; Hedegaard *et al.* 1996; Rosenberg *et al.* 2002; Dole *et al.* 2003, 2004; Heaman *et al.* 2005; Kramer *et al.* 2009;

* Address for correspondence: Dr K. D. László, Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital and Karolinska Institute, Eugeniahemmet T2, 17176 Stockholm, Sweden.
(Email: krisztina.laszlo@ki.se)

Sanchez *et al.* 2013; Barrios *et al.* 2014). Stress could also contribute to medically indicated PD by increasing the risk of pre-eclampsia (László *et al.* 2013*a*), placental abruption (László *et al.* 2014) and fetal growth restriction (Khashan *et al.* 2009; Class *et al.* 2011) through changes in some of the lifestyle and physiological factors mentioned above. We are aware of only one study investigating the effect of stress on medically indicated PD. This study found an increased risk only in women exposed to life events with a negative impact, but not in case of other investigated sources of stress (Dole *et al.* 2003).

It has been suggested that the role of stress in PD may differ also according to the severity of prematurity (Wadhwa *et al.* 2011). Only a few studies have investigated this question and findings have been inconsistent, possibly due to limited statistical power (Kramer *et al.* 2009) or retrospective assessment of stress (Sanchez *et al.* 2013; Barrios *et al.* 2014). The largest study found a slightly higher risk of very PD (<33 weeks) than of any PD (<37 weeks) after maternal exposure to death or severe illness affecting children, but not in case of events affecting other close relatives (Khashan *et al.* 2009).

We constructed a cohort of approximately 5 million births by linking individual-level data from several Danish and Swedish population-based registries. We used this cohort to investigate whether the association between maternal bereavement the year before or during pregnancy and the risk of PD differs (1) according to gestational age at delivery, and (2) between spontaneous and medically indicated PD.

Methods

Study population and design

We included information on 5 186 313 live singleton births from the Danish Medical Birth Register (DMBR, during 1978–2008), and from the Swedish Medical Birth Register (SMBR, during 1973–2006). Both registries contain computerized data on more than 98% of the deliveries in the country since 1973; the DMBR includes information on gestational age since 1978 (Knudsen & Olsen, 1998; National Board of Health and Welfare, 2003). After excluding births with (1) a gestational age shorter than 22 weeks, longer than 45 weeks in Denmark/46 weeks in Sweden or missing information on gestational age ($n = 72\,067$) and/or (2) a previous PD in the two birth registries ($n = 173\,856$), our study population consisted of 4 940 764 births. The reason for excluding women who had a record of a previous PD in the birth registries was to reduce the possibility that the association between death of a child and PD was due to the mother's biological vulnerability to recurrent PD; a history of PD is an important risk factor for both PD (Goldenberg *et al.* 2008) and the death of an older child (Moster *et al.* 2008; Crump *et al.* 2011). Thus, if a woman had a PD in the two birth registers, her subsequent deliveries were not included in the analyses.

The cohort was linked to several population-based registries to obtain information on death of family members and on maternal demographic and health-related factors using the unique personal identification number assigned to all residents; a description of the registries included in the linkage has been provided elsewhere (Li *et al.* 2011; László *et al.* 2013*a*, *b*, 2014, 2015).

The study was approved by the Scientific Ethics Committee of Central Region Jutland, the Danish Data Protection Agency in Copenhagen and the Research Ethics Committee at Karolinska Institutet in Stockholm. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Study variables

Bereavement

Women were linked to their close family members, i.e. older live-born children, parents, siblings and partner (the index child's father) through the Danish Civil Registration System and the Swedish Multigeneration Register. In Denmark during 1968–1978 registry linkage to parents, and thus to siblings, was possible if the woman was a Danish resident, was younger than 15 years, lived with her parents, and was unmarried and did not have children (Pedersen *et al.* 2006). After 1978, linkage to family members registered in Denmark was based on biological relationships (Pedersen *et al.* 2006). In Sweden, linkage to parents, and consequently to siblings, required that the woman was a Swedish resident, was born in 1932 or later, and that family members also had been registered in Sweden at some time since 1947 (Statistics Sweden, 2010; László *et al.* 2013*b*). Information on family members' death was retrieved from the Danish Civil Registration System and from the Swedish Cause of Death Register. We considered women exposed if they lost a close family member the year before or in the first 36 weeks of pregnancy. We categorized exposed women according to (1) their relationship to the deceased (older live-born child, partner, sibling, parent), (2) time of death (7–12 months before pregnancy, 0–6 months before pregnancy, first, second and third trimester of pregnancy), and (3) cause of death of the relative (unnatural and natural death)

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(László *et al.* 2013*a*, *b*, 2014). We defined unnatural deaths as losses due to violence, suicide, accident, complication of medical and surgical care, and other sudden unnatural deaths (László *et al.* 2013*a*, *b*, 2014), using International Classification of Diseases (ICD) codes (Supplementary Table S1).

Preterm delivery

We obtained information on length of gestation from the birth registries. Gestational age was estimated based on ultrasound scans performed generally early in the second trimester or, when this information was unavailable, based on the first day of the last menstrual period (National Board of Health and Welfare, 2003; Danish Health and Medicine Authority, 2013). Since the early 1990s, all pregnant women in Denmark and Sweden are invited to attend an ultrasound examination before the 20th week of gestation free of charge (National Board of Health and Welfare, 2003; Danish Health and Medicine Authority, 2013). In Sweden, 95% of the women accept this offer (Høgberg & Larsson, 1997). Gestational age has been recorded in weeks in the DMBR until 1996 and in days afterwards; in the SMBR, gestational age has been registered in days.

Deliveries before the completion of the 37th week of gestation were categorized as preterm. We further classified PDs as very and moderately preterm (<32 and 32–36 completed gestational weeks, respectively). In addition, in Sweden PDs can, since 1990, be classified also as medically indicated (i.e. cesarean section before onset of labor or induced labor because of maternal or fetal concerns), and spontaneous, using information recorded in checkboxes by the midwives attending the delivery. In addition, PDs with a diagnosis of preterm premature rupture of membranes (defined using the ICD codes presented in Supplementary Table S1) were always considered spontaneous PDs.

Covariates

Information on the offspring's date of birth, sex and birth weight, maternal age at delivery, parity and smoking in early pregnancy (since 1991 in Denmark and 1982 in Sweden) was obtained from the two birth registries. Data on maternal height and weight in early pregnancy are available in the SMBR since 1982 and 1992, respectively. Body mass index (BMI) was calculated by dividing height in kilograms with the square of the height in meters. We defined small for gestational age (SGA) as having a birth weight that was 2 standard deviations below the sex and gestational age-specific Swedish standard normal fetal growth curve (Marsál *et al.* 1996).

Data on maternal chronic hypertension, pre- and gestational diabetes, pre-eclampsia and placental abruption were obtained from the Danish National Hospital Register and from the SMBR. Information on maternal psychiatric diagnoses was retrieved from the Danish Central Psychiatric Register and from the Swedish Patient Register. The ICD codes used are presented in Supplementary Table S1. The Danish National Hospital Register includes data on all the inpatient diagnoses in Denmark since 1977 and on all the outpatient diagnoses since 1995 (Andersen *et al.* 1994). The Danish Central Psychiatric Register contains information on all inpatient psychiatric care in Denmark since 1969 and all outpatient care since 1995 (Munk-Jorgensen & Mortensen, 1997). The Swedish Patient Register covers all psychiatric inpatient care since 1973 in Sweden, except for five of the 26 counties where coverage became complete in the 1980s (National Board of Health and Welfare, 2009).

Data on the mother's country of origin was obtained from the Danish Integrated Database for Longitudinal Labour Market Research and from the SMBR. Information on maternal education was from the Danish Integrated Database for Longitudinal Labour Market Research and from the Swedish Education Register.

Statistical analysis

We performed Cox regression models to analyze the association between antenatal exposure to bereavement and PD. Follow-up started upon completion of the 22nd week of gestation and ended at the time of PD or the end of the preterm period. The SAS COWSANDWICH option was applied to account for the correlation among deliveries by the same woman. Analyses were performed with (1) any type of PD, and with PD categories according to (2) gestational age at delivery, and (3) the precursor of PD (in Sweden only, since 1990).

We treated exposure after the 22nd week of gestation as a time-dependent variable. In case of women who were unexposed or who experienced the death of a close family member the year before or during the first 21 weeks of pregnancy, exposure did not change during follow-up. Women who became bereaved between the 22nd and the 36th week of pregnancy contributed with time to the unexposed group until the day of exposure and to the exposed group afterwards (Precht *et al.* 2007; László *et al.* 2013*a*). In case of several losses during the exposure period, we considered the earliest death in the primary analysis. We conducted analysis with (1) any loss during the exposure period, and with exposure categorized according to the (2) relative's time of death, (3) cause of death, and (4)

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the mother's relationship to the deceased. The effect of loss of a child was estimated among women with at least one living child 1 year before pregnancy, whereas the effect of spousal bereavement was estimated among women with registry links to the index child's father. Analyses regarding parental and sibling loss were performed among women with registry links to at least one parent and at least one sibling, respectively, living at the start of the exposure period.

In the primary models, we adjusted for country, year of delivery, parity, mother's age, education, country of origin, chronic hypertension, psychiatric disorder before the exposure period and record of pre-eclampsia, placental abruption or a SGA infant in a previous pregnancy. In addition, we controlled for (1) maternal BMI in early pregnancy among women delivering in Sweden in 1992 or later, and for (2) height among women with deliveries in Sweden since 1982. To investigate whether the association between bereavement and medically indicated PD was due to pre-eclampsia, placental abruption or diabetic diseases, we repeated these analyses after excluding women with a record of these conditions in the index pregnancy. Similarly, we repeated the main analyses after excluding women who smoked in early pregnancy. We conducted stratified analysis and tests of multiplicative interaction to investigate effect modification. We repeated analyses regarding the association between any type of bereavement and bereavement by type of relative after – in case of women who experienced several losses during the exposure period – we gave coding priority according to the relationship to the deceased (i.e. loss of a child, partner, sibling, parent).

As infants born early term, i.e. at 37–38 gestational weeks, have higher mortality and morbidity than full-term infants (Crump *et al.* 2013), we also estimated the association between bereavement and the risk of early term delivery.

Analyses were conducted using SAS v. 9.4 (SAS Institute Inc., USA) and SPSS for Windows v. 19 (IBM Corp., USA).

Results

In the cohort of 4 940 764 pregnancies, 114 711 experienced the loss of a close relative the year before or in the first 36 weeks of pregnancy. The corresponding figures by type of loss were: (1) 33 621 deaths 7–12 months before pregnancy, 36 232 deaths 0–6 months before pregnancy, 16 529 deaths in the first, 17 323 in the second and 11 006 in the third trimester of pregnancy; (2) 13 343 deaths due to unnatural and 100 904 due to natural causes; (3) 11 816 deaths of children (among women with at least a live child at the start of the exposure period), 1265 partner deaths (among women with register linkage to the partner), 6518 sibling deaths (among women with register linkage to parents and at least a live sibling at the start of the exposure period), and 99 257 parental deaths (among women with register linkage to parents and at least a live parent at the start of the exposure period). Compared to unexposed women, bereaved women were older, more likely to give birth in earlier years of the study period, have a short education, be multiparous, smoke in early pregnancy, and have a placental dysfunction disorder in a previous pregnancy (Table 1).

In the cohort of 4 940 764 births, we identified 221 912 (4.5%) PDs of whom 29 346 (0.6%) were very preterm and 192 566 (3.9%) were moderately preterm. Compared with unexposed women, women who lost a close family member the year before or during pregnancy had an increased risk of PD [hazard ratio (HR) with 95% confidence intervals (CIs) 1.07 (1.04–1.10)] (Table 2). The point estimates did not differ substantially when exposure was stratified according to time or cause of death, albeit in some analyses the CIs included 1. The risk of PD was increased among women who lost a child, the partner or a parent, but not among those who lost a sibling. Death of a child and death of the partner was associated with higher risks of very PD than of moderately PD.

When exposure to death of a child was categorized according to time of death, the highest HR tended to be in the second trimester (Table 3). Both natural and unnatural deaths of children were associated with increased risks of very PD, whereas the risk of moderately PD was only increased after natural deaths. It was not possible to perform similar analyses with partner death, due to limited number of events.

The associations between loss of any relative, loss of a child, partner or parent the year before or in the first 36 weeks of pregnancy did not differ substantially between spontaneous and medically indicated PD (Table 4). However, only the association between loss of a child and spontaneous PD was statistically significant. Repeating our analysis regarding the association between death of a child and medically indicated PD after excluding women with pre-eclampsia, placental abruption or diabetes did not weaken this association [HR (95% CI) 1.70 (1.11–2.61)].

The associations between loss of any relative or loss of a child, partner or parent and the risk of PD did not change substantially after (1) adjusting for BMI in early pregnancy (in Sweden since 1992), (2) adjusting for maternal height (in Sweden since 1982), or (3) excluding women who smoked in early pregnancy (in Sweden since 1982 and in Denmark since 1991) (data not shown). The relation between loss of any relative and the risk of overall PD and of PD by subtype did

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Table 1. *Comparison of the exposed and the unexposed group according to the study variables*[a]

Variable	Exposed to the death of a close family member the year before or in the first 36 weeks of pregnancy, *N* (%)	
	No (*n* = 3 929 112)	Yes (*n* = 114 711)
Country		
Sweden	2 659 285 (67.7)	75 775 (66.1)
Denmark	1 269 827 (32.3)	38 936 (33.9)
Maternal country of origin		
Denmark/Sweden	3 807 837 (97.0)	111 866 (97.6)
Other country	119 343 (3.0)	2803 (2.4)
Missing	1932 (0)	42 (0)
Mother's age at delivery (years)		
⩽19	128 264 (3.3)	2302 (2.0)
20–24	857 067 (21.8)	17 627 (15.4)
25–29	1 489 078 (37.9)	37 826 (33.0)
30–34	1 050 147 (26.7)	36 103 (31.5)
⩾35	404 556 (10.3)	20 853 (18.2)
Year of delivery		
1973–1977	407 772 (10.4)	14 066 (12.3)
1978–1982	437 933 (11.2)	14 422 (12.6)
1983–1987	549 572 (14.0)	17 595 (15.3)
1988–1992	700 408 (17.8)	20 950 (18.3)
1993–1997	646 915 (16.5)	18 513 (16.1)
1998–2002	585 489 (14.9)	15 256 (13.3)
2003–2008	601 023 (15.3)	13 909 (12.1)
Maternal education		
Basic education	637 489 (16.5)	22 715 (19.8)
Secondary education	1 782 496 (45.4)	49 956 (43.5)
Higher education	1 452 245 (37.0)	40 624 (35.4)
Missing	56 882 (1.4)	1416 (1.2)
Parity		
Primiparous	1 839 629 (46.8)	41 878 (36.5)
Multiparous	2 089 482 (53.2)	72 833 (63.5)
Missing	1 (0)	0
Smoking in early pregnancy[b]		
No	2 086 642 (53.1)	53 834 (46.9)
Yes	539 137 (13.7)	18 238 (15.9)
Missing	1 303 333 (33.2)	42 639 (37.2)
Body mass index[c] (in kg/m^2)		
<18.5	24 108 (0.6)	464 (0.4)
18.5–24.99	630 800 (16.1)	13 920 (12.1)
⩾25	304 826 (7.6)	7987 (7.0)
Missing data	2 969 378 (75.6)	92 340 (80.5)
Maternal height[d] (in cm)		
<140	303 (0)	9 (0)
⩾140	1 642 277 (41.8)	42 484 (37.0)
Missing	2 286 532 (58.2)	72 218 (63.0)
Maternal psychiatric disease before the exposure period		
No	3 852 348 (98.1)	112 052 (97.7)
Yes	76 764 (2.0)	2659 (2.3)
Chronic hypertension		
No	3 916 190 (99.7)	114 235 (99.6)
Yes	12 922 (0.3)	476 (0.4)
Pre-gestational or gestational diabetes		
No	3 896 842 (99.2)	113 564 (99.0)
Yes	32 270 (0.8)	1147 (1.00)
Pre-eclampsia		
No	3 841 472 (97.8)	112 183 (97.8)
Yes	87 640 (2.2)	2528 (2.2)
Placental abruption		
No	3 908 361 (99.5)	114 076 (99.5)
Yes	20 751 (0.5)	635 (0.5)
Record of a pregnancy complication in a previous pregnancy[e]		
No	3 795 681 (96.6)	108 674 (94.7)
Yes	133 431 (3.4)	6037 (5.3)

Table 1 (*cont.*)

[a] Analyses were performed among women who had register links to parents and to the partner.

[b] Data were recorded since 1982 in Sweden and since 1991 in Denmark.

[c] Data are available only in Sweden since 1992.

[d] Data were registered only in Sweden, since 1982.

[e] Pregnancy complications in a previous pregnancy include pre-eclampsia, placental abruption, or small for gestational age.

not change substantially, when in case of women who experienced several losses during the exposure period (*n* = 1808), we gave coding priority according to the following hierarchy: loss of a child, partner, sibling or parent (data not shown). There were minor differences between the loss of any relative during the exposure period and the risk of PD by year of delivery, maternal age, mother's country of birth, maternal education, chronic hypertension and psychiatric diagnosis before the exposure period (Supplementary Table S2).

Bereavement the year before pregnancy or in the first 38 gestational weeks was associated with an increased risk of early term delivery [HR (95% CI) 1.08 (1.06–1.09)]. The risks were highest in case of losses of older children and the partner [HR (95% CI) 1.50 (1.06–1.09) and 1.33 (1.17–1.50), respectively] (Supplementary Table S3) and were confined to medically indicated

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Table 2. *Hazard ratios (HR) for any preterm delivery (PD) and for PD by gestational age at delivery according to bereavement*

		Any PD (⩽36 weeks)			Very PD (⩽31 weeks)		Moderately PD (32–36 weeks)	
Exposure groups	*N*	Events	Crude HR (95% CI)	aHR (95% CI)[a]	Events	aHR (95% CI)[a]	Events	aHR (95% CI)[a]
Unexposed	3 929 112	171 614	1.00	1.00	21 270	1.00	150 344	1.00
Any death during the exposure period[b]	114 711	5106	1.05 (1.02–1.08)	1.07 (1.04–1.10)	631	1.14 (1.05–1.23)	4475	1.06 (1.03–1.10)
Time of death[b]								
7–12 months before pregnancy	33 621	1548	1.06 (1.01–1.11)	1.09 (1.03–1.14)	210	1.19 (1.04–1.36)	1338	1.07 (1.02–1.13)
0–6 months before pregnancy	36 232	1587	1.00 (0.96–1.05)	1.05 (0.99–1.10)	196	1.04 (0.90–1.19)	1391	1.05 (0.99–1.10)
1st trimester of pregnancy	16 529	734	1.02 (0.95–1.10)	1.04 (0.97–1.12)	107	1.24 (1.02–1.49)	627	1.01 (0.94–1.09)
2nd trimester of pregnancy	17 323	852	1.14 (1.06–1.21)	1.14 (1.07–1.22)	108	1.20 (0.99–1.45)	744	1.13 (1.05–1.22)
3rd trimester of pregnancy	11 006	385	1.04 (0.94–1.15)	1.05 (0.95–1.16)	10	0.88 (0.47–1.63)	375	1.06 (0.96–1.17)
Cause of death[b]								
Natural death	100 904	4487	1.05 (1.01–1.08)	1.07 (1.04–1.11)	569	1.17 (1.08–1.28)	3918	1.06 (1.03–1.10)
Unnatural death	13 343	596	1.05 (0.97–1.14)	1.05 (0.97–1.14)	62	0.93 (0.72–1.20)	534	1.07 (0.98–1.16)
Relationship to the deceased								
Older child[c]	11 816	543	1.37 (1.26–1.49)	1.20 (1.10–1.31)	96	1.61 (1.29–2.01)	447	1.14 (1.03–1.26)
Partner[d]	1265	69	1.33 (1.05–1.68)	1.31 (1.03–1.66)	11	2.07 (1.15–3.74)	58	1.22 (0.94–1.58)
Sibling[e]	6518	288	1.03 (0.91–1.15)	0.98 (0.87–1.10)	35	0.99 (0.70–1.38)	253	0.98 (0.86–1.11)
Parent[f]	99 257	4495	1.05 (1.02–1.08)	1.07 (1.04–1.10)	568	1.12 (1.03–1.22)	3927	1.06 (1.03–1.09)

N, Number; aHR, adjusted hazard ratio; CI, confidence interval.

[a] Adjusted for country, year of delivery, maternal age, education, country of origin, parity, psychiatric disorder before the exposure window, chronic hypertension and record of pre-eclampsia, placental abruption or a small for gestational infant in a previous pregnancy.

[b] Analyses were performed among women with register linkage to parents and to the father of the index child ($n = 4\,043\,823$).

[c] Analyses were performed among women who had at least a live child at the start of the exposure window ($n = 2\,703\,085$).

[d] Analyses were performed among women with register linkage to the father of the index child ($n = 4\,880\,467$).

[e] Analyses were performed among women with register linkage to parents and at least a live sibling at the start of the exposure window ($n = 3\,728\,964$).

[f] Analyses were performed among women who had register linkage to parents and at least a live parent at the start of the exposure window ($n = 4\,049\,131$).

deliveries [HR (95% CI) 2.73 (2.46–3.04) and 2.47 (1.79–3.40), respectively] (Supplementary Table S4).

Discussion

We found that loss of a close relative the year before or in the first 36 weeks of pregnancy was associated with an increased risk of PD, especially if the loss was of an older child or of the partner. These losses tended to be associated with higher risks of very PD than of moderately PD. There were no substantial differences in the association between the loss of a child or partner and the risk of spontaneous and medically indicated PD.

Comparison with previous studies

This large population-based study allowed us to investigate with better precision and in more detail than previous studies whether the association between stress and PD differs by gestational age. Our study corroborated and extended on the findings by Khashan *et al.* (2009) who reported that risk of PD was foremost increased among women experiencing adverse life

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Table 3. *Hazard ratios for preterm delivery (PD) according to the time and the cause of the death of the older child*[a]

		Any PD		Very PD (⩽31 weeks)		Moderately PD (32–36 weeks)	
Exposure groups	*N*	Events	aHR (95% CI)[b]	Events	aHR (95% CI)[b]	Events	aHR (95% CI)[b]
Unexposed	2 626 031	89 367	1.00	11 221	1.00	78 146	1.00
Time of death of the child							
7–12 months before pregnancy	4205	197	1.20 (1.03–1.39)	36	1.73 (1.22–2.47)	161	1.12 (0.95–1.33)
0–6 months before pregnancy	6626	293	1.15 (1.01–1.30)	52	1.46 (1.07–1.99)	241	1.10 (0.96–1.26)
1st trimester of pregnancy	520	28	1.44 (0.98–2.13)	4	1.77 (0.66–4.72)	24	1.39 (0.92–2.13)
2nd trimester of pregnancy	297	19	1.92 (1.23–3.00)	4	3.40 (1.29–8.98)	15	1.72 (1.05–2.84)
3rd trimester of pregnancy	168	6	1.11 (0.46–2.66)	0	–	6	1. 15 (0.48–2.76)
Cause of death of the child							
Natural death	9217	432	1.21 (1.10–1.34)	73	1.55 (1.20–2.01)	359	1.17 (1.04–1.30)
Unnatural death	2529	109	1.16 (0.96–1.41)	23	1.88 (1.21–2.91)	86	1.06 (0.85–1.32)

N, number; aHR, adjusted hazard ratio; CI, confidence interval.

[a] Analyses were performed among women who had at least a live child at the start of the exposure window ($n = 2\,703\,085$).

[b] Adjusted for country, year of delivery, maternal age, education, country of origin, parity, psychiatric disorder before the exposure window, chronic hypertension and record of pre-eclampsia, placental abruption or a small for gestational infant in a previous pregnancy.

Table 4. *Hazard ratios for induced and spontaneous preterm delivery (PD) according to maternal bereavement among deliveries in Sweden during 1990–2006*

		Spontaneous PD		Medically indicated PD	
Exposure group	*N*	Events	aHR (95% CI)[a]	Events	aHR (95% CI)[a]
Unexposed	1 309 635	38 370	1.00	14 435	1.00
Exposed to any loss[b]	31 632	891	1.05 (0.98–1.12)	386	1.09 (0.98–1.20)
Exposure by type of relative					
Older child[c]	2504	71	1.42 (1.11–1.80)	34	1.40 (0.98–2. 01)
Partner[d]	333	12	1.34 (0.76–2.35)	5	1.49 (0.62–3.58)
Parent[e]	27 569	789	1.05 (0.98–1.13)	343	1.10 (0.99–1.23)

N, Number; aHR, adjusted hazard ratio; CI, confidence interval.

[a] Adjusted for year of delivery, maternal age, education, country of origin, parity, psychiatric disorder before the exposure window, chronic hypertension and record of pre-eclampsia, placental abruption or a small for gestational infant in a previous pregnancy.

[b] Analyses were performed among women who had links to parents and to the father of the index child, and in case their delivery was preterm, had information on the precursor of delivery ($n = 1\,341\,267$).

[c] Analyses were performed among women who had at least a live child at the start of the exposure window, and in case their delivery was preterm, had information on the precursor of delivery ($n = 865\,082$).

[d] Analyses were performed among women with register linkage to the father of the index child, and in case their delivery was preterm, had information on the precursor of delivery ($n = 1\,566\,083$).

[e] Analyses were performed among women who had register linkage to parents and at least a live parent at the start of the exposure window, and in case their delivery was preterm, had information on the precursor of delivery ($n = 1\,337\,466$).

events (death or severe illness) affecting older children, and risks were higher for very PD than for moderately PD. In addition to their findings, we could detect a modest association also for the loss of a partner during pregnancy, which also was stronger for very preterm compared to moderately PD. These findings are in line with those of two earlier investigations suggesting somewhat stronger association between depression – another condition related to hypothalamic pituitary adrenal axis dysregulation – and the risk of overall

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PD (Straub *et al.* 2012) or of medically indicated PD at earlier than at later gestations (Gavin *et al.* 2009). Results from other studies in this area have been mixed. One study reported an association between prenatal stress and an increased risk of PD only at 32–34 weeks of gestation (Buzaglo *et al.* 2012), while other investigations did not find consistent differences in the association between stress or depression and the risk of PD by gestational age (Neggers *et al.* 2006; Eskenazi *et al.* 2007; Kramer *et al.* 2009; Yonkers *et al.* 2012; Sanchez *et al.* 2013; Barrios *et al.* 2014). Differences in study designs, statistical power, assessment of stress, coping options, study populations or health care are likely to have contributed to differences in findings among these studies.

Our finding that death of an older child in the prenatal period was associated with an increased risk of spontaneous PD is in line with those of several case-control studies (Berkowitz & Kasl, 1983; Heaman *et al.* 2005; Sanchez *et al.* 2013; Barrios *et al.* 2014) and of one follow-up study regarding stress and risk of spontaneous PD (Copper *et al.* 1996). Furthermore, two follow-up studies found an association between negative life events and spontaneous PD only if the events were perceived as very stressful (Hedegaard *et al.* 1996; Dole *et al.* 2003), whereas a follow-up study of racial discrimination reported increased risks of spontaneous PD in case of some, but not all, investigated discrimination measures (Rosenberg *et al.* 2002). In contrast, a cohort study by Kramer *et al.* (2009) reported no significant association between any of the analyzed measures of prenatal stress and spontaneous preterm birth. Findings from prospective studies regarding the link between anxiety and depression and spontaneous PD risk have been mixed, with some studies reporting positive (Orr *et al.* 2002; Kramer *et al.* 2009), others mixed (Dayan *et al.* 2002, 2006; Dole *et al.* 2003; Ibanez *et al.* 2012) or no association (Copper *et al.* 1996; Andersson *et al.* 2004; Neggers *et al.* 2006; Gavin *et al.* 2009; Fransson *et al.* 2011; Straub *et al.* 2012; Yonkers *et al.* 2012).

The link between stress and the risk of medically indicated PD has received considerably less attention, despite some overlap in risk factors with spontaneous preterm birth (Berkowitz *et al.* 1998; Savitz *et al.* 2005; Klebanoff & Keim, 2011), and the fact that medically indicated PDs represent an important proportion of all PDs (Goldenberg *et al.* 2008). The only study, which to our knowledge, analyzed this question reported a two- to three-fold increased risk of medically indicated PD following life events with a negative impact on the woman's life, but no association in case of other measures of stressful life events, perceived neighborhood safety, racial or gender discrimination (Dole *et al.* 2003). The corresponding point estimates were generally higher than those observed in case of spontaneous PD (Dole *et al.* 2003). With some exception (Gavin *et al.* 2009), the few prospective studies analyzing the link between depression or anxiety and the risk of medically indicated PD do not provide support for such an association (Dole *et al.* 2003; Neggers *et al.* 2006; Fransson *et al.* 2011; Ibanez *et al.* 2012; Straub *et al.* 2012; Yonkers *et al.* 2012). Interestingly, we found a relatively strong association between the loss of a child and partner and the risk of medically indicated, but not spontaneous, early term delivery, suggesting that many inductions are postponed to this period.

Linking mechanisms

Our finding that bereavement of a child and partner was more closely related to the risk of very preterm than of moderately PD indicates that infection and inflammation may link stress to PD; the role of infection and inflammation in the etiology of PD increases with decreasing gestational age (Goldenberg *et al.* 2000, 2008). Emerging, though not consistent evidence (Culhane *et al.* 2001; Coussons-Read *et al.* 2005, 2007; Harville *et al.* 2005, 2007; Kramer *et al.* 2009) suggests that maternal stress during pregnancy increases the risk of genital tract infections and of pro-inflammatory activity. Cytokines may stimulate corticotropin-releasing hormone and prostaglandin production, uterine contractility and spontaneous PD (Gennaro & Hennessy, 2003; Borzychowski *et al.* 2006). In addition, they may also increase the risk of medically indicated PD through their effect on pre-eclampsia (Borzychowski *et al.* 2006).

Our finding that the point estimate corresponding to the association between death of a child the year before or during pregnancy and medically indicated PD was not substantially altered after exclusion of women with pre-eclampsia, placental abruption or diabetes is somewhat intriguing. We recently reported that death of an older child was associated with increased risks of early onset pre-eclampsia (László *et al.* 2013*a*) and placental abruption (László *et al.* 2014), and these pregnancy complications are the most important indications for induced PDs (Ananth & Vintzileos, 2006; Goldenberg *et al.* 2008). One potential explanation may be that women who lost a child shortly before or during pregnancy may have undergone antenatal examinations more often (László *et al.* 2013*b*), and the threshold for preterm induction of delivery – even in the absence of pre-eclampsia or placental abruption – may be lower in this group than among unexposed women.

We found no evidence that smoking may be part of the explanation of the association between loss of any

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relative and the risk of PD. Whether other potential mediators such as additional lifestyle factors, mood disorders, specific type of infections or placental ischemia contribute to the investigated association needs further examination.

Strengths and limitations

Our study has several strengths, including use of prospective data, large sample size and the high quality of data on death in Danish and Swedish population-based registries. The registration of bereavement before and independent of PD excludes the possibility of recall bias and reverse causation, which are possible sources of bias in several earlier investigations (László *et al.* 2013*a*). The death of a close relative is an objective and well defined source of stress that is likely to cause physiological arousal in most individuals, irrespective of the available coping resources (Khashan *et al.* 2009; László *et al.* 2013*a*, *b*, 2014); this further limits the possibility of exposure misclassification. The large sample size allowed us to consider a high number of possible confounders (including the strongest risk factor for PD, i.e. a history of PD) and to stratify the outcome by gestational age at delivery or by mode of delivery onset.

Our study also has some limitations. First, although we considered a large number of potential confounders, the possibility of residual confounding from unmeasured socioeconomic, lifestyle and health-related factors shared by family members or by women across pregnancies, cannot be excluded. Second, though the overall study population was large, the statistical power to detect modest effects may have been limited by the rarity of exposure in some of our sub-analyses, particularly in the analyses of spontaneous and medically indicated PDs. Third, some misclassification of the outcome, primarily during the period when the estimation of gestational age was based on the last menstrual period is possible. However, there were no substantial differences in the association between death of any relative and the risk of PD by year of delivery. Fourth, as we did not have information on death of family members residing outside the two investigated countries, our findings regarding bereavement of parents and siblings may be generalized only to women with families living in Denmark and Sweden in a limited time period.

Conclusions

Our results provide support for the hypotheses that severe stress increases risks of very and moderately PD, as well as of spontaneous and medically indicated PD. The finding that bereavement was foremost associated with increased risk of very PD points to the role of infection and inflammation as potential linking mechanisms. As the prevalence of maternal bereavement in the antenatal period is low and the observed associations are modest, the public health implications of our findings are limited. Large prospective studies are needed to estimate the effect of less severe, but more frequent sources of stress during pregnancy on risks of PD by gestational age and by precursors of birth onset and to investigate the mediating role of infection and inflammation in these associations.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715002688

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Declaration of Interest

None.

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