

# Risk of childhood injuries after prenatal exposure to maternal bereavement: a Danish National Cohort Study

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## ABSTRACT

**Objectives:** The aim of this study was to assess the risk of injuries among children exposed to a stressful life exposure (defined as bereavement) before conception or during fetal life.

**Design:** Population-based cohort study.

**Setting:** Denmark.

**Participants:** All singleton births in Denmark between 1 January 1995 and 31 December 2006 were identified. These newborns were then linked to mothers, fathers, grandparents and siblings using individually assigned civil personal registration numbers.

**Primary and secondary outcome measures:** We identified that data on childhood injuries were obtained from the Danish National Patient Registry, which contains data on all hospital stays and outpatient visits. Incidence rate ratios (IRRs) were estimated from birth using log-linear Poisson regression models, and person-years were used as the offset variable. Age, residence, calendar period, maternal education, maternal income and parental-cohabitation status are treated as time-dependent variables (records were extracted from the offspring's birth year).

**Results:** Exposure to maternal bereavement due to a father's death had the strongest association with childhood injuries, especially when the cause of death was due to a traumatic event (adjusted estimates of IRR (aIRR): 1.25, 95%CI: 0.99 to 1.58). We did not find an association for childhood injuries and maternal bereavement due to grandparent's death, and we only found an association for sibling death when restricting to deaths due to traumatic events (aIRR: 1.20, 95%CI: 1.03 to 1.39).

**Conclusions:** The aetiology of childhood injuries is complex and may be related to events that take place during prenatal life. This study suggests that exposure to a stressful life event during gestation may be linked to injury susceptibility in childhood. However, changes in postnatal family conditions related to loss or genetic factors may also play a role.

**Background:** Developmental plasticity related to early life exposures leading to disease programming in offspring is a theory with substantial theoretical and empirical support. Prenatal stress exposure has been linked to neurological outcomes, such as temperament, behavioural problems, cognitive function and affective disorders. If exposure modifies risk-seeking behaviour, perceived danger and reaction time, it is also expected to modify injury risk.

## ARTICLE SUMMARY

### Article focus

- The aim of this study was to assess the risk of injuries among children exposed to a stressful life exposure (defined as bereavement) before conception or during fetal life.

### Key messages

- This study suggests that exposure to a stressful life event during gestation may be linked to injury susceptibility in childhood.
- Changes in postnatal family conditions related to postnatal family dynamics, maternal and child attachment or paternal genetic factors related to injury-prone behaviours may also play a role in childhood injuries.

### Strengths and limitations of this study

- The main strengths of this study are the large cohort size and availability of population-based data. We were able to include several potential covariates due to the availability of data collected by the various Danish Registries.
- There are several important limitations in this study that should be considered. Not all injuries were captured since some will be treated in general practice or self-treated at home. We were also not able to include any postnatal factors that could contribute to the injuries, such as temperament or environmental factors, and, furthermore, other significant sources of stressors, such as major illnesses and/or social stressors.

## INTRODUCTION

Developmental plasticity, early life exposures and permanent programming of the offspring due to adverse exposures during critical periods of fetal organ development have been suggested. A number of studies have reported that stress during pregnancy may affect temperament, behavioural problems and cognitive function,<sup>1-7</sup> as well as increased risk of autism<sup>8,9</sup> and depression<sup>10</sup> in the offspring.<sup>11,12</sup> It has been hypothesised that these early fetal exposures modify an array of hormonal systems that control both physical growth and neurological development.

Several neuroendocrine systems appear to be involved,<sup>13</sup> but the most significant evidence points to the major hormonal systems which mediate the stress response, including the hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system, and insulin-like growth factors.<sup>14</sup>

Animal studies show that the HPA axis can be modified prenatally by nutrient restriction, maternal adversity or exposure to synthetic glucocorticoids, and postnatally by neonatal handling, maternal deprivation or infection.<sup>14</sup> The mechanisms underlying this phenomenon are hypothesised to involve changes in the expression of steroid receptors within the limbic system following gene methylation.<sup>15</sup> Chronic stress may also lead to in utero developmental changes including changes in dendritic branching and hypertrophy, cell proliferation and synaptic modelling leading to structural changes in brain areas that are important for cognitive and emotional functions, especially the hippocampus and amygdala,<sup>16</sup> which may have long-lasting effects on behaviour and mental health.<sup>11 17–20</sup>

Prenatal stress exposure has been linked to temperament, behavioural problems, cognitive function and affective disorders. If exposure modifies risk-seeking behaviour, perceived danger and reaction time, it may also modify injury risk during childhood. The aim of this study was to assess the risk of injuries among children exposed to maternal bereavement before conception or during fetal life. We included in our assessment the risk of head injuries and fractures in the offspring as they almost uniformly necessitate medical intervention with hospital contact.

## METHODS

Our study was based on data linkage from several national registers in Denmark.<sup>21 22</sup> We identified all singletons born in Denmark between 1 January 1995 and 31 December 2006 and then made links to birth mothers, fathers, grandparents and siblings using individually assigned civil personal registration numbers (CPR). The CPRs were also used to link individual-level data between registries. Information on birth outcome such as gestational age at birth and birth weight, were obtained from the Danish Medical Birth Registry<sup>23</sup>; and maternal education, residence and income were retrieved from the Fertility Database.<sup>24</sup> Date of conception was estimated by subtracting gestational age from the date of birth. Exposure to bereavement was assessed during each trimester of pregnancy: 0–12, 13–27 and 28–42 weeks of gestation; and during the preconceptional period, defined as 12 months before conception (table 1).

After kinship links were identified, exposure to kinship deaths were determined. Children were categorised as exposed to prenatal stress due to maternal bereavement if their mothers had lost a child, husband, sibling or parent during pregnancy or the prior 12 months; the remaining children were categorised as

unexposed. Data on childhood injuries were obtained from the Danish National Patient Registry, which contains data on all hospital stays and outpatient visits.<sup>25</sup> The patient registry collects information on the primary discharge diagnosis (the discharge diagnosis that best describes the condition leading to the admission or outpatient visit and, ie, the primary reason for the prescribed and completed course of tests and treatments) and up to 20 subsidiary diagnoses. Data were extracted with the use of the International Classification of Diseases, 10th Revision (ICD Website, 2007).

All injuries related to a disease or condition or not directly related to the externally caused injury, such as acts of violence, suicide or attempted suicide, late effects of unintentional injury or unspecified reasons for contact with medical care, were excluded from the analysis. The reason for contact codes were extracted using the second edition of the Nordic Medico-Statistical Committee's Classification of External Causes of Injuries. Furthermore, all head injuries and fractures were identified using ICD-10 codes: S00–S09 and ICD-10 codes: S02, S12, S32, S42, S52, S62, S72, S82, S92, T02, respectively.

The analysis was performed using PROC GENMOD in SAS V.9.1.3. Incidence rate ratios (IRRs) were estimated from the time of birth using log-linear Poisson regression models, and person-years were used as the offset variable. Adjusted estimates of IRRs (aIRR) include maternal age ( $\leq 18$ , 19–34, 35–40, 41+); residence (Copenhagen, cities with over 100 000 inhabitants and other); income (first, second, third and fourth quartiles); maternal education (primary, secondary and high); cohabitation status (shared address, do not share an address); gestational age at birth (<32, 32–36 and 37 + weeks); birth weight (<1500, 1500–2500 and 2500+ g); sibling order (1, 2, 3 and 4+); calendar-year (1995–1998, 1999–2002 and 2003–2006) and offspring's sex (male and female). Observations with incomplete demographic variables were defined as missing and not excluded from the analysis. Age, residence, calendar period, maternal education, maternal income and parental cohabitation status are treated as time-dependent variables (extracted from the offspring's birth year).

## RESULTS

In our cohort of 975 580 children, approximately 2.5% (N=24 596) children were exposed to maternal bereavement in fetal life. Among those exposed to maternal bereavement, 210, 2610 and 21 032 were exposed to bereavement due to the death of a father, sibling and grandparent, respectively. Background characteristics of cohort members were comparable, although mothers of the exposed offspring were older and reported a higher household income and education at the time of exposure. Offspring exposed to maternal bereavement also had lower gestational age compared with their unexposed counterparts. We found that children exposed

**Table 1** Maternal background statistics, includes all live Singleton Danish Births by Bereavement Status from 1995–2006\*

	Total cohort N=975580		Exposed N= 24596		Unexposed N=9509	
	N	(%)	N	(%)	N	(%)
Maternal age						
<18	11368	1.2	96	0.4	11272	1.2
19–34	816341	83.7	18760	76.3	797581	83.9
35–40	136300	14.0	5243	21.3	131057	13.8
41 +	11571	1.2	497	2.0	11074	1.2
Household income						
1st quartile	13036	1.3	83	0.3	12953	1.4
2nd quartile	320350	32.8	7319	29.8	313031	32.9
3rd quartile	363200	37.2	10173	41.4	353027	37.1
4th quartile	235639	24.2	6797	27.6	228842	24.1
Maternal education						
Primary	246371	25.6	6087	24.8	240284	25.3
Secondary	304559	32.1	8552	34.8	296007	31.1
High	365813	40.3	9607	39.1	356206	37.5
Cohabitation status						
Cohabit	384306	39.4	10246	41.7	374060	39.3
Do not cohabit	547929	56.2	14127	57.4	533802	56.1
Child's sex						
Male	500174	51.3	12545	51.0	487629	51.3
Female	475391	48.7	12051	49.0	463340	48.7
Maternal residence						
Copenhagen	251409	25.8	6039	24.6	245370	25.8
Big cities*	117304	12.0	2851	11.6	114453	12.0
Other	563522	57.8	15483	63.0	548039	57.6
Birth weight (g)						
<1500	65093	6.7	891	3.6	64202	6.8
1500–2500	39129	4.0	1201	4.9	37928	4.0
>2500	871358	89.3	22504	91.5	848854	89.3
Gestational age (weeks)						
<34	64313	6.6	840	3.4	63473	6.7
34–36	43012	4.4	1290	5.2	41722	4.4
>37	868255	89.0	22466	91.3	845789	88.9

\*Maternal age, household income, maternal education, cohabitation status and maternal residence are from the time of birth. Missing values: household income=43 355 (4.4%), maternal education=58 837 (6%), sex=15, cohabitation status & residence=43 345 (4.4%).

prenatally to maternal bereavement were more likely to have an injury during childhood compared with unexposed children (table 2). Exposure to maternal bereavement due to a father's death had the strongest association, especially when the cause of death was due to a traumatic event (aIRR 1.25, 95%CI 0.99 to 1.58). We found an association for sibling death only when restricting to deaths due to traumatic events for all injuries (aIRR 1.20, 95%CI 1.03 to 1.39), head injuries (aIRR 1.22, 95%CI 0.99 to 1.50) and fractures (aIRR 1.30, 95%CI 0.97 to 1.7). We did not find an elevated risk for maternal bereavement due to grandparent's death for any type of exposure. Furthermore, timing of bereavement or sex of the offspring did not modify the association.

## DISCUSSION

The aim of our study was to determine if the aetiology of childhood injuries has prenatal origins. We found that children exposed prenatally to bereavement due to a traumatic event were more likely to be hospitalised for

injuries. This was also the case for head injuries and fractures which are almost always treated in a hospital setting. Our findings were mainly related to unexpected death which may also indicate changes in postnatal family dynamics and maternal and child attachment. The underlying causes of unexpected deaths may also be related to cognitive function and linked to paternal genetic factors leading to injuries in the offspring. In our study, women exposed prenatally to bereavement tended to be older, which may explain their higher incomes and education at the time of birth, as well as their increased likelihood of bereavement exposure, especially due to a parental death.

The main strengths of this study are the large cohort size and availability of population-based data. In our analysis, we were able to include several potential covariates due to the availability of data collected by the various Danish Registries. Ascertainment of exposure information was extracted from the Civil Registration System and Death Registry. This information is considered to be highly accurate since reporting is mandated by Danish

**Table 2** Incidence rate ratios (IRR) of injuries by exposure to prenatal bereavement, relationship to the deceased and cause of death\*

	Injured children exposed to prenatal bereavement	Unadjusted IRR	Adjusted IRR	Lower CI	Upper CI
Any exposure					
Father	103	1.22	1.16	0.95	1.42
Sibling	1168	1.01	0.99	0.93	1.05
Grandparent	8592	1.04	1.02	1.00	1.05
Father/sibling	1271	1.02	1.00	0.94	1.06
Father/sibling/Grandparent	9863	1.04	1.02	1.00	1.04
Traumatic exposure†					
Father	75	1.30	1.25	0.99	1.58
Sibling	184	1.21	1.20	1.03	1.39
Grandparent	2797	1.04	1.02	0.98	1.06
Father/sibling	259	1.24	1.22	1.07	1.38
Father/sibling/grandparent	3056	1.05	1.03	1.00	1.07

\*Adjusted for maternal age at birth, place of birth, income, educational status, cohabitation status, year of birth, gestational age and birth weight.

†Traumatic exposure is defined as death due to an externally caused injury such as acts of violence, suicide or attempted suicide.

law. There are several important limitations in this study that should be considered. Not all injuries were captured since some will be treated in general practice or self-treated at home. We were also not able to include any postnatal factors that could contribute to injuries, such as temperament or environmental factors, and, furthermore, other significant sources of stressors, such as major illnesses and/or social stressors.

A number of studies have reported that stress during pregnancy may affect temperament, behavioural problems and cognitive function,<sup>1-7</sup> as well as increased risk of autism<sup>8-9</sup> and depression<sup>10</sup> in the offspring.<sup>11-12</sup> The role of prenatal stress in programming the HPA axis has been demonstrated to play a major role in the long-term health effects of the offspring.<sup>14</sup> Animals react to stress by mobilising energy stores, which involves a sequence of neurological and endocrine messages that results in the secretion of corticotropin-releasing factor and arginine vasopressin by the hypothalamus. This stimulates and releases the adrenocorticotropic hormone, which in turn releases glucocorticoids and mineralocorticoid steroid hormones. These corticosteroids enhance the catabolic processes and inhibit the anabolic processes by increasing the circulating levels of energy substrates. While short-term activation of the HPA axis allows for the rapid mobilisation of energy stores, in the long run it can lead to depletion of the energy stores and suppression of the anabolic processes and of the overall immune system.

Exposure to maternal and fetal stressors has been shown to alter the developmental trajectories of specific brain structures with persistent long-term effects.<sup>26-27</sup> Glucocorticoids play an important role for normal maturation of the fetus in many regions of the developing central nervous system,<sup>28-29</sup> which include the initiation of maturation and parturition, remodelling of axons and dendrites, and cell survival.<sup>30</sup> Prenatal glucocorticoid administration has been shown to retard brain weight at

birth in sheep,<sup>31</sup> delay maturation of neurons, myelination, glia and vasculature.<sup>32-33</sup> Furthermore, exposure to excess glucocorticoids in utero has widespread acute effects upon neuronal structure and synapse formation,<sup>34</sup> and may permanently alter the brain structure.<sup>35</sup> Both human and animal studies have demonstrated that altered hippocampal structure may be associated with a number of consequences in memory and behaviour.<sup>36-39</sup>

Observed behavioural changes in offspring prenatally exposed to glucocorticoids include altered activity and reduced attention, areas in which the dopaminergic system plays a central role. Altered dopamine receptor levels and dopamine turnover have been found in rat and non-human primate offspring prenatally exposed to stress during their fetal life.<sup>40-41</sup> Furthermore, animal models displaying abnormal activity and attention show alterations in the dopaminergic system.<sup>42</sup> Human studies examining the role between prenatal stress or prenatal glucocorticoid hyperexposure and offspring HPA axis suggest a reduction in fetal, newborn and infant HPA activity especially after pain-related stress,<sup>43</sup> in addition to disturbances in neurological and cognitive development.<sup>11</sup>

There is also evidence to suggest that infants born with adverse neonatal conditions have an increased risk of injury later in childhood. Sun *et al*<sup>44</sup> found increased incidence of childhood injuries with decreasing gestational age and birth weight, which implies that these factors are either directly associated with childhood injuries, or that they are intermediates downstream from factors associated during gestation, such as infections, pre-eclampsia or prenatal stress. Cognitive function and temperament in childhood have also been linked to injuries later in life. A study in Copenhagen of adult males found that cognitive function in childhood was associated with repeated hospital admissions for injuries as well as length of stay.<sup>45</sup> Another study on toddlers and preschoolers found that children who were high on

extraversion and low on inhibitory control tended to have more unintentional injuries at age six.<sup>46</sup>

Our findings were mainly related to unexpected paternal and sibling deaths, which may indicate that changes in postnatal family dynamics may explain the association. Paternal genetic factors related to high risk behaviours may also play a role. We had expected to see an association related to other types of death, especially loss of an older child, but only detected a small association for deaths due to traumatic causes. Not all sources of stress in this analysis are accounted for, though bereavement is a fairly random exposure and not likely to be associated with other stressors. Life course epidemiology is often used to conceptualise the proximal and distal determinants of health and disease; this framework has also been applied to injury research.<sup>47</sup> Future studies should examine other gestational or neonatal insults as predictors of injuries later in life, and also replicate these findings in different populations.

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**Contributors** JV, JLi and JØO made substantial contributions to the conception and design of the study. JV completed the analysis of the study, wrote the first draft of the manuscript and prepared subsequent revisions. JL provided insight on data analysis and interpretation. JLi, JL and JØO were involved in drafting the article and revising it critically for important intellectual content. All authors were involved with the final approval of the manuscript.

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**Data sharing statements** Research institutions may obtain access to the data by submitting a research protocol to Statistics Denmark. Denmark has many national and regional registers that contain individual health record data.

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