Increased utilization of primary health care in persons exposed to severe stress in prenatal life - A national population-based study in Denmark

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Increased utilization of primary health care in persons exposed to severe stress in prenatal life -

A national population-based study in Denmark

Jiong Li, MD, PhD 1, Yang Hu, PhD 1,2 Mai-Britt Guldin, PhD 4 Peter Vedsted, MD, PhD, 4 Mogens Vestergaard, MD, PhD 3,4

1. Section for Epidemiology, Department of Public Health, Aarhus University, Denmark
2. School of Statistics, Renmin University of China, Beijing, China
3. Section for General Practice, Department of Public Health, Aarhus University, Denmark
4. Research Unit of General Practice, Department of Public Health, Aarhus University, Denmark

Corresponding Author: Jiong Li, MD, PhD, Section for Epidemiology, Department of Public Health, Aarhus University, Bartholins Alle 2, DK 8000 Aarhus C, Denmark.
Tel: +45 8716 7972; Fax: +45 8613 1580; Email: jl@soci.au.dk

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Abstract

Objective: Recent studies have suggested that stress in a pregnant mother may affect the future health of the unborn child negatively. An excellent proxy for health problems is the use of health care resources. Using nationwide data, we examined whether persons born to mothers who lost a close relative during pregnancy have more contacts to general practice.

Design: Population-based cohort study.

Setting: Denmark.

Participants: We included all children born in Denmark from 1973 to 2002 (N=2 032 528). Exposure of prenatal stress was defined as maternal bereavement by the death of a close relative during the antenatal period. The outcome of interest was contact with general practice between 2003-2009 when the participants were between 1 and 35 years of age. Poisson regression was used to assess the association between exposure and outcome.

Outcome measures: Contacts to general practitioner.

Results: Overall, persons exposed to prenatal stress had 2% more GP contacts than those not exposed, primarily due to increased utilization of health care services during late adolescence and early adulthood. The exposed persons born to mothers who had lost a spouse had a higher risks [relative risk (RR) 1.12, 95%CI 1.10-1.14], and so did those born to mothers who had lost a close relative due to unexpected death (RR 1.06, 95% CI 1.05-1.06). Exposed persons had more contacts to general practice in daytime and more psychometric tests, talk therapies and C-reactive protein tests than unexposed persons.

Conclusions: Prenatal stress following maternal bereavement was associated with a slightly increased utilization of primary health care, mainly due to increased healthcare needs related to mental health and infections. Understanding how stress during pregnancy influences the future health of the child is an important aspect of prenatal care.
Key words: Primary health care; bereavement; cohort; prenatal stress; general practice.
ARTICLE SUMMARY

Article focus

• Exposure to prenatal stress may affect the future health of the unborn child negatively.

• An excellent proxy for health problems is the use of health care resources.

• We aimed to examine whether persons born to mothers who lost a close relative during pregnancy have more contacts to general practice.

Key messages

• Prenatal stress following maternal bereavement was associated with an increased utilization of primary health care, mainly due to more mental health care and infections.

• Understanding how stress during pregnancy influences the future health of the child is an important aspect of prenatal care.

Strengths and limitation of this study

• This is the first large population-based cohort study to examine the association between prenatal stress and primary health care use, with virtually complete follow-up and no recall and selection bias. Furthermore, through linkage to other national registers, we were able to adjust for a number of potential confounders applying to both children and their mothers.

• The limitation of the study is that we have no data on changes in the mothers’ glucocorticoid levels following bereavement, which is needed to examine dose-response patterns.
INTRODUCTION

A growing body of evidence suggests that exposure to environmental risk factors in foetal life plays a significant role in future health.\(^1\) Major life events during pregnancy may cause stress reactions that affect the development of the unborn child\(^2;3\) and lead to ill health. Recent studies have shown that prenatal stress can be associated with more hospital admissions in the offspring later in life due to mental and physical disease.\(^4;5\) However, most diseases are diagnosed and treated in primary health care, which makes health service utilization in general practice an important proxy for mental and physical health. Yet, no studies have addressed how prenatal stress affects the utilization of general practice services later in life.

Danish general practice provides tax-financed comprehensive and continuous medical care to registered patients.\(^6\) A total of 99% of the Danish population is registered with a general practice.\(^7\) General practitioners (GPs) are freely accessible serve as gatekeepers towards the rest the healthcare system.\(^7\) Except for emergencies, they must be contacted if a person needs medical advice. In this way, studying Danish general practice can provide a detailed and complete description of population’s health status.

We used maternal bereavement during prenatal life as an indicator of prenatal stress as bereavement is likely to cause stress regardless of one’s coping mechanisms.\(^8\) In a large population-based cohort study, we examined the associations between maternal bereavement during pregnancy and their offspring’s use of primary health care up to 35 years of age. We expected that the association would be stronger if the mothers experienced bereavement due to sudden and unexpected causes of death rather than other causes of death.\(^9;10\) We also expected that the death of another child in the family during pregnancy would affect the association more than the loss of a spouse or another relative.\(^11\)
METHODS

Study population, exposure and follow-up

The unique personal identification number assigned to all citizens in Denmark permits accurate linkage of data between national registers, and this population-based cohort study was based on data from several national registers in Denmark: the CPR registry, the Medical Birth Register (MBR) the Integrated Database for Longitudinal Labour Market Research (IDA), and the Danish National Health Insurance Service Registry (NHSR). The cohort included all persons born in Denmark from 1973 to 2002 (N=2,032,528). Those who were emigrant or had died before 2003 were excluded from the cohort (N=164,977). We also excluded the persons (N=47) who had visited GP for an unreasonable number of times in a year; for example, more than 100 times. The final study population included 1,867,504 persons.

We categorised children as having been exposed to stress during prenatal life if their mothers had lost a child, a spouse, a sibling, or a parent during their pregnancies or up to one year before conception (defined by gestational age). The remaining children were allocated to the unexposed cohort. Cohort members were followed from 1 January 2003 to 31 December 2009. To examine whether the associations were modified by type of experienced stress, we first categorised the exposed children into three groups based on maternal bereavement according to the mother’s relation to the deceased relative: a) loss of a spouse, b) loss of a child and c) loss of a parent or a sibling. We further categorised the exposed children into two groups according to the cause of death of the deceased relative: a) unexpected/traumatic death including suicide and accidents (ICD-8 codes: 795, 810-823, 950-959, 800-807, 825-949, 960-999; ICD-10 codes: R95-R98, V01-V89, X60-X84) and b) death by other causes.

Outcome measurements

We were interested in the overall use of general practice and specific procedures in relation to mental and physical health. Danish general practice is fully computerised with computer-based patient records
and submission of prescriptions digitally to pharmacies, etc. GPs are remunerated on a combination of capitation and fee-for-service (25/75%). The GP therefore registers every specific contact and procedure to receive payment for any services provided. The registration is collected electronically for administration in the National Health Services Register (NHSR) and is thus very complete and valid.

Information on health care utilization was obtained from the NHSR for exposed and unexposed persons. The NHSR provided data on consultations in daytime and out-of-hours (OOH) and on diagnostic tests performed during the daytime.

The main outcome of interest was the number of all GP visits per person year, the number of visits in daytime (Time code ‘1’) and the number of visits out of office hours (Time codes ‘8,9’). We also studied face-to-face contacts alone (activity code 0101) and telephone consultations alone (activity code 0201). To measure activity related to physical health, we assessed taking blood test (activity codes 2601, 2101), photometry test-B-haemoglobin (activity code 7108), C-reactive protein test (activity code 7120), spirometry/peakflow (activity codes 7113, 7121, 7183), ECG (7156) and urinary stix (activity code 7101). Measures of mental health activity were talk therapy/counselling (activity code 6101) and psychometric test (activity code 2149). Biological measurements (activity codes 2601, 2101, 7108, 7120, 7113, 7121, 7183, 7156, 7101) and psychometric activities (activity codes 6101, 2149) were merged together into two separate groups.

**Covariates**

Baseline characteristics were retrieved from registers in the child’s birth year.

Perinatal factors (gestational age, birth weight, sibling order, Apgar score at five minutes) were retrieved from the MBR. The MBR was established in 1968 and has been computerised since 1973. It holds data on all live births and stillbirths in Denmark, including characteristics of the mother and the newborn child, and variables with regard to pregnancy and delivery. Baseline socio-demographic
factors were obtained from IDA, which contains longitudinal information on demographic variables and socioeconomic data from 1980 onwards.\textsuperscript{16}

**Statistical analysis**

All data handling and statistical analyses were performed with the SAS version 9.2 statistical software package (SAS Institute, Inc., Cary, North Carolina). Follow-up started from 2003 and ended in 2009.

We used Poisson regression model (SAS PROC PHREG procedure, version 9.1) to estimate relative ratios (RRs) with a 95\% confidence interval (CI) to assess the association between prenatal bereavement and the risk of utilization of general practice. The procedure of PROC MEANS was used to compute the total number of visits to general practice and the sum of person years for each patient. The procedure of PROC GENMOD was employed to estimate the RRs.

The following potential confounders were included in the analysis: calendar year (2003-2009), gender (male, female), age, gestational age (0=37+ weeks, 1= less than 37 weeks), Apgar score at five minutes (0-7, 8-9, 10, unknown), parity (1, 2, 3, unknown), maternal age group (<27 years, 27-30 years, 31 years and over) and maternal education (0-9 years, 10-11 years, 12+ years).
RESULTS

The baseline characteristics of the cohorts are presented in Table 1. Exposed children were more likely to have low birth weight, to be born preterm, to be second or later in birth order, or to be born to mothers having lower education. Fewer children born early in the study period were categorised as exposed because the registration of grandparents was incomplete.17

Table 2 shows that during follow-up, persons in the exposed group had 2% more contacts to general practice [Relative risk (RR) 1.02, 95% CI 1.02-1.03] than persons in the unexposed group. Similar results were seen for face-to-face contact and telephone consultation We found a stronger association between maternal bereavement and the offspring's RR of subsequent health care utilization if the mother had lost a spouse ( RR 1.12, 95% CI 1.10-1.14) than if she had lost an older child (RR 1.05, 95%CI 1.05-1.06). Persons of mothers who lost a close relative due to unexpected death had a higher health care utilization (RR 1.06, 95%CI 1.05-1.06) than persons of mothers who had lost a relative due to natural death (RR 1.01, 95% CI 1.01-1.01) (Table 3).

The mean annual number of contacts to GPs was the same for exposed and unexposed persons during childhood, but exposed persons tended to have more contacts after reaching early adulthood (Figure 1). The increase in GP service utilization occurred during daytime but not during OOHs. From adolescence and early adulthood, psychometric tests and counselling were more frequent in the exposed group than in the non-exposed group. In the same age groups, the use of biological examinations (including blood tests, C-reactive protein tests) was also higher among the exposed than among the unexposed persons.
DISCUSSION

We are the first to observe that prenatal stress following maternal bereavement is associated with a slightly higher use of primary health care in the offspring during late adolescence and early adulthood. The association was stronger if the mother lost her spouse than if she lost another relative. Sudden death of mothers’ relatives was associated with a higher risk than other causes of death. An excess number of visits were found both for mental health problems (talk-therapies, psychometric tests) and for physical tests (blood tests, ECGs, C-reactive protein tests).

A large body of literature has concluded that bereavement is one of the most stressful life events and that it affects most people regardless of their coping mechanisms.\(^{18,19}\) The use of bereavement as an indicator of stress in research therefore seems justified as it provides a good exposure contrast between exposed and unexposed. We collected information on bereavement prospectively without relying on the participants’ memory. The registration of the day of death is known to be of very high quality in Danish nationwide registries, and our data on bereavement from the Danish Civil Registration System are therefore valid and complete (close to 100%). This yields accurate information on the exposure in focus.\(^{17}\) The unique nature of the Danish national register data provides our study with a number of other important methodological strengths. For example, the study was based on a large population-based cohort of all children born in Denmark, and follow-up during the period 2003-2009 was virtually complete.\(^{17}\) Bias due to selection of study participants and non-response is therefore an unlikely explanation of our findings. Furthermore, through linkage to other national registers, we were able to adjust for a number of potential confounders applying to both children and their mothers.

One limitation of the study is that we have no data on changes in the mothers’ glucocorticoid levels following bereavement, which is needed to examine dose-response patterns. Yet, it is hardly realistic to have a biological measurement in such a large study population. Furthermore, we have no data on lifestyle factors that could confound the associations. However, the socio-demographic factors included in
the model will, to some extent, adjust for the effects of life style factors. Another limitation is the heterogeneity of the data on GP contacts and the inclusion of contacts from all causes which may prevent us from examining the associations between prenatal stress and specific diseases or health problems. However, this was not defined as the main interest of this study.

The findings support our hypothesis of a possible dose-response association between cause of death and stress level. Previous studies have also shown that unexpected deaths are more stressful than expected deaths\textsuperscript{10}, and that the loss of a relative in the nuclear family is more stressful than the loss of another relative.\textsuperscript{11}

To our knowledge, this is the first population-based study to examine how prenatal stress is associated with health service use in later life. Previous research of health outcomes has focused on birth outcomes, hospital diagnoses related to physical diseases,\textsuperscript{4} psychiatric disorders\textsuperscript{5,20} and social/emotional problems.\textsuperscript{21,22} Our findings of increased health care utilization support the hypothesis of prenatal stress programming,\textsuperscript{2,3,23} albeit from a new point of view. Prenatal stress programming refers to the underlying biological mechanisms that result from the disruption of the normal pattern of foetal development by an abnormal stimulus or insult at a critical time point.\textsuperscript{24,25} Excessive glucocorticoid levels following stress in pregnant mothers can cause dysfunction of the hypothalamo-pituitary-adrenocortical (HPA) axis with permanent effects on the development of a number of body systems in the foetus,\textsuperscript{24,25} which may lead to adverse health outcomes in future life. Strong evidence from animal studies suggests that maternal stress during pregnancy may significantly affect the neurodevelopment of the foetus. These animal studies have recently been followed by a number of studies in human populations.\textsuperscript{5,26,27} Confirming these studies, our findings showed more frequent visits for psychometric tests and counselling in exposed than in unexposed persons, particularly from early adulthood onwards. Our findings of a higher number of blood tests in general practice among exposed than among unexposed persons may lend support to the argument that prenatal stress may/might be
linked to metabolic syndrome, obesity risk, or cardiovascular diseases.\textsuperscript{28-30} Lastly, the more frequent testing of C-reaction protein in exposed than in unexposed persons is also in line with observations in animal studies that prenatal stress affects immune function development,\textsuperscript{31} and in one recent human study that prenatal stress was associated with more hospitalisations due to severe infectious diseases.\textsuperscript{32}

Another interesting finding to be mentioned is the higher risks related to the death of a spouse than another older child during pregnancy. Little is known about the effects of spousal loss in pregnancy on the mother herself or on the offspring, probably because it is a very rare event and because it is very challenging to obtain data on this relation. One recent study has shown that loss of a spouse during pregnancy is related to substance abuse in the offspring.\textsuperscript{33} Our study suggests that the loss of a father during prenatal life may have more severe consequences than the loss of other family members on future health. The underlying reasons for this association is unclear, but the loss of a father may affect the child’s upbringing, socioeconomic surroundings, parental resources and the threshold for attending health care.\textsuperscript{34,35}

It should be noted that bereavement during pregnancy is only one of many stressful life events and that it accounts for only a small fraction of the overall stress level in pregnant mothers. Many other stressful events could affect women in pregnancy and causes stress in the unexposed group as well, and an increase in health service use in later life following prenatal stress may therefore be anticipated due to other causes. The mildly increased utilization in health service use following this specific event is therefore what could be expected and severe types of loss have a more noteworthy effect in early adulthood. This should be investigated in future studies to shed further light on the effects of prenatal stress.

In conclusion, offspring exposed to prenatal stress utilized general practice more than unexposed offspring, but only in later adolescence and early adulthood. Our findings contribute to our understanding of the aetiology of stress-related ill health from the view of disease programming.
Severe stress during prenatal life may programme future health in future life, which highlights the importance of better care in women’s health during pregnancy. This information should be taken into account when implementing preventive programmes in maternal and child health.

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**Competing Interests** None.

**Contributors** JL conceived the research, HY analysed the data. JL wrote the first draft of the manuscript. JL, HY, MBG, PV, MV contributed to data analysis, interpretation of results, and critical revision of the manuscript. All authors approved the final manuscript.

**Ethics approval** The study was approved by Danish Data Protection Agency (j nr. 2008-41-2680), Scientific Ethics Committee of Central Region Jylland (VEK, sagnr. M-20100252).

**Patient consent** not needed for register-based research according to laws in Denmark.

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**Data sharing statement** There are no additional data available.
REFERENCES

(1) Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of In Utero and Early-Life Conditions on Adult Health and Disease. *New Engl J Med* 2008;**359**:61-73.

(2) Kapoor A, Dunn E, Kostaki A, Andrews MH, Matthews SG. Fetal programming of hypothalamo-pituitary-adrenal function: prenatal stress and glucocorticoids. *J Physiol (Lond)* 2006;**572**:31-44.

(3) Markham JA, Koenig JI. Prenatal stress: role in psychotic and depressive diseases. *Psychopharmacology (Berl)* 2011;**214**:89-106.

(4) Hansen D, Lou HC, Olsen J. Serious life events and congenital malformations: a national study with complete follow-up. *Lancet* 2000;**356**:875-880.

(5) Khashan AS, Abel KM, McNamee R et al. Higher Risk of Offspring Schizophrenia Following Antenatal Maternal Exposure to Severe Adverse Life Events. *Arch Gen Psychiatry* 2008;**65**:146-152.

(6) Pedersen KM, Andersen JS, Soendergaard J. General Practice and Primary Health Care in Denmark. *The Journal of the American Board of Family Medicine* 2012;**25**:S34-S38.

(7) Christiansen T. Organization and financing of the Danish health care system. *Health Policy* 2002;**59**:107-118.

(8) Stroebe M, Schut H, Stroebe W. Health outcomes of bereavement. *Lancet* 2007;**370**:1960-1973.

(9) Kristensen P, Weisæth L, Heir T. Bereavement and Mental Health after Sudden and Violent Losses: A Review. *Psychiatry: Interpersonal and Biological Processes* 2012;**75**:76-97.

(10) Li J, Precht DH, Mortensen PB, Olsen J. Mortality in parents after death of a child in Denmark: a nationwide follow-up study. *Lancet* 2003;**361**:363-367.

(11) Skodol AE, Shrout PE. Use of DSM-III axis IV in clinical practice: rating etiologically significant stressors. *Am J Psychiatry* 1989;**146**:61-66.

(12) Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;**287**:2398-2399.

(13) Li J, Vestergaard M, Obel C, Cnattingus S, Giissler M, Olsen J. Cohort Profile: The Nordic Perinatal Bereavement Cohort. *Int J Epidemiol* 2010;**40**:1161-1167.

(14) Olivarius NF, Hollnagel H, Krasnik A, Pedersen PA, Thorsen H. The Danish National Health Service Register. A tool for primary health care research. *Dan Med Bull* 1997;**44**:449-453.

(15) Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;**45**:320-323.

(16) Denmark Statistics. IDA-an integrated database for labor market research. (In Danish).(http://www.dst.dk/) (under IDA (Intergrated Database for Arbejdsmarkedsforskning)). 1991.
(17) Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441-449.

(18) Holmes TH, Rahe RH. The Social Readjustment Rating Scale. *J Psychosom Res* 1967;11:213-218.

(19) Osterweis M, Solomon F, Green M. *Bereavement: Reactions, Consequences, and Care*. Washington DC: National Academy Press, 1984.

(20) Huttunen MO, Niskanen P. Prenatal loss of father and psychiatric disorders. *Arch Gen Psychiatry* 1978;35:429-431.

(21) Van den Bergh BR, Mulder EJ, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neurosci Biobehav Rev* 2005;29:237-258.

(22) O'Connor TG, Heron J, Golding J, Glover V. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *J Child Psychol Psychiatry* 2003;44:1025-1036.

(23) Weinstock M. The potential influence of maternal stress hormones on development and mental health of the offspring. *Brain Behav Immun* 2005;19:296-308.

(24) Viltart O, Vanbesien-Mailliot CC. Impact of prenatal stress on neuroendocrine programming. *ScientificWorldJournal* 2007;7:1493-1537.

(25) Welberg LA, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain. *J Neuroendocrinol* 2001;13:113-128.

(26) Abel KM, Heuvelman HP, Jorgensen L et al. Severe bereavement stress during the prenatal and childhood periods and risk of psychosis in later life: population based cohort study. *BMJ* 2014;348:f7679.

(27) Li J, Vestergaard M, Obel C et al. A nationwide study on the risk of autism after prenatal stress exposure to maternal bereavement. *Pediatrics* 2009;123:1102-1107.

(28) Reynolds RM. Corticosteroid-mediated programming and the pathogenesis of obesity and diabetes. *J Steroid Biochem Mol Biol* 2010;122:3-9.

(29) Reynolds RM. Glucocorticoid excess and the developmental origins of disease: Two decades of testing the hypothesis - 2012 Curt Richter Award Winner. *Psychoneuroendocrinology* 2013;38:1-11.

(30) Entringer S, Buss C, Wadhwa PD. Prenatal stress and developmental programming of human health and disease risk: concepts and integration of empirical findings. *Current Opinion in Endocrinology, Diabetes and Obesity* 2010;17:507-516.
(31) Parker VJ, Menzies JRW, Douglas AJ. Differential Changes in the Hypothalamic-Pituitary-Adrenal Axis and Prolactin Responses to Stress in Early Pregnant Mice. *Journal of Neuroendocrinology* 2011;23:1066-1078.

(32) Nielsen NM, Hansen AV, Simonsen J, Hviid A. Prenatal Stress and Risk of Infectious Diseases in Offspring. *Am J Epidemiol* 2011;173:990-997.

(33) Liang H, Olsen J, Cnattingus S et al. Risk of substance use disorders following prenatal or postnatal exposure to bereavement. *Drug and Alcohol Dependence* 2013;132:277-282.

(34) East L, Jackson D, O'Brien L. Father absence and adolescent development: a review of the literature. *Journal of Child Health Care* 2006;10:283-295.

(35) McLanahan S, Tach L, Schneider D. The Causal Effects of Father Absence. *Annu Rev Sociol* 2013;399:399-427.
### Table 1 Baseline characteristics of the cohorts

| Variables                  | Non-bereaved          | Bereaved            |
|----------------------------|-----------------------|---------------------|
|                            | N=1,826,806 (97.8%)   | N=40,698 (2.2%)     |
| **Gender**                 |                       |                     |
| Male                       | 942715 (52)           | 20763 (51)          |
| Female                     | 884089 (48)           | 19935 (49)          |
| missing                    | 2 (0)                 |                     |
| **Apgar score at 5 minutes** |                       |                     |
| 10                         | 1264861 (89)          | 36222 (95)          |
| 8-9                        | 32734 (2)             | 950 (2)             |
| 0-7                        | 7073 (1)              | 234 (1)             |
| missing                    | 109619 (8)            | 809 (2)             |
| **Birth Weight**           |                       |                     |
| >=2500g                    | 1245876 (88)          | 35432 (93)          |
| <2500g                     | 64623 (5)             | 2133 (6)            |
| missing                    | 103788 (7)            | 650 (2)             |
| **Gestational age**        |                       |                     |
| 0=37+ weeks                | 1222362 (86)          | 34990 (92)          |
| 1=less than 37 weeks       | 70316 (5)             | 2303 (6)            |
| missing                    | 121609 (9)            | 922 (2)             |
| **Parity**                 |                       |                     |
| 1                          | 645886 (46)           | 14321 (37)          |
| Maternal age        | Row 1 | Row 2 |
|---------------------|-------|-------|
| <27 years           | 714820(39) | 15024(37) |
| 27-30 years         | 551663(30) | 16734(41) |
| 31 years and over   | 553484(30) | 8932(22)   |
| missing             | 6839(0)    | 8(0)      |

| Maternal education*| Row 1 | Row 2 |
|-------------------|-------|-------|
| 0-9 years         | 14398(29) | 505480(21) |
| 10-11 years       | 15345(31) | 527633(22) |
| 12+ years         | 16163(32) | 578323(24) |
| missing           | 4199(8)   | 795812(33) |

| Birth year        | Row 1 | Row 2 |
|-------------------|-------|-------|
| 1973-1979         | 412519(23) | 2483(6)   |
| 1980-1989         | 549237(30) | 12708(31) |
| 1990-1999         | 667059(37) | 20222(50) |
| 2000-2003         | 197991(11) | 5285(13)  |

* Data available from 1980.
### Table 2 Relative risk of any general practice (GP) visit by way of contact

| Exposure     | Type of GP contact          | No. visits | Person years | Adjusted RR* (95%CI) |
|--------------|-----------------------------|------------|--------------|----------------------|
| Bereaved     | All GP contacts             | 1635761    | 280902       | 1.02 (1.02-1.02)     |
|              | Contacts in office hours    | 1453761    | 280902       | 1.02 (1.02-1.02)     |
|              | Contacts out of hours       | 181358     | 280902       | 1.03 (1.02-1.03)     |
|              | Face-to-face contacts       | 685094     | 280902       | 1.02 (1.01-1.02)     |
|              | Phone consultation          | 451553     | 280902       | 1.02 (1.02-1.03)     |
| Non-bereaved |                             | 12465586   | 1826806      | 1.00 (ref)           |

*Adjusted for age, calendar, sex, Apgar score at 5 minutes, preterm birth, parity, low birth weight, maternal age and maternal education.
Table 3 Relative risk (RR) of any general practice (GP) visit according to type of loss (bereavement).

| Type of loss                        | Type of GP contact          | No. Visits | Person years | Adjusted RR* (95%CI) |
|------------------------------------|-----------------------------|------------|--------------|----------------------|
| Non-bereaved                        | All contacts                | 12465586   | 1826806      | 1.00 (ref)           |
| Bereaved - Relation to the deceased relative |                            |            |              |                      |
| Sibling                             | All contacts                | 338235     | 50630        | 1.06 (1.06-1.07)     |
| Father                              | All contacts                | 28164      | 3752         | 1.12 (1.11-1.14)     |
| Other                               | All contacts                | 1269362    | 226520       | 1.01 (1.00-1.01)     |
| Sibling                             | Contacts in office hours    | 303921     | 50630        | 1.05 (1.05-1.06)     |
| Father                              | Contacts in office hours    | 25271      | 3752         | 1.12 (1.10-1.14)     |
| Other                               | Contacts in office hours    | 1124569    | 226520       | 1.00 (1.00-1.01)     |
| Sibling                             | Contacts out-of-hours       | 34219      | 50630        | 1.15 (1.13-1.16)     |
| Father                              | Contacts out-of-hours       | 2889       | 3752         | 1.18 (1.13-1.24)     |
| Other                               | Contacts out-of-hours       | 144250     | 226520       | 1.02 (1.01-1.03)     |
| Sibling                             | Face-to-face contacts       | 137561     | 50630        | 1.07 (1.06-1.07)     |
| Father                              | Face-to-face contacts       | 11572      | 3752         | 1.13 (1.10-1.15)     |
| Other                               | Face-to-face contacts       | 535961     | 226520       | 1.00 (1.00-1.00)     |
| Sibling                             | Phone consultation          | 95612      | 50630        | 1.10 (1.09-1.11)     |
|                  |                      |          |          |              |
|------------------|----------------------|----------|----------|--------------|
| Father Phone consultation | 8019 | 3752 | 1.13(1.09-1.16) |
| Other Phone consultation | 347922 | 226520 | 1.01(1.01-1.02) |

*Bereaved - Type of death*

|                  |                      |          |          |              |
|------------------|----------------------|----------|----------|--------------|
| Sudden death All contacts | 262489 | 42011 | 1.06(1.05-1.06) |
| Other deaths All contacts | 1353226 | 235373 | 1.01(1.01-1.01) |
| Sudden death Contacts in office hours | 233219 | 42011 | 1.05(1.05-1.06) |
| Other deaths Contacts in office hours | 1202551 | 235373 | 1.01(1.00-1.01) |
| Sudden death Contacts out-of-hours | 42011 | 42011 | 1.11(1.10-1.13) |
| Other deaths Contacts out-of-hours | 150121 | 235373 | 1.03(1.02-1.03) |
| Sudden death Face-to-face contacts | 109286 | 42011 | 1.05(1.04-1.06) |
| Other deaths Face-to-face contacts | 567144 | 235373 | 1.00(1.00-1.01) |
| Sudden death Phone consultation | 73049 | 42011 | 1.08(1.07-1.09) |
| Other deaths Phone consultation | 373081 | 235373 | 1.02(1.01-1.02) |

*Adjusted for age, calendar, sex, Apgar sores at 5 minutes, preterm birth, parity, low birth weight, maternal age and maternal education.
Figure 1. Contacts with GP, by type of contact and time of contact
Figure 2. Contacts with GP, by reasons of contact.
Increased utilization of primary health care in persons exposed to severe stress in prenatal life - A national population-based study in Denmark

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Increased utilization of primary health care in persons exposed to severe stress in prenatal life -

A national population-based study in Denmark

Jiong Li, MD, PhD 1, Yang Hu, PhD 1,2 Mai-Britt Guldin, PhD 4 Peter Vedsted, MD, PhD, 4 Mogens Vestergaard, MD, PhD 3,4

1. Section for Epidemiology, Department of Public Health, Aarhus University, Denmark
2. School of Information, Central University of Finance and Economics, Beijing, China
3. Section for General Practice, Department of Public Health, Aarhus University, Denmark
4. Research Unit of General Practice, Department of Public Health, Aarhus University, Denmark

Corresponding Author: Jiong Li, MD, PhD, Section for Epidemiology, Department of Public Health, Aarhus University, Bartholins Alle 2, DK 8000 Aarhus C, Denmark.
Tel: +45 8716 7972; Fax: +45 8613 1580; Email: jl@soci.au.dk

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Abstract

Objective: Recent studies have suggested that stress in a pregnant mother may affect the future health of the unborn child negatively. An excellent proxy for health problems is the use of health care resources. Using nationwide data, we examined whether persons born to mothers who lost a close relative during pregnancy have more contacts to general practice.

Design: Population-based cohort study.

Setting: Denmark.

Participants: We included all children born in Denmark from 1973 to 2002 (N=2,032,528). Exposure of prenatal stress was defined as maternal bereavement by the death of a close relative during the antenatal period. The outcome of interest was contact with general practice between 2003-2009 when the participants were between 1 and 35 years of age. Poisson regression was used to assess the association between exposure and outcome.

Outcome measures: Contacts to general practitioner.

Results: Overall, persons exposed to prenatal stress had 2% more GP contacts than those not exposed, primarily due to increased utilization of health care services during late adolescence and early adulthood. The exposed persons born to mothers who had lost a spouse had a higher risks [relative risk (RR) 1.12, 95%CI 1.10-1.14], and so did those born to mothers who had lost a close relative due to unexpected death (RR 1.06, 95% CI 1.05-1.06). Exposed persons had more contacts to general practice in daytime and more psychometric tests, talk therapies and C-reactive protein tests than unexposed persons.

Conclusions: Prenatal stress following maternal bereavement was associated with a slightly increased utilization of primary health care, mainly due to increased healthcare needs related to mental health and infections. Understanding how stress during pregnancy influences the future health of the child is an important aspect of prenatal care.
Key words: Primary health care; bereavement; cohort; prenatal stress; general practice.
ARTICLE SUMMARY

Article focus

- Exposure to prenatal stress may affect the future health of the unborn child negatively.
- An excellent proxy for health problems is the use of health care resources.
- We aimed to examine whether persons born to mothers who lost a close relative during pregnancy have more contacts to general practice.

Key messages

- Prenatal stress following maternal bereavement was associated with an increased utilization of primary health care, mainly due to more mental health care and infections.
- Understanding how stress during pregnancy influences the future health of the child is an important aspect of prenatal care.

Strengths and limitation of this study

- This is the first large population-based cohort study to examine the association between prenatal stress and primary health care use, with virtually complete follow-up and no recall and selection bias. Furthermore, through linkage to other national registers, we were able to adjust for a number of potential confounders applying to both children and their mothers.
- The limitation of the study is that we have no data on changes in the mothers’ glucocorticoid levels following bereavement, which is needed to examine dose-response patterns.
INTRODUCTION

A growing body of evidence suggests that exposure to environmental risk factors in foetal life plays a
significant role in future health. Major life events during pregnancy may cause stress reactions that
affect the development of the unborn child and lead to ill health. Recent studies have shown that
prenatal stress can be associated with more hospital admissions in the offspring later in life due to
mental and physical disease. However, most diseases are diagnosed and treated in primary health
care, which makes health service utilization in general practice an important proxy for mental and
physical health. Yet, no studies have addressed how prenatal stress affects the utilization of general
practice services later in life.

Danish general practice provides tax-financed comprehensive and continuous medical care to
registered patients. A total of 99% of the Danish population is registered with a general practice.
General practitioners (GPs) are freely accessible serve as gatekeepers towards the rest the healthcare
system. Except for emergencies, they must be contacted if a person needs medical advice. In this way,
studying Danish general practice can provide a detailed and complete description of population’s
health status.

We used maternal bereavement during prenatal life as an indicator of prenatal stress as
bereavement is likely to cause stress regardless of one’s coping mechanisms. In a large population-
based cohort study, we examined the associations between maternal bereavement during pregnancy
and their offspring’s use of primary health care up to 35 years of age. We expected that the association
would be stronger if the mothers experienced bereavement due to sudden and unexpected causes of
death rather than other causes of death. We also expected that the death of another child in the
family during pregnancy would affect the association more than the loss of a spouse or another relative.
METHODS

Study population, exposure and follow-up

The unique personal identification number assigned to all citizens in Denmark permits accurate linkage of data between national registers, and this population-based cohort study was based on data from several national registers in Denmark: the CPR registry, the Medical Birth Register (MBR) the Integrated Database for Longitudinal Labour Market Research (IDA), and the Danish National Health Insurance Service Registry (NHSR). The cohort included all persons born in Denmark from 1973 to 2002 (N=2,032,528). Those who were emigrant or had died before 2003 were excluded from the cohort (N=164,977). We also excluded the persons (N=47) who had visited GP for an unreasonable number of times in a year (more than 100 times). The final study population included 1,867,504 persons.

We categorised children as having been exposed to stress during prenatal life if their mothers had lost a child, a spouse, a sibling, or a parent during their pregnancies or up to one year before conception (defined by gestational age). The remaining children were allocated to the unexposed cohort. Cohort members were followed from 1 January 2003 to 31 December 2009. To examine whether the associations were modified by type of experienced stress, we first categorised the exposed children into three groups based on maternal bereavement according to the mother’s relation to the deceased relative: a) loss of a spouse, b) loss of a child and c) loss of a parent or a sibling. We further categorised the exposed children into two groups according to the cause of death of the deceased relative: a) unexpected/traumatic death including suicide and accidents (ICD-8 codes: 795, 810-823, 950-959, 800-807, 825-949, 960-999; ICD-10 codes: R95-R98,V01-V89,X60-X84) and b) death by other causes.

Outcome measurements

We were interested in the overall use of general practice and specific procedures in relation to mental and physical health. Danish general practice is fully computerised with computer-based patient records and submission of prescriptions digitally to pharmacies, etc. GPs are remunerated on a combination
of capitation and fee-for-service (25/75%). The GP therefore registers every specific contact and
procedure to receive payment for any services provided. The registration is collected electronically for
administration in the National Health Services Register (NHSR) and is thus very complete and valid. Information on health care utilization was obtained from the NHSR for exposed and unexposed persons. The NHSR provided data on consultations in daytime and out-of-hours (OOH) and on diagnostic tests performed during the daytime.¹⁴

The main outcome of interest was the number of all GP visits per person year, the number of visits in daytime (Time code ‘1’) and the number of visits out of office hours (Time codes ‘8,9’). We also studied face-to-face contacts alone (activity code 0101) and telephone consultations alone (activity code 0201). We also examined the reasons for contacts as we want to know whether prenatal stress lead to differences in GP visit in the ways of treatment or management. For example, to measure activities related to physical health, we assessed taking blood test (activity codes 2601, 2101), photometry test-B-haemoglobin (activity code 7108), C-reactive protein test (activity code 7120), spirometry/peakflow (activity codes 7113,7121,7183), ECG (7156) and urinary stix (activity code 7101). Measures of mental health activity were talk therapy/counselling (activity code 6101) and psychometric test (activity code 2149). Biological measurements (activity codes 2601, 2101, 7108, 7120, 7113, 7121, 7183, 7156, 7101) and psychometric activities (activity codes 6101, 2149) were merged together into two separate groups. ¹⁴

Covariates
Baseline characteristics were retrieved from registers in the child’s birth year. Perinatal factors (gestational age, birth weight, sibling order, Apgar score at five minutes) were retrieved from the MBR. ¹⁵ The MBR was established in 1968 and has been computerised since 1973. It holds data on all live births and stillbirths in Denmark, including characteristics of the mother and the newborn child, and variables with regard to pregnancy and delivery. Baseline socio-demographic
factors were obtained from IDA, which contains longitudinal information on demographic variables and socioeconomic data from 1980 onwards.  

**Statistical analysis**

All data handling and statistical analyses were performed with the SAS version 9.2 statistical software package (SAS Institute, Inc., Cary, North Carolina). Follow-up started from 2003 and ended in 2009.

We used Poisson regression model (SAS PROC PHREG procedure, version 9.1) to estimate relative ratios (RRs) with a 95% confidence interval (CI) to assess the association between prenatal bereavement and the risk of utilization of general practice. The procedure of PROC MEANS was used to compute the total number of visits to general practice and the sum of person years for each patient. The procedure of PROC GENMOD was employed to estimate the RRs.

The following potential confounders were included in the analysis: calendar year (2003-2009), gender (male, female), age, gestational age (0=’>37 weeks’, 1= ‘less than 37 weeks’), Apgar score at five minutes (0-7, 8-9, 10, unknown), parity (1, 2, 3, unknown), maternal age group (<27 years, 27-30 years, 31 years and over) and maternal education (0-9 years, 10-11 years, 12+ years), and birthweight (1=’less than 2500 g’, 0=’>2055 g’).
RESULTS

The baseline characteristics of the cohorts are presented in Table 1. Exposed children were more likely to have low birth weight, to be born preterm, to be second or later in birth order, or to be born to mothers having lower education. Fewer children born early in the study period were categorised as exposed because the registration of grandparents was incomplete.17

Table 2 shows that during follow-up, persons in the exposed group had 2% more contacts to general practice [Relative risk (RR) 1.02, 95% CI 1.02-1.03] than persons in the unexposed group. Similar results were seen for face-to-face contact and telephone consultation. We found a stronger association between maternal bereavement and the offspring’s RR of subsequent health care utilization if the mother had lost a spouse (RR 1.12, 95% CI 1.10-1.14) than if she had lost an older child (RR 1.05, 95% CI 1.05-1.06). Persons of mothers who lost a close relative due to unexpected death had a higher health care utilization (RR 1.06, 95% CI 1.05-1.06) than persons of mothers who had lost a relative due to natural death (RR 1.01, 95% CI 1.01-1.01) (Table 3).

The mean annual number of contacts to GPs was the same for exposed and unexposed persons during childhood, but exposed persons tended to have more contacts after reaching early adulthood (Figure 1). The increase in GP service utilization occurred during daytime but not during OOHs. From adolescence and early adulthood, psychometric tests and counselling were more frequent in the exposed group than in the non-exposed group. In the same age groups, the use of biological examinations (including blood tests, C-reactive protein tests) was also higher among the exposed than among the unexposed persons (Figure 2).
DISCUSSION

We are the first to observe that prenatal stress following maternal bereavement is associated with a slightly higher use of primary health care in the offspring during late adolescence and early adulthood. The association was stronger if the mother lost her spouse than if she lost another relative. Sudden death of mothers’ relatives was associated with a higher risk than other causes of death. An excess number of visits were found both for mental health problems (talk-therapies, psychometric tests) and for physical tests (blood tests, ECGs, C-reactive protein tests).

A large body of literature has concluded that bereavement is one of the most stressful life events and that it affects most people regardless of their coping mechanisms.\(^*\) The use of bereavement as an indicator of stress in research therefore seems justified as it provides a good exposure contrast between exposed and unexposed. We collected information on bereavement prospectively without relying on the participants’ memory. The registration of the day of death is known to be of very high quality in Danish nationwide registries, and our data on bereavement from the Danish Civil Registration System are therefore valid and complete (close to 100%). This yields accurate information on the exposure in focus.\(^*\) The unique nature of the Danish national register data provides our study with a number of other important methodological strengths. For example, the study was based on a large population-based cohort of all children born in Denmark, and follow-up during the period 2003-2009 was virtually complete.\(^*\) Bias due to selection of study participants and non-response is therefore an unlikely explanation of our findings. Furthermore, through linkage to other national registers, we were able to adjust for a number of potential confounders applying to both children and their mothers.

One limitation of the study is that we have no data on changes in the mothers’ glucocorticoid levels following bereavement, which is needed to examine dose-response patterns. Yet, it is hardly realistic to have a biological measurement in such a large study population. Furthermore, we have no data on life style factors that could confound the associations. However, the socio-demographic factors included in
the model will, to some extent, adjust for the effects of life style factors. Another limitation is the heterogeneity of the data on GP contacts and the inclusion of contacts from all causes which may prevent us from examining the associations between prenatal stress and specific diseases or health problems. However, this was not defined as the main interest of this study.

The findings support our hypothesis of a possible dose-response association between cause of death and stress level. Previous studies have also shown that unexpected deaths are more stressful than expected deaths\(^{10}\), and that the loss of a relative in the nuclear family is more stressful than the loss of another relative.\(^{11}\)

To our knowledge, this is the first population-based study to examine how prenatal stress is associated with health service use in later life. Previous research of health outcomes has focused on birth outcomes, hospital diagnoses related to physical diseases,\(^4\) psychiatric disorders\(^5;20\) and social/emotional problems.\(^{21;22}\) Our findings of increased health care utilization support the hypothesis of prenatal stress programming,\(^2;3;23\) albeit from a new point of view. Prenatal stress programming refers to the underlying biological mechanisms that result from the disruption of the normal pattern of foetal development by an abnormal stimulus or insult at a critical time point.\(^{24;25}\) Excessive glucocorticoid levels following stress in pregnant mothers can cause dysfunction of the hypothalamo-pituitary-adrenocortical (HPA) axis with permanent effects on the development of a number of body systems in the foetus,\(^{24;25}\) which may lead to adverse health outcomes in future life. Strong evidence from animal studies suggests that maternal stress during pregnancy may significantly affect the neurodevelopment of the foetus. These animal studies have recently been followed by a number of studies in human populations.\(^5;26;27\) Confirming these studies, our findings showed more frequent visits for psychometric tests and counselling in exposed than in unexposed persons, particularly from early adulthood onwards. Our findings of a higher number of blood tests in general practice among exposed than among unexposed persons may lend support to the argument that prenatal stress may/might be
linked to metabolic syndrome, obesity risk, or cardiovascular diseases.\textsuperscript{28-30} Lastly, the more frequent testing of C-reactive protein in exposed than in unexposed persons is also in line with observations in animal studies that prenatal stress affects immune function development,\textsuperscript{31} and in one recent human study that prenatal stress was associated with more hospitalisations due to severe infectious diseases.\textsuperscript{32}

Another interesting finding to be mentioned is the higher risks related to the death of a spouse than another older child during pregnancy. Little is known about the effects of spousal loss in pregnancy on the mother herself or on the offspring, probably because it is a very rare event and because it is very challenging to obtain data on this relation. One recent study has shown that loss of a spouse during pregnancy is related to substance abuse in the offspring.\textsuperscript{33} Our study suggests that the loss of a father during prenatal life may have more severe consequences than the loss of other family members on future health. The underlying reasons for this association is unclear, but the loss of a father may affect the child’s upbringing, socioeconomic surroundings, parental resources and the threshold for attending health care.\textsuperscript{34,35}

It might not be of very clinical significance, as we only observed a mildly increased utilization in health service use following this specific event of bereavement. However, it should be noted that bereavement during pregnancy is only one of many stressful life events and that it accounts for only a small fraction of the overall stress level in pregnant mothers. Many other stressful events could affect women in pregnancy and causes stress in the unexposed group as well, and an increase in health service use in later life following prenatal stress may therefore be anticipated due to other causes. It is therefore important to recognize the potential effects of stress at the first step. How the combined maternal psychological stress affects future health service use is warranted to be investigated in future studies. On the other hand, it remains to be elucidated whether the associations are different for specific stress exposures, depending on the treatment and specific disease outcomes.
In conclusion, offspring exposed to prenatal stress utilized general practice more than unexposed offspring, but only in later adolescence and early adulthood. Our findings contribute to our understanding of the aetiology of stress-related ill health from the view of disease programming. Severe stress during prenatal life may programme future health in future life, which highlights the importance of better care in women’s health during pregnancy. This information should be taken into account when implementing preventive programmes in maternal and child health.

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**Competing Interests** None.

**Contributors** JL conceived the research, HY analysed the data. JL wrote the first draft of the manuscript. JL, HY, MBG, PV, MV contributed to data analysis, interpretation of results, and critical revision of the manuscript. All authors approved the final manuscript.

**Ethics approval** The study was approved by Danish Data Protection Agency (j nr. 2008-41-2680), Scientific Ethics Committee of Central Region Jylland (VEK, sagnr. M-20100252).

**Patient consent** not needed for register-based research according to laws in Denmark.

**Provenance and peer review** Not commissioned; externally peer reviewed.
Data sharing statement There are no additional data available.

Figure Legends

Figure 1. Contacts with GP, by type of contact and time of contact

Figure 2. Contacts with GP, by reasons of contact.
REFERENCES

(1) Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of In Utero and Early-Life Conditions on Adult Health and Disease. *New Engl J Med* 2008;**359**:61-73.

(2) Kapoor A, Dunn E, Kostaki A, Andrews MH, Matthews SG. Fetal programming of hypothalamo-pituitary-adrenal function: prenatal stress and glucocorticoids. *J Physiol (Lond)* 2006;**572**:31-44.

(3) Markham JA, Koenig JI. Prenatal stress: role in psychotic and depressive diseases. *Psychopharmacology (Berl)* 2011;**214**:89-106.

(4) Hansen D, Lou HC, Olsen J. Serious life events and congenital malformations: a national study with complete follow-up. *Lancet* 2000;**356**:875-880.

(5) Khashan AS, Abel KM, McNamee R et al. Higher Risk of Offspring Schizophrenia Following Antenatal Maternal Exposure to Severe Adverse Life Events. *Arch Gen Psychiatry* 2008;**65**:146-152.

(6) Pedersen KM, Andersen JS, Soendergaard J. General Practice and Primary Health Care in Denmark. *The Journal of the American Board of Family Medicine* 2012;**25**:S34-S38.

(7) Christiansen T. Organization and financing of the Danish health care system. *Health Policy* 2002;**59**:107-118.

(8) Stroebe M, Schut H, Stroebe W. Health outcomes of bereavement. *Lancet* 2007;**370**:1960-1973.

(9) Kristensen P, Weisaeth L, Heir T. Bereavement and Mental Health after Sudden and Violent Losses: A Review. *Psychiatry: Interpersonal and Biological Processes* 2012;**75**:76-97.

(10) Li J, Precht DH, Mortensen PB, Olsen J. Mortality in parents after death of a child in Denmark: a nationwide follow-up study. *Lancet* 2003;**361**:363-367.

(11) Skodol AE, Shrout PE. Use of DSM-III axis IV in clinical practice: rating etiologically significant stressors. *Am J Psychiatry* 1989;**146**:61-66.

(12) Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;**287**:2398-2399.

(13) Li J, Vestergaard M, Obel C, Cnattingus S, Gissler M, Olsen J. Cohort Profile: The Nordic Perinatal Bereavement Cohort. *Int J Epidemiol* 2010;**40**:1161-1167.

(14) Olivarius NF, Hollnagel H, Krasnik A, Pedersen PA, Thorsen H. The Danish National Health Service Register. A tool for primary health care research. *Dan Med Bull* 1997;**44**:449-453.

(15) Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;**45**:320-323.

(16) Denmark Statistics. IDA-an intergrated database for labor market research. (In Danish).(http://www.dst.dk/) (under IDA (Intergrated Database for Arbejdsmarkedsforskning)). 1991.
(17) Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441-449.

(18) Holmes TH, Rahe RH. The Social Readjustment Rating Scale. *J Psychosom Res* 1967;11:213-218.

(19) Osterweis M, Solomon F, Green M. Bereavement: Reactions, Consequences, and Care. Washington DC: National Academy Press, 1984.

(20) Huttunen MO, Niskanen P. Prenatal loss of father and psychiatric disorders. *Arch Gen Psychiatry* 1978;35:429-431.

(21) Van den Bergh BR, Mulder EJ, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neurosci Biobehav Rev* 2005;29:237-258.

(22) O'Connor TG, Heron J, Golding J, Glover V. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *J Child Psychol Psychiatry* 2003;44:1025-1036.

(23) Weinstock M. The potential influence of maternal stress hormones on development and mental health of the offspring. *Brain Behav Immun* 2005;19:296-308.

(24) Viltart O, Vanbesien-Mailliot CC. Impact of prenatal stress on neuroendocrine programming. *ScientificWorldJournal* 2007;7:1493-1537.

(25) Welberg LA, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain. *J Neuroendocrinol* 2001;13:113-128.

(26) Abel KM, Heuvelman HP, Jorgensen L et al. Severe bereavement stress during the prenatal and childhood periods and risk of psychosis in later life: population based cohort study. *BMJ* 2014;348:f7679.

(27) Li J, Vestergaard M, Obel C et al. A nationwide study on the risk of autism after prenatal stress exposure to maternal bereavement. *Pediatrics* 2009;123:1102-1107.

(28) Reynolds RM. Corticosteroid-mediated programming and the pathogenesis of obesity and diabetes. *J Steroid Biochem Mol Biol* 2010;122:3-9.

(29) Reynolds RM. Glucocorticoid excess and the developmental origins of disease: Two decades of testing the hypothesis - 2012 Curt Richter Award Winner. *Psychoneuroendocrinology* 2013;38:1-11.

(30) Entringer S, Buss C, Wadhwa PD. Prenatal stress and developmental programming of human health and disease risk: concepts and integration of empirical findings. *Current Opinion in Endocrinology, Diabetes and Obesity* 2010;17:507-516.
(31) Parker VJ, Menzies JRW, Douglas AJ. Differential Changes in the Hypothalamic-Pituitary-Adrenal Axis and Prolactin Responses to Stress in Early Pregnant Mice. *Journal of Neuroendocrinology* 2011;23:1066-1078.

(32) Nielsen NM, Hansen AV, Simonsen J, Hviid A. Prenatal Stress and Risk of Infectious Diseases in Offspring. *Am J Epidemiol* 2011;173:990-997.

(33) Liang H, Olsen J, Cnattingus S et al. Risk of substance use disorders following prenatal or postnatal exposure to bereavement. *Drug and Alcohol Dependence* 2013;132:277-282.

(34) East L, Jackson D, O'Brien L. Father absence and adolescent development: a review of the literature. *Journal of Child Health Care* 2006;10:283-295.

(35) McLanahan S, Tach L, Schneider D. The Causal Effects of Father Absence. *Annu Rev Sociol* 2013;399:399-427.
Table 1 Baseline characteristics of the cohorts

| Variables                  | 1980–2002 | 1973–2002 |
|----------------------------|-----------|-----------|
|                            | Non-bereaved | Bereaved | Non-bereaved | Bereaved |
|                            | N=1,414,287 | N=38,215 | N=1,826,806 | N=40,698 |
| Gender                     |            |           |            |           |
| Male                       | 726671(51) | 19439(51) | 942715(52) | 20763(51) |
| Female                     | 687614(49) | 18776(49) | 884089(48) | 19935(49) |
| missing                    | 2(0)       | 2(0)      | 2(0)       | 2(0)      |
| Apgar score at 5 minutes   |            |           |            |           |
| 10                         | 1264861(89)| 36222(95)| 1366773(75)| 37201(91)|
| 8-9                        | 32734(2)   | 950(2)    | 34774(2)   | 985(2)   |
| 0-7                        | 7073(1)    | 234(1)    | 7371(0)    | 238(1)   |
| Missing                    | 109619(8)  | 809(2)    | 417888(23)| 2274(6)  |
| Birth Weight*              |            |           |            |           |
| >=2500g                    | 1245876(88)| 35432(93)| 1295492(71)| 36006(88)|
| <2500g                     | 64623(5)   | 2133(6)   | 67151(4)   | 2180(5)  |
| Missing                    | 103788(7)  | 650(2)    | 464163(25)| 2512(6)  |
| Gestational age*           |            |           |            |           |
| 0=37+ weeks                | 1222362(86)| 34990(92)| 1294836(71)| 35681(88)|
| 1=less than 37 weeks       | 70316(5)   | 2303(6)   | 73720(4)   | 2359(6)  |
| missing                    | 121609(9)  | 922(2)    | 458250(25)| 2658(7)  |
| Parity                     |            |           |            |           |
| 1                          | 645886(46)| 14321(37)| 956594(52)| 15024(37)|
| 2                          | 525185(37)| 15270(40)| 616084(34)| 16734(41)|
| 3                          | 234560(17)| 8621(23) | 242170(13)| 8932(22) |
| missing                    | 8656(1)    | 3(0)      | 11958(1)  | 8(0)     |
| Maternal age               |            |           |            |           |
| <27 years                  | 495432(35)| 11267(29)| 714820(39)| 12682(31)|
| 27-30 years                | 439574(31)| 11618(30)| 551663(30)| 12270(30)|
| 31 years and over          | 473560(33)| 15330(40)| 553484(30)| 15746(39)|
| missing                    | 5721(0)    |          | 6839(0)   |          |
| Maternal education*        |            |           |            |           |
| 0-9 years                  | 428202(30)| 12658(33)| 428202(23)| 12658(31)|
| 10-11 years                | 416669(29)| 12351(32)| 416669(23)| 12351(30)|
| 12+ years                  | 394823(28)| 11748(31)| 394823(22)| 11748(29)|
| missing                    | 174593(12)| 1458(4)  | 587112(32)| 3941(10)|

* Data available from 1980.
Table 2 Relative risk of any general practice (GP) visit by way of contact

| Exposure   | Type of GP contact     | No. visits | Person years | Adjusted RR* (95%CI) |
|------------|------------------------|------------|--------------|----------------------|
| Bereaved   | All GP contacts        | 1635761    | 280902       | 1.02 (1.02-1.02)     |
|            | Contacts in office hours | 1453761    | 280902       | 1.02 (1.02-1.02)     |
|            | Contacts out of hours  | 181358     | 280902       | 1.03 (1.02-1.03)     |
|            | Face-to-face contacts  | 685094     | 280902       | 1.02 (1.01-1.02)     |
|            | Phone consultation     | 451553     | 280902       | 1.02 (1.02-1.03)     |
| Non-bereaved|                        | 78178124   | 12465586     | 1.00 (ref)           |

*Adjusted for age, calendar, sex, Apgar score at 5 minutes, preterm birth, parity, low birth weight, maternal age and maternal education.
Table 3 Relative risk (RR) of any general practice (GP) visit according to type of loss (bereavement).

| Type of loss                      | Type of GP contact     | No. Visits | Person years | Adjusted RR* (95%CI) |
|----------------------------------|------------------------|------------|--------------|----------------------|
| **Non-bereaved**                 | All contacts           | 78178124   | 12465586     | 1.00 (ref)           |
| **Bereaved - Relation to the deceased relative** | | | | |
| Sibling                          | All contacts           | 338235     | 50630        | 1.06 (1.06-1.07)     |
| Father                           | All contacts           | 28164      | 3752         | 1.12 (1.11-1.14)     |
| Other                            | All contacts           | 1269362    | 226520       | 1.01 (1.00-1.01)     |
| Sibling                          | Contacts in office hours | 303921   | 50630        | 1.05 (1.05-1.06)     |
| Father                           | Contacts in office hours | 25271   | 3752         | 1.12 (1.10-1.14)     |
| Other                            | Contacts in office hours | 1124569 | 226520       | 1.00 (1.00-1.01)     |
| Sibling                          | Contacts out-of-hours  | 34219      | 50630        | 1.15 (1.13-1.16)     |
| Father                           | Contacts out-of-hours  | 2889       | 3752         | 1.18 (1.13-1.24)     |
| Other                            | Contacts out-of-hours  | 144250     | 226520       | 1.02 (1.01-1.03)     |
| Sibling                          | Face-to-face contacts  | 137561     | 50630        | 1.07 (1.06-1.07)     |
| Father                           | Face-to-face contacts  | 11572      | 3752         | 1.13 (1.10-1.15)     |
| Other                            | Face-to-face contacts  | 535961     | 226520       | 1.00 (1.00-1.00)     |
| Sibling                          | Phone consultation     | 95612      | 50630        | 1.10 (1.09-1.11)     |
| Bereaved - Type of death† | Father  | Other  |  |  |
|---------------------------|---------|--------|---|---|
| Sudden death              | Phone consultation | 8019     | 3752   | 1.13(1.09-1.16) |
| Other deaths              | Phone consultation | 347922   | 226520 | 1.01(1.01-1.02) |
| Sudden death              | All contacts     | 262489   | 42011  | 1.06(1.05-1.06) |
| Other deaths              | All contacts     | 1353226  | 235373 | 1.01(1.01-1.01) |
| Sudden death              | Contacts in office hours | 233219   | 42011  | 1.05(1.05-1.06) |
| Other deaths              | Contacts in office hours | 1202551  | 235373 | 1.01(1.00-1.01) |
| Sudden death              | Contacts out-of-hours | 42011    | 42011  | 1.11(1.10-1.13) |
| Other deaths              | Contacts out-of-hours | 150121   | 235373 | 1.03(1.02-1.03) |
| Sudden death              | Face-to-face contacts | 109286   | 42011  | 1.05(1.04-1.06) |
| Other deaths              | Face-to-face contacts | 567144   | 235373 | 1.00(1.00-1.01) |
| Sudden death              | Phone consultation | 73049    | 42011  | 1.08(1.07-1.09) |
| Other deaths              | Phone consultation | 373081   | 235373 | 1.02(1.01-1.02) |

*Adjusted for age, calendar, sex, Apgar sores at 5 minutes, preterm birth, parity, low birth weight, maternal age and maternal education. †: Sudden death: unexpected /traumatic death, mostly from suicide and accidents.
Increased utilization of primary health care in persons exposed to severe stress in prenatal life -

A national population-based study in Denmark

Jiong Li, MD, PhD 1, Yang Hu, PhD 1,2 Mai-Britt Guldin, PhD 4 Peter Vedsted, MD, PhD, 4 Mogens Vestergaard, MD, PhD 3,4

1. Section for Epidemiology, Department of Public Health, Aarhus University, Denmark
2. School of Statistics, Information, Renmin University of China, Central University of Finance and Economics, Beijing, China
3. Section for General Practice, Department of Public Health, Aarhus University, Denmark
4. Research Unit of General Practice, Department of Public Health, Aarhus University, Denmark

Corresponding Author: Jiong Li, MD, PhD, Section for Epidemiology, Department of Public Health, Aarhus University, Bartholins Alle 2, DK 8000 Aarhus C, Denmark.
Tel: +45 8716 7972; Fax: +45 8613 1580; Email: jl@soci.au.dk

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Abstract

Objective: Recent studies have suggested that stress in a pregnant mother may affect the future health of the unborn child negatively. An excellent proxy for health problems is the use of health care resources. Using nationwide data, we examined whether persons born to mothers who lost a close relative during pregnancy have more contacts to general practice.

Design: Population-based cohort study.

Setting: Denmark.

Participants: We included all children born in Denmark from 1973 to 2002 (N=2 032 528). Exposure of prenatal stress was defined as maternal bereavement by the death of a close relative during the antenatal period. The outcome of interest was contact with general practice between 2003-2009 when the participants were between 1 and 35 years of age. Poisson regression was used to assess the association between exposure and outcome.

Outcome measures: Contacts to general practitioner.

Results: Overall, persons exposed to prenatal stress had 2% more GP contacts than those not exposed, primarily due to increased utilization of health care services during late adolescence and early adulthood. The exposed persons born to mothers who had lost a spouse had a higher risks [relative risk (RR) 1.12, 95%CI 1.10-1.14], and so did those born to mothers who had lost a close relative due to unexpected death (RR 1.06, 95% CI 1.05-1.06). Exposed persons had more contacts to general practice in daytime and more psychometric tests, talk therapies and C-reactive protein tests than unexposed persons.

Conclusions: Prenatal stress following maternal bereavement was associated with a slightly increased utilization of primary health care, mainly due to increased healthcare needs related to mental health and infections. Understanding how stress during pregnancy influences the future health of the child is an important aspect of prenatal care.
Key words: Primary health care; bereavement; cohort; prenatal stress; general practice.
ARTICLE SUMMARY

Article focus

- Exposure to prenatal stress may affect the future health of the unborn child negatively.
- An excellent proxy for health problems is the use of health care resources.
- We aimed to examine whether persons born to mothers who lost a close relative during pregnancy have more contacts to general practice.

Key messages

- Prenatal stress following maternal bereavement was associated with an increased utilization of primary health care, mainly due to more mental health care and infections.
- Understanding how stress during pregnancy influences the future health of the child is an important aspect of prenatal care.

Strengths and limitation of this study

- This is the first large population-based cohort study to examine the association between prenatal stress and primary health care use, with virtually complete follow-up and no recall and selection bias. Furthermore, through linkage to other national registers, we were able to adjust for a number of potential confounders applying to both children and their mothers.
- The limitation of the study is that we have no data on changes in the mothers’ glucocorticoid levels following bereavement, which is needed to examine dose-response patterns.
INTRODUCTION

A growing body of evidence suggests that exposure to environmental risk factors in foetal life plays a significant role in future health. Major life events during pregnancy may cause stress reactions that affect the development of the unborn child and lead to ill health. Recent studies have shown that prenatal stress can be associated with more hospital admissions in the offspring later in life due to mental and physical disease. However, most diseases are diagnosed and treated in primary health care, which makes health service utilization in general practice an important proxy for mental and physical health. Yet, no studies have addressed how prenatal stress affects the utilization of general practice services later in life.

Danish general practice provides tax-financed comprehensive and continuous medical care to registered patients. A total of 99% of the Danish population is registered with a general practice. General practitioners (GPs) are freely accessible serve as gatekeepers towards the rest the healthcare system. Except for emergencies, they must be contacted if a person needs medical advice. In this way, studying Danish general practice can provide a detailed and complete description of population’s health status.

We used maternal bereavement during prenatal life as an indicator of prenatal stress as bereavement is likely to cause stress regardless of one’s coping mechanisms. In a large population-based cohort study, we examined the associations between maternal bereavement during pregnancy and their offspring’s use of primary health care up to 35 years of age. We expected that the association would be stronger if the mothers experienced bereavement due to sudden and unexpected causes of death rather than other causes of death. We also expected that the death of another child in the family during pregnancy would affect the association more than the loss of a spouse or another relative.
METHODS

Study population, exposure and follow-up

The unique personal identification number assigned to all citizens in Denmark permits accurate linkage of data between national registers, and this population-based cohort study was based on data from several national registers in Denmark: the CPR registry, the Medical Birth Register (MBR), the Integrated Database for Longitudinal Labour Market Research (IDA), and the Danish National Health Insurance Service Registry (NHSR). The cohort included all persons born in Denmark from 1973 to 2002 (N=2,032,528). Those who were emigrant or had died before 2003 were excluded from the cohort (N=164,977). We also excluded the persons (N=47) who had visited GP for an unreasonable number of times in a year (for example, more than 100 times). The final study population included 1,867,504 persons.

We categorised children as having been exposed to stress during prenatal life if their mothers had lost a child, a spouse, a sibling, or a parent during their pregnancies or up to one year before conception (defined by gestational age). The remaining children were allocated to the unexposed cohort. Cohort members were followed from 1 January 2003 to 31 December 2009. To examine whether the associations were modified by type of experienced stress, we first categorised the exposed children into three groups based on maternal bereavement according to the mother’s relation to the deceased relative: a) loss of a spouse, b) loss of a child and c) loss of a parent or a sibling. We further categorised the exposed children into two groups according to the cause of death of the deceased relative: a) unexpected/traumatic death including suicide and accidents (ICD-8 codes: 795, 810-823, 950-959, 800-807, 825-949, 960-999; ICD-10 codes: R95-R98, V01-V89, X60-X84) and b) death by other causes.

Outcome measurements

We were interested in the overall use of general practice and specific procedures in relation to mental and physical health. Danish general practice is fully computerised with computer-based patient records
and submission of prescriptions digitally to pharmacies, etc. GPs are remunerated on a combination of capitation and fee-for-service (25/75%). The GP therefore registers every specific contact and procedure to receive payment for any services provided. The registration is collected electronically for administration in the National Health Services Register (NHSR) and is thus very complete and valid.

Information on health care utilization was obtained from the NHSR for exposed and unexposed persons. The NHSR provided data on consultations in daytime and out-of-hours (OOH) and on diagnostic tests performed during the daytime.

The main outcome of interest was the number of all GP visits per person year, the number of visits in daytime (Time code ‘1’) and the number of visits out of office hours (Time codes ‘8,9’). We also studied face-to-face contacts alone (activity code 0101) and telephone consultations alone (activity code 0201). We also examined the reasons for contacts as we want to know whether prenatal stress lead to differences in GP visit in the ways of treatment or management. For example, to measure activities related to physical health, we assessed taking blood test (activity codes 2601, 2101), photometry test-B-haemoglobin (activity code 7108), C-reactive protein test (activity code 7120), spirometry/peakflow (activity codes 7113,7121,7183), ECG (7156) and urinary stix (activity code 7101). Measures of mental health activity were talk therapy/counselling (activity code 6101) and psychometric test (activity code 2149). Biological measurements (activity codes 2601, 2101, 7108, 7120, 7113, 7121, 7183, 7156, 7101) and psychometric activities (activity codes 6101, 2149) were merged together into two separate groups.

Covariates

Baseline characteristics were retrieved from registers in the child’s birth year.

Perinatal factors (gestational age, birth weight, sibling order, Apgar score at five minutes) were retrieved from the MBR. The MBR was established in 1968 and has been computerised since 1973. It holds data on all live births and stillbirths in Denmark, including characteristics of the mother and the
newborn child, and variables with regard to pregnancy and delivery. Baseline socio-demographic factors were obtained from IDA, which contains longitudinal information on demographic variables and socioeconomic data from 1980 onwards.  

**Statistical analysis**

All data handling and statistical analyses were performed with the SAS version 9.2 statistical software package (SAS Institute, Inc., Cary, North Carolina). Follow-up started from 2003 and ended in 2009. We used Poisson regression model (SAS PROC PHREG procedure, version 9.1) to estimate relative ratios (RRs) with a 95% confidence interval (CI) to assess the association between prenatal bereavement and the risk of utilization of general practice. The procedure of PROC MEANS was used to compute the total number of visits to general practice and the sum of person years for each patient. The procedure of PROC GENMOD was employed to estimate the RRs.

The following potential confounders were included in the analysis: calendar year (2003-2009), gender (male, female), age, gestational age (0='≥37 weeks', 1='less than 37 weeks'), Apgar score at five minutes (0-7, 8-9, 10, unknown), parity (1, 2, 3, unknown), maternal age group (<27 years, 27-30 years, 31 years and over) and maternal education (0-9 years, 10-11 years, 12+ years), and birthweight (1='less than 2500 g', 0='≥2055 g').
RESULTS

The baseline characteristics of the cohorts are presented in Table 1. Exposed children were more likely to have low birth weight, to be born preterm, to be second or later in birth order, or to be born to mothers having lower education. Fewer children born early in the study period were categorised as exposed because the registration of grandparents was incomplete.17

Table 2 shows that during follow-up, persons in the exposed group had 2% more contacts to general practice [Relative risk (RR) 1.02, 95% CI 1.02-1.03] than persons in the unexposed group. Similar results were seen for face-to-face contact and telephone consultation. We found a stronger association between maternal bereavement and the offspring's RR of subsequent health care utilization if the mother had lost a spouse (RR 1.12, 95% CI 1.10-1.14) than if she had lost an older child (RR 1.05, 95% CI 1.05-1.06). Persons of mothers who lost a close relative due to unexpected death had a higher health care utilization (RR 1.06, 95% CI 1.05-1.06) than persons of mothers who had lost a relative due to natural death (RR 1.01, 95% CI 1.01-1.01) (Table 3).

The mean annual number of contacts to GPs was the same for exposed and unexposed persons during childhood, but exposed persons tended to have more contacts after reaching early adulthood (Figure 1). The increase in GP service utilization occurred during daytime but not during OOHs. From adolescence and early adulthood, psychometric tests and counselling were more frequent in the exposed group than in the non-exposed group. In the same age groups, the use of biological examinations (including blood tests, C-reactive protein tests) was also higher among the exposed than among the unexposed persons (Figure 2).
DISCUSSION

We are the first to observe that prenatal stress following maternal bereavement is associated with a slightly higher use of primary health care in the offspring during late adolescence and early adulthood. The association was stronger if the mother lost her spouse than if she lost another relative. Sudden death of mothers’ relatives was associated with a higher risk than other causes of death. An excess number of visits were found both for mental health problems (talk-therapies, psychometric tests) and for physical tests (blood tests, ECGs, C-reactive protein tests).

A large body of literature has concluded that bereavement is one of the most stressful life events and that it affects most people regardless of their coping mechanisms.\cite{18,19} The use of bereavement as an indicator of stress in research therefore seems justified as it provides a good exposure contrast between exposed and unexposed. We collected information on bereavement prospectively without relying on the participants’ memory. The registration of the day of death is known to be of very high quality in Danish nationwide registries, and our data on bereavement from the Danish Civil Registration System are therefore valid and complete (close to 100%). This yields accurate information on the exposure in focus.\cite{17} The unique nature of the Danish national register data provides our study with a number of other important methodological strengths. For example, the study was based on a large population-based cohort of all children born in Denmark, and follow-up during the period 2003-2009 was virtually complete.\cite{17} Bias due to selection of study participants and non-response is therefore an unlikely explanation of our findings. Furthermore, through linkage to other national registers, we were able to adjust for a number of potential confounders applying to both children and their mothers.

One limitation of the study is that we have no data on changes in the mothers’ glucocorticoid levels following bereavement, which is needed to examine dose-response patterns. Yet, it is hardly realistic to have a biological measurement in such a large study population. Furthermore, we have no data on life style factors that could confound the associations. However, the socio-demographic factors included in
the model will, to some extent, adjust for the effects of life style factors. Another limitation is the
heterogeneity of the data on GP contacts and the inclusion of contacts from all causes which may
prevent us from examining the associations between prenatal stress and specific diseases or health
problems. However, this was not defined as the main interest of this study.

The findings support our hypothesis of a possible dose-response association between cause of death
and stress level. Previous studies have also shown that unexpected deaths are more stressful than
expected deaths, and that the loss of a relative in the nuclear family is more stressful than the loss of
another relative.

To our knowledge, this is the first population-based study to examine how prenatal stress is
associated with health service use in later life. Previous research of health outcomes has focused on
birth outcomes, hospital diagnoses related to physical diseases, psychiatric disorders and
social/emotional problems. Our findings of increased health care utilization support the hypothesis
of prenatal stress programming, albeit from a new point of view. Prenatal stress programming
refers to the underlying biological mechanisms that result from the disruption of the normal pattern of
foetal development by an abnormal stimulus or insult at a critical time point. Excessive
glucocorticoid levels following stress in pregnant mothers can cause dysfunction of the hypothalamo-
pituitary-adrenocortical (HPA) axis with permanent effects on the development of a number of body
systems in the foetus, which may lead to adverse health outcomes in future life. Strong evidence
from animal studies suggests that maternal stress during pregnancy may significantly affect the
neurodevelopment of the foetus. These animal studies have recently been followed by a number of
studies in human populations. Confirming these studies, our findings showed more frequent visits
for psychometric tests and counselling in exposed than in unexposed persons, particularly from early
adulthood onwards. Our findings of a higher number of blood tests in general practice among exposed
than among unexposed persons may lend support to the argument that prenatal stress may/might be
linked to metabolic syndrome, obesity risk, or cardiovascular diseases. Lastly, the more frequent testing of C-reactive protein in exposed than in unexposed persons is also in line with observations in animal studies that prenatal stress affects immune function development, and in one recent human study that prenatal stress was associated with more hospitalisations due to severe infectious diseases.

Another interesting finding to be mentioned is the higher risks related to the death of a spouse than another older child during pregnancy. Little is known about the effects of spousal loss in pregnancy on the mother herself or on the offspring, probably because it is a very rare event and because it is very challenging to obtain data on this relation. One recent study has shown that loss of a spouse during pregnancy is related to substance abuse in the offspring. Our study suggests that the loss of a father during prenatal life may have more severe consequences than the loss of other family members on future health. The underlying reasons for this association is unclear, but the loss of a father may affect the child’s upbringing, socioeconomic surroundings, parental resources and the threshold for attending health care.

It might not be of very clinical significance, as we only observed a mildly increased utilization in health service use following this specific event of bereavement. However, it should be noted that bereavement during pregnancy is only one of many stressful life events and that it accounts for only a small fraction of the overall stress level in pregnant mothers. Many other stressful events could affect women in pregnancy and causes stress in the unexposed group as well, and an increase in health service use in later life following prenatal stress may therefore be anticipated due to other causes. It is therefore important to recognize the potential effects of stress at the first step. The mildly increased utilization in health service use following this specific event is therefore what could be expected and severe types of loss have a more noteworthy effect in early adulthood. How the combined maternal psychological stress affects future health service use is warranted to should be investigated in future studies. On the other hand, it remains to be elucidated whether the
associations are different for specific stress exposures, depending on the treatment and specific disease outcomes, to shed further light on the effects of prenatal stress.

In conclusion, offspring exposed to prenatal stress utilized general practice more than unexposed offspring, but only in later adolescence and early adulthood. Our findings contribute to our understanding of the aetiology of stress-related ill health from the view of disease programming. Severe stress during prenatal life may programme future health in future life, which highlights the importance of better care in women’s health during pregnancy. This information should be taken into account when implementing preventive programmes in maternal and child health.

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Competing Interests None.

Contributors JL conceived the research, HY analysed the data. JL wrote the first draft of the manuscript. JL, HY, MBG, PV, MV contributed to data analysis, interpretation of results, and critical revision of the manuscript. All authors approved the final manuscript.

Ethics approval The study was approved by Danish Data Protection Agency (j nr. 2008-41-2680), Scientific Ethics Committee of Central Region Jylland (VEK, sagnr. M-20100252).

Patient consent not needed for register-based research according to laws in Denmark.
Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There are no additional data available.

Figure Legends

**Figure 1. Contacts with GP, by type of contact and time of contact**

**Figure 2. Contacts with GP, by reasons of contact.**
REFERENCES

(1) Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of In Utero and Early-Life Conditions on Adult Health and Disease. *New Engl J Med* 2008;359:61-73.

(2) Kapoor A, Dunn E, Kostaki A, Andrews MH, Matthews SG. Fetal programming of hypothalamo-pituitary-adrenal function: prenatal stress and glucocorticoids. *J Physiol (Lond)* 2006;572:31-44.

(3) Markham JA, Koenig JI. Prenatal stress: role in psychotic and depressive diseases. *Psychopharmacology (Berl)* 2011;214:89-106.

(4) Hansen D, Lou HC, Olsen J. Serious life events and congenital malformations: a national study with complete follow-up. *Lancet* 2000;356:875-880.

(5) Khashan AS, Abel KM, McNamee R et al. Higher Risk of Offspring Schizophrenia Following Antenatal Maternal Exposure to Severe Adverse Life Events. *Arch Gen Psychiatry* 2008;65:146-152.

(6) Pedersen KM, Andersen JS, Soendergaard J. General Practice and Primary Health Care in Denmark. *The Journal of the American Board of Family Medicine* 2012;25:S34-S38.

(7) Christiansen T. Organization and financing of the Danish health care system. *Health Policy* 2002;59:107-118.

(8) Stroebe M, Schut H, Stroebe W. Health outcomes of bereavement. *Lancet* 2007;370:1960-1973.

(9) Kristensen P, Weisæth L, Heir T. Bereavement and Mental Health after Sudden and Violent Losses: A Review. *Psychiatry: Interpersonal and Biological Processes* 2012;75:76-97.

(10) Li J, Precht DH, Mortensen PB, Olsen J. Mortality in parents after death of a child in Denmark: a nationwide follow-up study. *Lancet* 2003;361:363-367.

(11) Skodol AE, Shrout PE. Use of DSM-III axis IV in clinical practice: rating etiologically significant stressors. *Am J Psychiatry* 1989;146:61-66.

(12) Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;287:2398-2399.

(13) Li J, Vestergaard M, Obel C, Cnattingus S, Gissler M, Olsen J. Cohort Profile: The Nordic Perinatal Bereavement Cohort. *Int J Epidemiol* 2010;40:1161-1167.

(14) Olivarius NF, Hollnagel H, Krasnik A, Pedersen PA, Thorsen H. The Danish National Health Service Register. A tool for primary health care research. *Dan Med Bull* 1997;44:449-453.

(15) Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;45:320-323.

(16) Denmark Statistics. IDA-an intergrated database for labor market research. (In Danish). (http://www.dst.dk/) (under IDA (Intergrated Database for Arbejdsmarkedsforskning)). 1991.
(17) Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441-449.

(18) Holmes TH, Rahe RH. The Social Readjustment Rating Scale. *J Psychosom Res* 1967;11:213-218.

(19) Osterweis M, Solomon F, Green M. *Bereavement: Reactions, Consequences, and Care*. Washington DC: National Academy Press, 1984.

(20) Huttunen MO, Niskanen P. Prenatal loss of father and psychiatric disorders. *Arch Gen Psychiatry* 1978;35:429-431.

(21) Van den Bergh BR, Mulder EJ, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neurosci Biobehav Rev* 2005;29:237-258.

(22) O'Connor TG, Heron J, Golding J, Glover V. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *J Child Psychol Psychiatry* 2003;44:1025-1036.

(23) Weinstock M. The potential influence of maternal stress hormones on development and mental health of the offspring. *Brain Behav Immun* 2005;19:296-308.

(24) Viltart O, Vanbesien-Mailliot CC. Impact of prenatal stress on neuroendocrine programming. *ScientificWorldJournal* 2007;7:1493-1537.

(25) Welberg LA, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain. *J Neuroendocrinol* 2001;13:113-128.

(26) Abel KM, Heuvelman HP, Jorgensen L et al. Severe bereavement stress during the prenatal and childhood periods and risk of psychosis in later life: population based cohort study. *BMJ* 2014;348:f7679.

(27) Li J, Vestergaard M, Obel C et al. A nationwide study on the risk of autism after prenatal stress exposure to maternal bereavement. *Pediatrics* 2009;123:1102-1107.

(28) Reynolds RM. Corticosteroid-mediated programming and the pathogenesis of obesity and diabetes. *J Steroid Biochem Mol Biol* 2010;122:3-9.

(29) Reynolds RM. Glucocorticoid excess and the developmental origins of disease: Two decades of testing the hypothesis - 2012 Curt Richter Award Winner. *Psychoneuroendocrinology* 2013;38:1-11.

(30) Entringer S, Buss C, Wadhwa PD. Prenatal stress and developmental programming of human health and disease risk: concepts and integration of empirical findings. *Current Opinion in Endocrinology, Diabetes and Obesity* 2010;17:507-516.
(31) Parker VJ, Menzies JRW, Douglas AJ. Differential Changes in the Hypothalamic-Pituitary-Adrenal Axis and Prolactin Responses to Stress in Early Pregnant Mice. *Journal of Neuroendocrinology* 2011;**23**:1066-1078.

(32) Nielsen NM, Hansen AV, Simonsen J, Hviid A. Prenatal Stress and Risk of Infectious Diseases in Offspring. *Am J Epidemiol* 2011;**173**:990-997.

(33) Liang H, Olsen J, Cnattingus S et al. Risk of substance use disorders following prenatal or postnatal exposure to bereavement. *Drug and Alcohol Dependence* 2013;**132**:277-282.

(34) East L, Jackson D, O’Brien L. Father absence and adolescent development: a review of the literature. *Journal of Child Health Care* 2006;**10**:283-295.

(35) McLanahan S, Tach L, Schneider D. The Causal Effects of Father Absence. *Annu Rev Sociol* 2013;**399**:399-427.
| Variables                  | 1980–2002 Non-bereaved | 1980–2002 Bereaved | 1973–2002 Non-bereaved | 1973–2002 Bereaved |
|----------------------------|------------------------|--------------------|------------------------|--------------------|
| N=1,414,287 (97.30%)       | N=38,215 (2.70%)       | N=1,826,806 (97.826%) | N=40,698 (2.18%)      |
| Gender                     |                        |                    |                        |                    |
| Male                       | 726671 (51)            | 19439 (51)         | 942715 (52)           | 20763 (31)         |
| Female                     | 687614 (49)            | 18776 (49)         | 884089 (48)           | 19935 (49)         |
| missing                    | 2 (0)                  | 2 (0)              |                        |                    |
| Apgar score at 5 minutes   |                        |                    |                        |                    |
| 10                         | 1264861 (89)           | 36222 (95)         | 1366773 (75)          | 37201 (91)         |
| 8-9                        | 32734 (2)              | 950 (2)            | 34774 (2)             | 985 (2)            |
| 0-7                        | 7073 (1)               | 234 (1)            | 7371 (0)              | 238 (1)            |
| missing                    | 109619 (8)             | 809 (2)            | 417888 (23)           | 2274 (6)           |
| Birth Weight*              |                        |                    |                        |                    |
| >=2500g                    | 1245876 (88)           | 35432 (93)         | 1295492 (71)          | 36006 (88)         |
| <2500g                     | 64623 (5)              | 2133 (6)           | 67151 (4)             | 2180 (5)           |
| missing                    | 103788 (7)             | 650 (2)            | 464163 (25)           | 2512 (6)           |
| Gestational age*           |                        |                    |                        |                    |
| 0=37+ weeks                | 1222362 (86)           | 34990 (29)         | 1294836 (71)          | 35688 (88)         |
| 1=less than 37 weeks       | 70346 (5)              | 2303 (6)           | 77204 (4)             | 2359 (6)           |
| missing                    | 121609 (9)             | 922 (2)            | 458250 (25)           | 2658 (7)           |
| Parity                     |                        |                    |                        |                    |
| 1                          | 645868 (46)            | 14321 (37)         | 956594 (52)           | 15024 (37)         |
| 2                          | 525185 (37)            | 15270 (40)         | 616084 (34)           | 16734 (41)         |
| 3                          | 234560 (17)            | 8621 (23)          | 242170 (13)           | 8932 (22)          |
| missing                    | 8656 (1)               | 30 (0)             | 11958 (1)             | 80 (0)             |
| Maternal age*              |                        |                    |                        |                    |
| <27 years                  | 495432 (35)            | 11267 (39)         | 714820 (37)           | 12682 (31)         |
| 27-30 years                | 439574 (31)            | 11618 (30)         | 551663 (30)           | 12270 (30)         |
| 31 years and over          | 473566 (33)            | 15330 (40)         | 553484 (30)           | 15746 (39)         |
| missing                    | 5721 (0)               | 6839 (0)           |                        |                    |
| Maternal education*        |                        |                    |                        |                    |
| 0-9 years                  | 428202 (30)            | 12658 (33)         | 428202 (33)           | 12658 (31)         |
| 10-11 years                | 416669 (29)            | 12351 (32)         | 416669 (33)           | 12351 (30)         |
| 12+ years                  | 394283 (28)            | 11748 (31)         | 394283 (22)           | 11748 (29)         |
| missing                    | 174593 (12)            | 14584 (4)          | 587112 (32)           | 3941 (10)          |

* Data available from 1980.
| Variables          | Non-bereaved N=1,826,806 (97.8%) | Bereaved N=40,698 (2.2%) |
|--------------------|----------------------------------|--------------------------|
| **Gender**         |                                  |                          |
| Male               | 942715(52)                       | 20763(51)                |
| Female             | 884089(48)                       | 19935(49)                |
| missing            | 2(0)                             |                          |
| **Apgar score at 5 minutes** |                          |                          |
| 10                 | 1264861(89)                      | 36222(95)                |
| 8-9                | 32734(2)                         | 950(2)                   |
| 0-7                | 2073(1)                          | 234(1)                   |
| missing            | 109619(8)                        | 809(2)                   |
| **Birth Weight**   |                                  |                          |
| >=2500g            | 1245876(88)                      | 35432(93)                |
| <2500g             | 64623(5)                         | 2133(6)                  |
| missing            | 103788(7)                        | 650(2)                   |
| **Gestational age**|                                  |                          |
| 0=37+ weeks        | 1222362(86)                      | 34090(92)                |
| 1=less than 37 weeks| 70316(5)                         | 2303(6)                  |
| missing            | 121609(9)                        | 922(2)                   |
| **Parity**         |                                  |                          |
| 1                  | 645886(46)                       | 14321(37)                |
| 2                  | 525185(37)                       | 15230(40)                |
| Maternal age       | Maternal education* | Birth year               |
|--------------------|---------------------|--------------------------|
| <27 years          | 21420(39)           | 412519(23)               |
| 27-30 years        | 551663(30)          | 549237(30)               |
| 31 years and over  | 553484(30)          | 667059(37)               |
| missing            | 6839(0)             | 795812(33)               |

| Maternal education* | Birth year               |
|---------------------|--------------------------|
| 0-9 years           | 14398(29)                |
| 10-11 years         | 15345(31)                |
| 12+ years           | 16163(32)                |
| missing             | 4199(8)                  |

| Birth year               | |
|--------------------------|--------------------------|
| 1973-1979                | 2483(6)                  |
| 1980-1989                | 12708(31)                |
| 1990-1999                | 20232(50)                |
| 2000-2003                | 5285(13)                 |

* Data available from 1980.
Table 2 Relative risk of any general practice (GP) visit by way of contact

| Exposure   | Type of GP contact       | No. visits | Person years | Adjusted RR* (95% CI) |
|------------|--------------------------|------------|--------------|-----------------------|
| Bereaved   | All GP contacts          | 163576     | 280902       | 1.02 (1.02-1.02)      |
|            | Contacts in office hours | 145376     | 280902       | 1.02 (1.02-1.02)      |
|            | Contacts out of hours    | 181358     | 280902       | 1.03 (1.02-1.03)      |
|            | Face-to-face contacts    | 685094     | 280902       | 1.02 (1.01-1.02)      |
|            | Phone consultation       | 451553     | 280902       | 1.02 (1.02-1.03)      |
| Non-bereaved|                           | 781781     | 12465587     | 1.00 (ref)            |
|            |                          | 13465586   | 6806         |                       |

*Adjusted for age, calendar, sex, Apgar score at 5 minutes, preterm birth, parity, low birth weight, maternal age and maternal education.
Table 3 Relative risk (RR) of any general practice (GP) visit according to type of loss (bereavement).

| Type of loss                  | Type of GP contact | No. Visits  | Person years | Adjusted RR* (95%CI) |
|-------------------------------|--------------------|-------------|--------------|----------------------|
| Non-bereaved                  | All contacts       | 781781241246 | 12465586182  | 1.00 (ref)           |
|                               |                    | 5586        | 6806         |                      |
| Bereaved - Relation to the deceased relative | | | | |
| Sibling                       | All contacts       | 338235      | 50630        | 1.06(1.06-1.07)      |
|                               | Contacts in office hours | 303921   | 50630        | 1.05(1.05-1.06)      |
|                               | Contacts out-of-hours | 34219    | 50630        | 1.15(1.13-1.16)      |
|                               | Face-to-face contacts | 137561   | 50630        | 1.07(1.06-1.07)      |
| Father                        | All contacts       | 28164      | 3752         | 1.12(1.11-1.14)      |
|                               | Contacts in office hours | 25271   | 3752         | 1.12(1.10-1.14)      |
|                               | Contacts out-of-hours | 2889    | 3752         | 1.18(1.13-1.24)      |
|                               | Face-to-face contacts | 11572   | 3752         | 1.13(1.10-1.15)      |
| Other                         | All contacts       | 1269362    | 226520       | 1.01(1.00-1.01)      |
|                               | Contacts in office hours | 1124569 | 226520       | 1.00(1.00-1.01)      |
|                               | Contacts out-of-hours | 144250  | 226520       | 1.02(1.01-1.03)      |
|                               | Face-to-face contacts | 535961  | 226520       | 1.00(1.00-1.00)      |
| Bereaved - Type of death† | Bereaved - Type of death† |
|---------------------------|---------------------------|
| Sibling Phone consultation | Father Phone consultation |
| 95612                     | 8019                      |
| 50630                     | 3752                      |
| 1.10(1.09-1.11)           | 1.13(1.09-1.16)           |
| Other Phone consultation  | Other Phone consultation  |
| 347922                    | 226520                    |
| 1.01(1.01-1.02)           |                           |

*Bereaved - Type of death†* Sudden death: unexpected /traumatic death, mostly from suicide and accidents.

*Adjusted for age, calendar, sex, Apgar scores at 5 minutes, preterm birth, parity, low birth weight, maternal age and maternal education.†: Sudden death: unexpected /traumatic death, mostly from suicide and accidents.
Figure 1. Contacts with GP, by type of contact and time of contact
Figure 2. Contacts with GP, by reasons of contact.
Figure 1. Contacts with GP, by type of contact and time of contact
173x136mm (300 x 300 DPI)
Figure 2. Contacts with GP, by reasons of contact
173x140mm (300 x 300 DPI)