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Original article

Determinants of Asthma

Maternal life and work stressors during pregnancy and asthma in offspring

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Abstract

Background: Maternal stressors during pregnancy are potential risk factors for asthma in offspring. However, previous studies have been limited by the use of self-reported data focusing on stressors either in private life or at work. This study examined the association between maternal stressors both in private life and at work during pregnancy and asthma in offspring.

Methods: In the Danish National Birth Cohort, 75 156 live-born singletons born during 1996–2002 were identified. Maternal information on job title were available around weeks 12–16 of gestation. Data on maternal bereavement, life-threatening illness, suicide attempt and alcohol or drug abuse of a close relative and offspring childhood asthma (3–10 years of age) were obtained from Danish nationwide registers. Maternal psychosocial work stressors (job control, psychological job demands, emotional job demands, work-

related violence and threats of work-related violence) were estimated by the use of job-exposure matrices. The association between maternal stress and childhood asthma was analysed in Cox models adjusted for maternal age, comorbidity and parity.
Results: Neither private-life nor work stressors were related to onset of asthma in offspring. Separate analyses by parental atopy or onset of asthma in offspring supported the main findings.
Conclusions: This study does not support an elevated risk of childhood asthma related to exposure to stress during pregnancy.

Key words: Negative life events, bereavement, stress, occupational exposure, job-exposure matrix, childhood asthma

Key Messages

- Exposure to maternal life and work stressors during pregnancy do not seem to affect the risk of asthma in offspring (3–10 years of age).
- The results were similar for boys and girls.
- We did not identify an interaction between job control and psychological job demands.

Background

Asthma is the most common chronic disease in childhood[1–3] and the incidence has increased considerably during the last 30 years.[1,3] Stress during pregnancy has been related to offspring childhood asthma.[4–7] The underlying mechanisms are not elucidated in human studies.[6] In animal studies, stress during pregnancy alters the offspring's immune system in a direction that predisposes to asthma and allergic diseases.[8] Disturbances of the hypothalamic–pituitary–adrenal (HPA) axis and autonomic imbalance or dysfunction may provide key biological pathways.[9,10]

Earlier studies of maternal exposure to stressors during pregnancy and asthma in the offspring have mainly focused on private-life stressors,[11–16] whereas psychosocial stressors at work are often not accounted for. Only three studies have directly examined psychosocial work stressors during pregnancy and asthma in offspring[17–19] and two used the job-strain model.[20] In these studies, the observed associations between psychosocial work stressors and asthma in offspring were weak and inconsistent.[17–19]

Studies of maternal exposure to negative life events, including bereavement, suggest an association with asthma in the children,[11,13–16,19] albeit some studies only for specific time windows of exposure or specific ages of the children. Two large population-based studies report no association.[12,18] The association between maternal stress during pregnancy and asthma in offspring might be modified by the sex of the child and boys may be more vulnerable to maternal stress during pregnancy than girls.[8,15,16]

Heterogeneity in results across studies is substantial with regard to e.g. differences in measures of stress exposure, time windows, definition of childhood asthma and ages of asthma onset. Most studies rely on self-administered questionnaire data from the mothers and only a few studies, mainly on bereavement, use register-based information.

We hypothesize that maternal exposure to stressors during pregnancy increases the risk of asthma in the child. We tested the hypothesis in a large birth cohort and explored a range of stressors at work as well as in private life using independent, register-based measures of both maternal exposure and asthma in the children. Further, we aimed to investigate whether the sex of the offspring modified the association.

Methods

Study design and population

The study is based on mother–child pairs from the Danish National Birth Cohort (DNBC),[21] in which 101 42 pregnant women were invited to participate between 1996 and 2002. We linked them to multiple nationwide

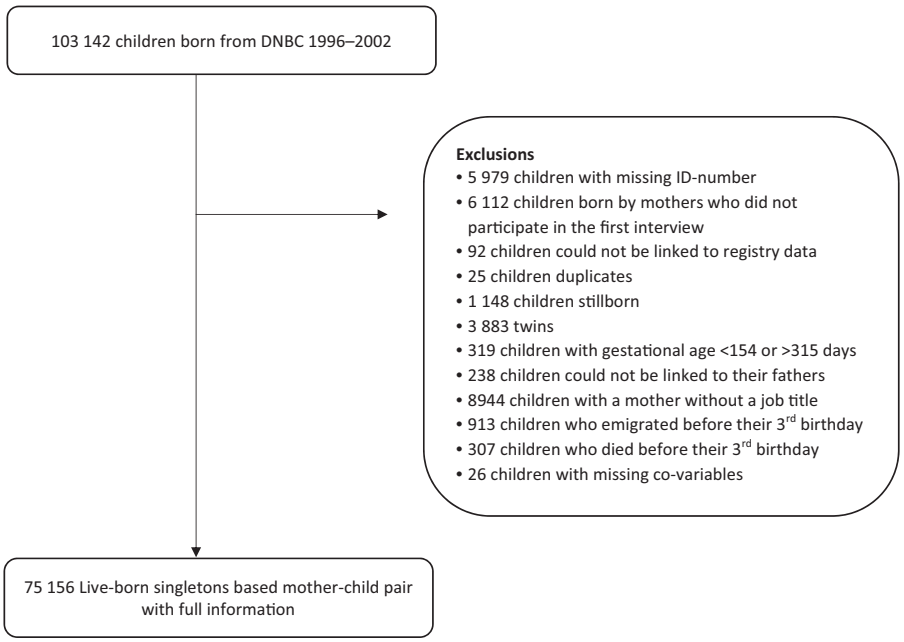

Figure 1 Flowchart illustrating the inclusion process of the study population

administrative registries using the unique personal identification number assigned to all Danish residents at birth.[22] Finally, the cohort was linked with survey data [the Danish Work Environment Cohort Study 2000 (DWECS)].[23] More details about the study design are available from the online protocol https://doi.org/10.6084/m9.figshare.5868588.v1.24.

Eligibility criteria

Mother–child pairs from the DNBC were eligible for inclusion if the mother participated in the first pregnancy interview at around gestation weeks 12–16, had a job title or was a student, her child was a live-born singleton who had a gestational age of between 154 and 315 days and she a personal identification number allowing linkage to national-registry data. Mother–child pairs were excluded if they emigrated before the age of 3 years ($n = 913$), died before the child's third birthday ($n = 307$) or had missing co-variables ($n = 26$). This resulted in 75 156 live-born singletons-based mother–child pairs (Figure 1).

Life stressors: negative life events

Negative life events (NLEs) were defined as bereavement (loss of a close relative)[24] and events of life-threatening illness,[25] suicide attempt and/or alcohol or drug abuse in a close relative of the mother (another child, the father of the index child, a parent or a sibling) (Figure 2). The window of exposure was 1 year prior to conception until the day of

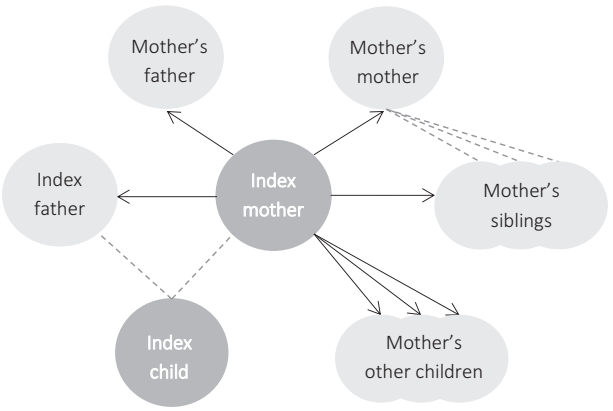

Figure 2 Close relatives of the mother (apart from the index child) linked via the Danish Civil Registration System.

birth. Information on bereavement was obtained from the Danish Register of Causes of Death. Information on life-threatening illness (cancer—ICD-10 codes: C00–97; acute myocardial infarction—ICD-10 codes: I21–23), suicide attempt (ICD-10 codes: X60–84 and Y87.0) and alcohol and drug abuse (ICD-10 codes: F10–19) was obtained from the Danish National Patient Register.

To examine an aggregated measure of life stressors, we analysed an index of negative life events (NLE-index). The NLE-index includes all five NLEs mentioned above. Each NLE was dichotomized into 0 or ≥1 NLE. Only one event in each category of a NLE was counted per relative, i.e. multiple suicide attempts only counted as one NLE per relative. Bereavement was also analysed separately, as it is considered the ultimate stressful life event.[26]

Work stressors: psychosocial job-exposure matrices

Work stressors were obtained via psychosocial job-exposure matrices (JEMs) generated from DWECS data.[27,28] Five psychosocial stressor matrices were included: (i) job control, (ii) psychological job demands, (iii) emotional job demands, (iv) work-related violence and (v) threats of work-related violence. Questions regarding job control and psychological job demands were based on an adapted version of the Job Content Questionnaire originally designed by Karasek and co-workers.[29]

The women's job titles were linked to the JEMs in which each woman was assigned an 'exposure' for each psychosocial work stressor based on the average for that specific job title. We used the job title held by the mothers at the first DNBC interview (around weeks 12–16 of gestation, median 15 weeks). Job titles were coded according to the Danish International Standard Classification of Occupations 1988 (DISCO88), with four hierarchical levels.[30] We used the most detailed available digit DISCO88-code level for each JEM. Participants who were students at the time of the interview were assigned a DISCO88-code of '2', 'Professionals'.

The JEM for job control was based on two sub-scales: decision authority (four items) and skill discretion (four items). The JEMs for psychological and emotional job demands both consisted of three items. The JEMs for violence and threats of violence were based on a single question each.[27,28]

Work stress is often assessed based on Karasek's original job-strain model.[29] However, considering methodological shortcomings in this approach (e.g. lacking interactions[31]), by dichotomizing and combining dimension scores, we used a total approach[32] to examine job control and psychological job demands separately, as independent exposures. Further, to examine an aggregated measure of psychosocial work stressors, we conducted an analysis based on a JEMs-index generated from all five JEMs. Job control, psychological job demands and emotional job demands were dichotomized by the median, whereas work-related violence and threats of work-related violence were dichotomized as yes/no. The index was treated as a categorical variable with a range from 0 to 5.

Childhood asthma

Asthma was defined as the first hospital contact ever due to asthma (date of first inpatient admission, outpatient visit or emergency-room visit) or at least two prescriptions of any anti-asthmatic medication within 1 year, whichever came first. It is challenging to diagnose children with asthma before the age of 3 years.[33] We therefore a priori decided only to include asthma in children between the ages of 3 and 10 years. Asthma hospital contact (ICD-10 codes: J45–46) was obtained from the Danish National Patient Register.[34]Anti-asthmatic medication defined by the Anatomical Therapeutical Chemical classification codes[35] [inhaled b2-agonists (R03AC02-04, R03AC12 and R03AC13), inhaled glucocorticoids (R03BA01, R03BA02 and R03BA05), fixed-dose combination of inhaled b2-agonists and glucocorticoids (R03AK06 and R03AK07) and leukotriene receptor antagonists (R03DC03)[36]] were obtained from the Danish National Prescription Register.[34]

Statistical procedures

In line with the study protocol,[37] Cox proportional-hazards regression models were used to estimate the hazard ratios (HRs) with 95% confidence intervals (CIs) of offspring childhood asthma by exposure to maternal stressors. Bereavement was dichotomized (0/≥1), whereas job control and psychological job demands were included as continuous variables, all mutually adjusted for and tested for interactions (Model 1). Job control ranged from high (77.4) to low (14.2). A 10-point decrease was the unit used in the analysis. In contrast, psychological job demands ranged from low (10.7) to high (53.3) demands. A 10-point increase was the unit used in the analysis. Job control and psychological job demands were included in the models as continuous variables, as linear splines with knots at tertiles based on the distribution of children with asthma were not different from a linear model. The NLE-index was dichotomized (0/≤1) and the JEM-index ranged from 0–5 events (Model 2). Exposure variables were mutually adjusted for and tested for multiplicative interaction. Cox-regression analyses were conducted with delayed entry from the child's third birthday, using right censoring at the age of 10 years and with repeated measurements for mothers with more than one child in the DNBC. Both children with and without asthma prior to their 3-year birthday were included in the analysis. All analyses were stratified by sex of the child based on the a priori hypothesis that boys may be more vulnerable to prenatal stress compared with girls.[8,15,16] All variables were included as time-independent variables.

Potential confounders were identified from current literature and by Acyclic Directed Graphs (DAGs) (see Supplementary Figure 1, available as Supplementary data at *IJE* online). Based on the minimal sufficient adjustment, the analyses were adjusted for maternal age at delivery (years, continuous) and parity (1^{st}/≥2), obtained from the National Medical Birth Registry, as well as maternal

comorbidity before delivery measured as the Charlson Comorbidity Index (yes/no), retrieved from the National Patient Registry.[38,39] Asthma diagnosis was not included in the comorbidity index but we adjusted for parental atopic status. Parental atopic status was defined from self-reports at the first interview in the DNBC and, if missing, based on records of either allergic rhinitis without bronchial asthma (ICD-8 codes: 507 and ICD-10 codes: J30.1, J30.2, J30.3, J30.4), asthma (ICD-8 codes: 493, ICD-10 codes: J45–46) and/or atopic dermatitis (ICD-8 codes: 691.0, ICD-10 codes: L20),[40] obtained from the National Patient Registry. A large number of variables, such as lifestyle factors, were, based on the DAG, assumed to possibly be in the causal pathway between maternal stressors and asthma in offspring. These were therefore not included in the analyses, to avoid the possible introduction of collider bias.

We conducted a sensitivity analysis in which the highest achieved parental educational level at the child's birth year was included as a proxy for socio-economic status. We classified education into three levels: primary education (ISCED level 0–2)/secondary education (ISCED level 3)/tertiary or higher education (ISCED level 4–8) based on the International Standard Classification of Education (ISCED-2011).[41,42]

Two subgroup analyses were conducted to test for possible effect modification by parental atopic status (yes/no) and whether the offspring had asthma or not before the age of 3 years (yes/no). We also included separate analyses of bereavement as well as job control separated by high and low physiological job demands.

Table 1. Baseline characteristics of the study population

Characteristics	Boys	Girls
n	38 490	36 666
Maternal age at delivery, mean (SD)	29.9 (4.3)	29.9 (4.3)
Parity, *n* (%)		
1st	18 251 (47)	17 342 (47)
≥2	20 239 (53)	19 324 (53)
Maternal comorbidity, *n* (%)		
No	37 358 (97)	35 535 (97)
Yes	1132 (3)	1131 (3)
Parental educational level, *n* (%)		
Primary	2080 (5)	1904 (5)
Secondary	17 162 (45)	16 418 (45)
Tertiary or higher	19 248 (50)	18 344 (50)
Parental atopic status, *n* (%)		
No	28 484 (74)	27 190 (74)
Yes	10 006 (26)	9476 (26)
Maternal smoking during pregnancy, *n* (%)		
No	28 557 (74)	27 096 (74)
Yes	9933 (26)	9570 (26)
Calendar year of birth, *n* (%)		
1996–1998	4855 (13)	4446 (12)
1999–2000	16 814 (44)	16 079 (44)
2001–2002	16 821 (44)	16 141 (44)
Maternal work status as a student, *n* (%)		
No	34 767 (90)	33 228 (91)
Yes	3723 (10)	3438 (9)
Child's asthma status 3–10 years, *n* (%)		
No	33 508 (87)	33 470 (91)
Yes	4982 (13)	3196 (9)
Child's 'asthma' status 0–3 years, *n* (%)		
No	33 005 (86)	33 232 (91)
Yes	5485 (14)	3434 (9)

Results

Baseline characteristics of the 38 490 boys and 36 666 girls are presented in Table 1. Mothers were on average 29.9 years old when they gave birth to their offspring. There were no differences between the sex of the offspring except for asthma status, as more boys (13%) than girls (9%) developed asthma before the age of 10 years.

All analyses were stratified by sex of the offspring due to the a priori hypothesis, but no interaction between sex and maternal stress exposures were found for development of asthma.

Neither maternal bereavement status nor the NLE-index during pregnancy was associated with the offspring's childhood asthma (Table 2). Maternal exposure to job control was slightly associated with a decreased risk of childhood asthma per 10-unit decrease: adjusted HR boys: HR = 0.97, 95% CI 0.94–1.00; and girls: HR = 0.98, 95% CI 0.94–1.01. Higher levels of psychological job demands were not associated with asthma in offspring. No association between maternal exposure to psychosocial work stressors expressed in the JEM-index and asthma in offspring was found. Including parents' educational level in the analysis revealed similar results. No interactions were found between bereavement, job control or psychological job demands (all *P*-values >0.05, data not shown).

Subgroup analysis

Our main results remained largely similar across strata by parental atopy (Supplementary Table 1, available as Supplementary data at *IJE* online) or onset of asthma in offspring (Supplementary Table 2, available as Supplementary data at *IJE* online). Our main findings of maternal exposure to lower levels of job control and decreased asthma in offspring were robust across strata of psychological job demands dichotomized into 'high' or 'low' (see Supplementary Table 3, available as Supplementary data at *IJE* online).

Table 2 Maternal prenatal exposures of stress and hazard ratios of developing childhood asthma (3–10 years) by offspring sex

	Range	*n*	Cases	Cases per 10 000 person-years	Crude HR	95% CI	HR[a]	95% CI	HR[b]	95% CI
Boys, *n* = 38 490										
Model 1										
Bereaved	≥1	1041	141	216.08	1.05	[0.89–1.24]	1.07	[0.90–1.26]	1.06	[0.89–1.25]
Job control	77.4–14.2	38 490	4982	205.76	0.97	[0.94–1.00]	0.97	[0.95–1.00]	0.97	[0.94–1.00]
Psychological Job demands	10.7–53.3	38 490	4982	205.76	1.04	[0.98–1.10]	1.03	[0.98–1.09]	1.03	[0.98–1.09]
Model 2										
NLEs-index	≥1	2925	403	220.75	1.07	[0.97–1.19]	1.09	[0.98–1.20]	1.08	[0.97–1.19]
JEM-index	0	1769	238	214.51		ref				
JEM-index	1	9438	1184	198.64	0.92	[0.80–1.06]	0.92	[0.80–1.05]	0.92	[0.80–1.05]
JEM-index	2	9729	1256	205.59	0.96	[0.84–1.10]	0.95	[0.82–1.09]	0.95	[0.82–1.09]
JEM-index	3	7883	1018	204.85	0.95	[0.83–1.10]	0.95	[0.82–1.09]	0.95	[0.82–1.09]
JEM-index	4	7202	980	217.35	1.01	[0.87–1.16]	0.99	[0.86–1.15]	0.99	[0.86–1.15]
JEM-index	5	2469	297	189.40	0.88	[0.74–1.04]	0.86	[0.72–1.02]	0.86	[0.72–1.02]
Girls, *n* = 36 666										
Model 1										
Bereaved	≥1	1042	89	130.45	0.98	[0.80–1.21]	1.00	[0.81–1.23]	0.99	[0.80–1.22]
Job control	77.4–14.2	36 666	3196	133.99	0.98	[0.94–1.01]	0.98	[0.94–1.01]	0.98	[0.94–1.01]
Psychological Job demands	10.7–53.3	36 666	3196	133.99	1.02	[0.95–1.09]	1.03	[0.96–1.10]	1.03	[0.96–1.10]
Model 2										
NLEs-index	≥1	2814	228	123.75	0.92	[0.80–1.05]	0.93	[0.82–1.07]	0.93	[0.81–1.06]
JEMs-index	0	1744	160	140.78						
JEMs-index	1	8493	753	136.31	0.98	[0.82–1.16]	0.99	[0.83–1.18]	0.99	[0.83–1.17]
JEMs-index	2	9611	832	133.07	0.95	[0.80–1.13]	0.96	[0.81–1.14]	0.96	[0.81–1.14]
JEMs-index	3	7582	667	135.24	0.97	[0.81–1.15]	0.98	[0.82–1.16]	0.98	[0.82–1.16]
JEMs-index	4	6833	560	125.58	0.90	[0.75–1.07]	0.91	[0.76–1.09]	0.91	[0.76–1.09]
JEMs-index	5	2403	224	143.55	1.03	[0.84–1.27]	1.05	[0.86–1.29]	1.05	[0.86–1.28]

Bereavement is dichotomized (0/1), job control ranges from high to low levels of control by a 10-points decrease, psychological job demands range from low to high demands by a 10-points increase. NLEs-index includes events of bereavement, events of life-threatening illness, suicide attempts and/or alcohol or drug abuse. JEM-index includes job control, psychological job demands, emotional job demands, violence and threats of violence.

HR, hazard ratio; CI, confidence interval, NLEs, negative life events; JEMs, job-exposure matrices.

[a]Adjusted for maternal: age, comorbidity (except asthma), parental atopic status and parity.

[b]Further adjusted for parental educational level. Exposure variables are mutually adjusted.

Discussion

Our results do not support our hypothesis of an association between NLEs and work stressors during pregnancy and asthma in offspring. We did not identify interactions between life and work stressors. We did not find any interactions between job control and psychological job demands. No effect-measure modification was observed between boys and girls.

Life stressors

Findings in studies on maternal experience of NLE during pregnancy and asthma in offspring are inconsistent. Some studies suggest NLE to be a risk factor for asthma in offspring[11,13–15,19] but this is not corroborated by other population-based cohort studies apart from some sex- and age-specific findings.[12,16,18,43]

In a Danish register-based cohort study of 750 058 mother–child pairs born between 1996 and 2007,[43] maternal bereavement was not associated with asthma in children aged 4–15 years. A Swedish register-based cohort study[12] of 920 147 mother–child pairs born in 1997–2002 or 2002–2008 found slightly higher risk of asthma (1–4 years) among boys, but not girls, of bereaved mothers. In a study based on 63 626 mother–child pairs born during 2000–2007 from the Norwegian Mother and Child Cohort Study,[19] there was no evidence of an association between NLE including self-reported bereavement and medication-defined asthma in offspring at age 7 years. Strong associations between maternal bereavement and asthma in offspring were observed in a Swedish register-based study of

3 019 003 mother–child pairs born in 1973–2004,[14] defining bereavement as the death of a spouse or a child. In our definition of bereavement, we also included the death of a parent or a sibling of the mother. In the most recent meta-analysis[5] of maternal stress and asthma in offspring, the 30 studies showed that loss of a child or a spouse, but not a parent or a sibling, of the mother was associated with higher risk of asthma in offspring. These findings offer a potential explanation for the differences between our study compared with earlier studies. Including only the loss of a partner or a child, our study revealed similar estimates for boys [adjusted HR 1.06 (0.59–1.89)] but increased estimates for asthma in girls [adjusted HR 1.72 (0.93–3.01)]. This could support the findings of the meta-analysis of increased risk of childhood asthma by maternal experiences of loss of a partner or a child only and not for other family members.[5]

Typically, multiple stressors are faced in everyday life and it seems reasonable to view NLEs (bereavement, life-threatening illness, suicide attempt and/or alcohol or drug abuse) as cumulative, especially since they all could be associated to perceived stress. In the recent meta-analysis,[5] only anxiety (and not bereavement or NLE in general) was associated with increased risk of asthma (RR 1.28, 95% CI 1.16–1.41; $I^2 = 0\%$). Previous studies that reported associations between NLEs[11,13,15,19] and risk of asthma in the offspring were questionnaire-based, focusing more on perceived stress rather than exposures of 'independent' stressors, which could explain the discrepant results. Our exposure measure was obtained completely independently from the study participants due to the use of register data, precluding recall bias. Finally, the meta-analysis[5] showed that only exposure during the third trimester of pregnancy was associated with increased risk of asthma, although it is cautioned that this could reflect cumulative effects of ongoing negative events rather than the effects of that specific time window.

Psychosocial work stressors

We observed that, as the levels of job control decreased, so did the risk of asthma in offspring, mainly among boys. A cohort study of 32 271 mother–child pairs also from the DNBC[17] found that offspring of mothers with 'active jobs' (high job control and high job demands) according to the job-strain model had a higher risk of asthma at age 7 years. A Danish register-based study[18] found that children of mothers in 'passive jobs' (low job control and low job demands) presented with an increased risk of both early- and late-onset asthma, whereas 'high-strain jobs' were associated with reduced risk of early-onset persistent asthma. We did not find any interactions between job control and psychological job demands. However, to compare with earlier findings, we included subgroup analyses of maternal bereavement and job control analysed separately for mothers with 'high' and 'low' psychological job demands (Supplementary Table 3, available as Supplementary data at *IJE* online). The results remained largely similar to those of the main models and were therefore not in line with earlier findings, indicating that the effect of job control depended on psychological job demands. Of note, there are substantial differences between these studies[17,18] and our study with regard to exposure (especially in the other Danish study based on the DNBC[17]) outcome and statistical analyses. In the Norwegian Mother and Child Cohort Study,[19] maternal work stress (measured using eight questions, with answers on a four-point Likert scale) were not associated with asthma in the offspring. The slightly decreased risk of offspring childhood asthma in our study is possibly due to residual confounding. Parental educational level was used as a proxy for socio-economic status of the child's family. However, this variable does not account for health habits or parents' personality traits when it comes to e.g. taking the child to the doctor to get diagnosed, which could have influenced the results.

Sex of the offspring

In general, this study did not reveal evidence of differences by sex in the offspring as has otherwise been suggested.[8,15,16]

Methodological considerations

It is debated which method provides the most reliable measure of maternal stress during pregnancy.[4] Our study includes multiple life and work stressors, measured completely independently of the study participants by the use of register data. However, the use of JEMs may introduce misclassifications of exposures. The women's job titles are used as a proxy for psychosocial work stressors based on an average for each specific job title. However, it is unlikely that the null findings are due to exposure misclassification of the JEMs. JEMs are not using individual values of exposure but average exposures on a group level and are therefore mainly affected by Berkson error, which results in nearly unbiased effect estimates but at a loss of statistical power.[44] Considerable bias is therefore not anticipated. Berkson error is statistically independent of the observed variable whereas, in contrast, classical error is statistically independent of the true variable.[45] To strengthen the accuracy of the exposure measure, women's self-reported job titles from the DNBC were used instead of register-based information about job titles. A Danish validation study showed that, for individual four-digit

DISCO 88 codes, the sensitivity varied substantially from 0.51 to 0.71.4 and Cohen's kappa for agreement ranged from 0.73 to 0.81.[46]

It is a limitation of the study that the included indexes are additive scores of 'unweighted' individual components that may not contribute equally to the development of 'maternal stress'.

Another limitation of the study is that we examined asthma in children of 3–10 years of age, which conditions on the survival of the children before the age of 3 years. As very few children died, bias related to selective survival is minimal.

In conclusion, our results do not support that maternal exposure to stressors during pregnancy increases the risk of asthma during childhood, neither for boys nor for girls.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

K.P.: principal author, conception and design of the work, statistical analysis, interpretation of data, drafting the manuscript. X.L., C.S.S., N.A.W.A., A.D.L., H.B., H.A.K., J.P.E.B., J.O., C.S., K.S.H., R.R., K.S.H. and V.S.: conception and design of the work, acquisition and interpretation of data and revising for important intellectual content. All have approved the final version.

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The study was approved by the Danish Data Protection Agency. The original DNBC study has an approval from the Ethics Committee. Furthermore, no informed consent is required for a register-based study with public-health interest based on encrypted data according to the legislation in Denmark. Data cannot be made freely available, as they are subject to regulations at Statistic Denmark and EU General Data Protection Regulation, although data can be made available on request for authorized research units.

Conflict of interest

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References

1. Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis* 2014;**18**:1269–78.
2. Global Initiative for Asthma. (*NEW) 2017 GINA Report: Global Strategy for Asthma Management and Prevention. 2017. http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/ (20 July 2020, date last accessed).
3. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. *Allergy* 2004;**59**:469–78.
4. Andersson NW, Hansen MV, Larsen AD, Hougaard KS, Kolstad HA, Schlünssen V. Prenatal maternal stress and atopic diseases in the child: a systematic review of observational human studies. *Allergy* 2016;**71**:15–26.
5. Flanigan C, Sheikh A, DunnGalvin A, Brew BK, Almqvist C, Nwaru BI. Prenatal maternal psychosocial stress and offspring's asthma and allergic disease: a systematic review and meta-analysis. *Clin Exp Allergy* 2018;**48**:403–14.
6. Rosa MJ, Lee AG, Wright RJ. Evidence establishing a link between prenatal and early-life stress and asthma development. *Curr Opin Allergy Clin Immunol* 2018;**18**:148–58.
7. van de Loo KFE, van Gelder MMHJ, Roukema J, Roeleveld N, Merkus PJFM, Verhaak CM. Prenatal maternal psychological stress and childhood asthma and wheezing: a meta-analysis. *Eur Respir J* 2016;**47**:133–46.
8. Veru F, Laplante DP, Luheshi G, King S. Prenatal maternal stress exposure and immune function in the offspring. *Stress* 2014;**17**:133–48.
9. Beijers R, Buitelaar JK, de Weerth C. Mechanisms underlying the effects of prenatal psychosocial stress on child outcomes: beyond the HPA axis. *Eur Child Adolesc Psychiatry* 2014;**23**:943–56.
10. Wright RJ. Stress-related programming of autonomic imbalance: role in allergy and asthma. *Chem Immunol Allergy* 2012;**98**:32–47.
11. de Marco R, Pesce G, Girardi P *et al.* Foetal exposure to maternal stressful events increases the risk of having asthma and atopic diseases in childhood. *Pediatr Allergy Immunol* 2012;**23**:724–29.
12. Fang F, Höglund CO, Arck P *et al.* Maternal bereavement and childhood asthma—analyses in two large samples of Swedish children. *PLoS ONE* 2011;**6**:e27202e27202.
13. Hartwig IRV, Sly PD, Schmidt LA *et al.* Prenatal adverse life events increase the risk for atopic diseases in children, which is

enhanced in the absence of a maternal atopic predisposition. *J Allergy Clin Immunol* 2014;**134**:160–69.e7.
14. Khashan AS, Wicks S, Dalman C *et al.* Prenatal stress and risk of asthma hospitalization in the offspring: a Swedish population-based study. *Psychosom Med* 2012;**74**:635–41.
15. Lee A, Mathilda Chiu Y-H, Rosa MJ *et al.* Prenatal and postnatal stress and asthma in children: temporal- and sex-specific associations. *J Allergy Clin Immunol* 2016;**138**:740–47.e3.
16. Turcotte-Tremblay A-M, Lim R, Laplante DP, Kobzik L, Brunet A, King S. Prenatal maternal stress predicts childhood asthma in girls: project ice storm. *BioMed Res Int* 2014;**2014**:e201717.
17. Larsen AD, Schlünssen V, Christensen BH *et al.* Exposure to psychosocial job strain during pregnancy and odds of asthma and atopic dermatitis among 7-year old children—a prospective cohort study. *Scand J Work Environ Health* 2014;**40**:639–48.
18. Liu X, Madsen KP, Sejbaek CS *et al.* Risk of childhood asthma following prenatal exposure to negative life events and job stressors: a nationwide register-based study in Denmark. *Scand J Work Environ Health* 2019;**45**:174–82.
19. Magnus MC, Wright RJ, Røysamb E *et al.* Association of maternal psychosocial stress with increased risk of asthma development in offspring. *Am J Epidemiol* 2018;**187**:1199–209.
20. Karasek R, Theorell T. *Healthy Work: Stress, Productivity, and the Reconstruction of Working Life*. New York: Basic Books, 1990.
21. Olsen J, Melbye M, Olsen SF *et al.* The Danish National Birth Cohort: its background, structure and aim. *Scand J Public Health* 2001;**29**:300–07.
22. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011;**39**:12–6.
23. European Foundation for the Improvement of Living and Working Conditions. *Danish Work Environment Cohort Study, 2000 (DWECS)*. Dublin: European Foundation for the Improvement of Living and Working Conditions, 2007.
24. Li J, Olsen J, Vestergaard M, Obel C, Baker JL, Sørensen T. Prenatal stress exposure related to maternal bereavement and risk of childhood overweight. *PLoS ONE* 2010;**5**:e11896.
25. Hansen D, Lou HC, Olsen J. Serious life events and congenital malformations: a national study with complete follow-up. *Lancet* 2000;**356**:875–80.
26. Skodol AE, Shrout PE. Use of DSM-III axis IV in clinical practice: rating the severity of psychosocial stressors. *Psychiatry Res* 1989;**30**:201–11.
27. Wieclaw J, Agerbo E, Bo Mortensen P, Burr H, Tuchsen F, Bonde JP. Psychosocial working conditions and the risk of depression and anxiety disorders in the Danish workforce. *BMC Public Health* 2008;**8**:280.
28. Wieclaw J, Agerbo E, Mortensen PB, Burr H, Tüchsen F, Bonde JP. Work related violence and threats and the risk of depression and stress disorders. *J Epidemiol Community Health* 2006;**60**:771–75.
29. Karasek R, Brisson C, Kawakami N, Houtman I, Bongers P, Amick B. The Job Content Questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics. *J Occup Health Psychol* 1998;**3**:322–55.
30. Danmarks Statistik. DISCO-88 1988. 1996. http://www.dst.dk/da/Statistik/Publikationer/VisPub? cid=4831 (12 April 2017, date last accessed).
31. Mikkelsen S, Andersen JH, Bonde JP, Hansen ÅM, Kolstad H, Thomsen JF. Letter to the Editor: Job strain and clinical depression. *Psychol Med* 2018;**48**:347–48.
32. Courvoisier DS, Perneger TV. Validation of alternative formulations of job strain. *J Occup Health* 2010;**52**:5–13.
33. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;**332**:133–38.
34. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;**39**:30–33.
35. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC Classification and DDD Assignment 2013*. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 2012, p. 276.
36. Liu X, Andersen SL, Olsen J *et al.* Maternal hypothyroidism in the perinatal period and childhood asthma in the offspring. *Allergy* 2018;**73**:932–39.
37. Pape K, Sejbæk CS, Bay H, *et al.* Maternal stress at work and in private life during pregnancy and childhood asthma in the offspring: a study protocol. 2018. https://figshare.com/articles/Maternal_stress_at_work_and_in_private_life_during_pregnancy_and_childhood_asthma_in_the_offspring_a_study_protocol/5868588 (20 July 2020, date last accessed).
38. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83.
39. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;**47**:1245–51.
40. Qin P, Mortensen PB, Waltoft BL, Postolache TT. Allergy is associated with suicide completion with a possible mediating role of mood disorder: a population-based study. *Allergy* 2011;**66**:658–64.
41. European Commission. Denmark: Overview-Eurydice. 2016. https://webgate.ec.europa.eu/fpfis/mwikis/eurydice/index.php/Denmark: Redirect (12 April 2017, date last accessed).
42. UNESCO UNES and CO, UNESCO Institute for Statistics. *International Standard Classification of Education: ISCED 2011*. Monteral: UNESCO Institute for Statistics, 2012.
43. Liu X, Olsen J, Agerbo E, Yuan W, Sigsgaard T, Li J. Prenatal stress and childhood asthma in the offspring: role of age at onset. *Eur J Public Health* 2015;**25**:1042–46.
44. Armstrong BG. Effect of measurement error on epidemiological studies of environmental and occupational exposures. *Occup Environ Med* 1998;**55**:651–56.
45. Heid IM, Küchenhoff H, Miles J, Kreienbrock L, Wichmann HE. Two dimensions of measurement error: classical and Berkson error in residential radon exposure assessment. *J Expo Sci Environ Epidemiol* 2004;**14**:365–77.
46. Petersen SB, Flachs EM, Svendsen SW *et al.* Influence of errors in job codes on job exposure matrix-based exposure assessment in the register-based occupational cohort DOC*X. *Scand J Work Environ Health* 2020;**46**:259–67.