ORIGINAL ARTICLE

Wheezing, asthma, hay fever, and atopic eczema in relation to maternal occupations in pregnancy

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Objectives: To examine whether prenatal occupational exposures, especially to organic solvents, are associated with atopic diseases in childhood.

Methods: The study comprised children born in Odense or Aalborg, Denmark between 1984 and 1987. Occupational job titles were derived from questionnaires filled out by the mothers when attending midwife centres. Assessment of organic solvent exposures was based on job titles selected by occupational specialists. A follow up questionnaire to the parents provided data on medical diagnoses as well as wheezing symptoms for 7844 children aged 14–18. Multivariate logistic regression analyses were performed to estimate the cumulative risk for wheezing (early wheezing not diagnosed as asthma), asthma, hay fever, and atopic eczema during childhood by means of odds ratios (OR) and 95% confidence intervals (CI).

Results: Explorative analyses by maternal job titles in pregnancy showed elevated odds ratios concerning different atopic diseases for occupational groups such as ''bakers, pastry cooks, and confectionary makers'', ''dental assistants'', ''electrical and electronic assemblers'', ''sewers and embroiders'', and ''bookbinders and related workers''. An excess risk ratio for hay fever (OR 2.8, CI 1.1 to 7.5) was found following maternal gestational exposure to organic solvents. Furthermore, a slightly raised odds ratio for asthma was observed in children of shift workers (OR 1.2, CI 1.0 to 1.5).

Conclusion: The data suggest links between certain maternal occupations during pregnancy and atopic diseases, which merits further scrutiny. However, no consistent pattern was seen across the different atopic diseases.

Atopic diseases such as asthma, atopic dermatitis, and allergic rhinitis, characterised by a T helper 2 (Th2) phenotype and production of immunoglobulin E (IgE) antibodies in response to antigens,[1 2] are today among the most common chronic diseases in children in Western countries. The apparent epidemic of asthma and allergies during recent decades is most likely attributable to changes in environmental exposures.[3] Early exposures (or lack of exposures), for example while in the intrauterine environment, may cause asthma and allergy in childhood.[4]

Female participation in the workforce has increased considerably during the last 40–50 years[5] and many women are now employed in occupations with potential exposure to chemical, physical, and biological agents as well as to physical exertion and stress. Whether these changes are linked to the epidemic of atopic diseases is unknown, but over 250 work related agents have been reported to cause asthma and allergy in adults, a number of them by inducing IgE mediated responses.[6]

Organic solvents are among the most widespread occupational exposures. These chemicals are volatile and lipophilic compounds, likely to pass the placenta.[7] It has been shown that the relative amounts of low molecular weight volatile organic constituents in cord blood closely correspond to, or may even exceed, quantities in the maternal blood.[8] Exposure to volatile organic compounds (VOCs) in non-industrial settings has been linked to an increased risk of childhood asthma[9] as well as asthma-like symptoms among adults.[10] Moreover, maternal exposure to VOCs has been associated with an increase in type 2 T cells and a reduction in type 1 T cells in newborns' cord blood.[11] A shift in the balance between the type 1 and type 2 response towards allergens, leading to a persistent type 2 (Th2) skewed response, has been suggested to predispose children to asthma and atopy.[12]

Shift work is also considered as a potential risk to reproduction and is associated with, for example, hormonal disturbances through changes in circadian rhythm (sleep deprivation) and/or stress.[13] Exposure to hormones and/or stress during pregnancy has been found to be related with elevated cord blood IgE[14] and ability to alter the Th1/Th2 balance.[15]

We aimed to examine whether maternal occupation in pregnancy (including shift work) as well as maternal organic solvent exposure is associated with atopic disorders (wheezing, asthma, hay fever, and atopic eczema) in childhood.

METHODS

Study population

The study comprised children born to mothers who participated in a community trial in the two Danish cities Odense and Aalborg during April 1984 to April 1987. All women who visited midwife centres at approximately the 36th week of gestation were given a self-administrated questionnaire about lifestyle, work, and other social conditions. The response proportion was around 87% (n = 11 980) of the identified women in the study.

They subsequently gave birth to 11 144 live singletons. A more comprehensive description of the cohort can be found elsewhere.[16] In the year 2002, 10 636 of these children and their mothers were still alive, residents in Denmark, and could be traced by means of the Civil Registration System. To obtain information about the child's health, a follow up questionnaire was sent to the parents of these children including an assessment of atopic diseases. Response to the questionnaire was retrieved for approximately 74% (n = 7844) of the children at the age of 14–18 years, of whom 4045 (51.6%) were boys and 3798 (48.4%) were girls.

Exposure assessment

The questionnaire provided data on maternal work status during pregnancy. We excluded 1426 children of mothers who reported not to have worked during gestation. Maternal job titles, preconceptional and/or gestational, were recorded on the basis of a Danish occupational classification,[17] corresponding to the International Classification of Occupations (ISCO), 1968 version.[18] Children were classified into an occupational category during pregnancy based on the maternal job titles, consisting of five digit codes. If a woman reported a change of job during gestation (n = 685), the new job title was used, while the preconceptional job titles were used for women with missing data on this parameter (n = 156). The occupational categories were further classified into occupational groups based on the three or four first digits of the codes. Moreover, children were classified as exposed to shift work if the mothers recorded that they were shift workers during pregnancy.

Three Danish medical specialists in occupational medicine separately performed an assessment of occupational exposure to organic solvents at Danish workplaces in the mid 1980s. The classification of exposure was based on threshold limit values (TLVs) as they have been found to reflect relative levels of exposure across industries as well as absolute levels.[19] Some examples of Danish TLVs from that period include: benzene 19 ppm, trichloroethylene 50 ppm, toluene and xylene 100 ppm, white spirit and isopropylacetate 200 ppm, as well as acetone and ethanol 1000 ppm. Each occupational category were independently classified as (0) most likely not exposed to organic solvents, (1) most likely exposed at time weighted average levels below the Danish threshold limit value, or (2) most likely exposed at time weighted average levels at or above the Danish TLV, and the final rating was computed as the rounded mean value. Kappa statistics showed an agreement of 0.50 (moderate) for exposure category 0, 0.38 (fair) for exposure category 1, and 0.29 (fair) for exposure category 2. The overall kappa value was 0.44, which indicate moderate agreement. The assignment of the final exposure class was, however, that suggested by all or at least two of the raters in the majority of cases. The three independent exposure ratings resulted in the same value in 88.2% of the cases and in 99.4% of the cases at least two of the raters agreed. Occupations with solvent exposure considered below TLV included occupational groups such as laboratory workers, dental workers, dry cleaners, fitters/solderers, and manufactory workers. Occupations with exposure considered at or above TLV mainly included categories related to painting, printing, furniture manufacturing, and engineering industry.

Outcomes

The outcomes of interest were asthma, hay fever, atopic eczema, and wheezing. Asthma, hay fever, and atopic eczema were defined on the basis of parental report of a physician's diagnosis by the time of follow up. The questions were partly derived from a Danish questionnaire (questions 1–7) developed from the UK Party's questionnaire for atopic dermatitis.[20 21] To assess medical diagnoses of atopic eczema the following question was also included: ''Have you ever been informed by a doctor that your child has eczema?''. Questions concerning wheezing were originally developed for the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (questions 1–5 and 7–8 from the core questionnaire wheezing module for 13–14 year olds).[22] Question number 1 from the ISAAC questionnaire was, however, modified as follows: ''Have your child *before 3 years of age* ever had wheezing or whistling in the chest?''. Children with an affirmative answer to this question, but who had not received a physician's diagnosis of asthma, were defined as having wheezing. Data on hospitalisations with bronchitis, asthma, allergic rhinitis, and atopic eczema until June 2003 were also available and were used for validation.[23]

Potential confounders

As potential confounders we considered a number of potential risk factors or protective factors for atopic diseases that could be imbalanced between groups to be compared. These included variables collected by questionnaires in pregnancy, accompanied with data from medical records, such as maternal educational level (primary school or lower, lower secondary school, upper secondary school, or higher), age (15–19, 20–24, 25–29, 30–34, 35+), smoking (yes/no),[24] alcohol consumption (−1, 1–4, 5–9, 10+ drinks/week), coffee and tea consumption (0–3, 4–7, 8+ cups/day), intake of fish (0, 1–2, 3–4, 5+ times/month), vitamins/minerals (yes/no), folic acid (yes/no), parity (0, 1, 2, 3+), as well as infant birth weight (<2500 g, 2500–4000 g, >4000 g), gestational age, and gender. Parental socioeconomic conditions were also used and classified into seven groups based on the parent with the highest rating: group 1, employees with academic background or with executive jobs; group 2, employees in lower levels of management or employees with an intermediate vocational training like nurses or school teachers; group 3, employees with lower levels of management tasks or workers with a shorter education like policemen or nurse aids; group 4, skilled workers; group 5, unskilled or semiskilled workers; group 6, students; and group 7, others like housewives and unemployed. Moreover, potential confounding factors from the postnatal period that was considered were derived from the follow up questionnaire and included data on parental smoking (yes/no), breast feeding (no breast feeding, exclusive less than 4 months, exclusive more than 4 months), number of children in the household (1, 2, 3, 4+), day care attendance, and animal contact during the first year.

Data analysis

The study is a follow up study with recordings performed twice, in pregnancy and 14–18 years later, and a longitudinal recording of hospitalisations. Since we have no data on incidence between these two measures, except for hospitalisations, we calculated prevalence odds ratios (OR) with 95% confidence intervals (CI) on the basis of logistic regression analyses using data from the latest follow up recording. The analyses on occupational groups were based on the first four digits of the job codes, and included all occupations that had at least four cases. Clerical workers were used as the reference group. We excluded 63 children with no maternal job title recorded and 14 children with coding errors in the job titles. Concerning shift work, no data were available for 189 (2.9%) children. All analyses were adjusted for gender. Other potential confounding variables were included in the final models if they changed the point estimate by 5% or more. Sensitivity analyses were performed to assess the impact of expert rating differences of organic solvent exposure. Data analyses were performed with Stata Statistical Software 8.2.[25] Ethical approval was obtained from the ethical committee, Aarhus Amt (Videnskabsetiske komité for Århus Amt).

RESULTS

The overall prevalence of wheezing, asthma diagnosis, hay fever diagnosis, and atopic eczema diagnosis at the age of 14–18 years was 16.8%, 10.9%, 13.8%, and 15.9%, respectively. Table 1 shows some characteristics such as socioeconomic group, maternal education, maternal age, parity, and maternal smoking by occupational status as well as solvent exposure. Women with shift work did not differ

Table 1 Number of children according to parental characteristics and maternal occupational status and organic solvent exposure in pregnancy

	Any occupation		Shift work		Solvents <TLV*		Solvents ⩾TLV*	
Characteristic	**n**	**%†**	**n**	**%†**	**n**	**%†**	**n**	**%†**
All	6418	100	926	100	479	100	20	100
Socioeconomic group‡								
Academic/managerial	3135	48.9	463	50.0	160	34.0	0	–
Non-academic	3280	51.1	463	50.0	309	65.7	20	100
Maternal education								
Primary school or lower	691	10.8	92	9.9	75	16.0	7	35.0
Lower secondary school	3132	48.8	377	40.7	249	53.0	13	65.0
Upper secondary school or higher	2578	40.2	455	49.1	145	30.9	0	–
Maternal age								
15–24	1528	23.8	172	18.6	165	35.1	7	35.0
25–29	2877	44.8	477	51.5	196	41.7	6	30.0
30+	2011	31.3	277	29.9	109	23.2	7	35.0
Maternal smoking								
Yes	2563	39.9	387	41.8	203	43.2	12	60.0
No	3833	59.7	537	58.0	262	55.7	8	40.0
Maternal parity								
0	3128	48.7	508	54.9	250	53.2	14	70.0
1	2475	38.6	312	33.7	179	38.1	4	20.0
2+	815	12.7	106	11.5	41	8.7	2	10.0

The groupings of maternal occupational status into any occupation, shift work, and solvent exposure are not mutually exclusive. For categorisation of covariates used in the analyses, see Methods.
*Most likely exposure, at time weighted average, in relation to Danish threshold limit values (TLVs).
†Percentages might not add up to 100% due to missing information.
‡Socioeconomic group was classified according to the parent having the highest socioeconomic group; academic/managerial includes group 1–3 and non-academic group 4–7.

considerably, whereas women classified as exposed to solvents (both <TLV and ⩾TLV) more often reported lower educational level, smoking during pregnancy, and generally belonged to lower socioeconomic groups compared to women with any occupation.

In total, 14.4% (n = 926) of the children had mothers with shift work during pregnancy.

Analyses of shift work in pregnancy gave adjusted odds ratios of 1.1 (CI 0.9 to 1.3) for wheezing, 1.2 (CI 1.0 to 1.5) for asthma, 0.9 (CI 0.7 to 1.1) for hay fever, and 1.0 (CI 0.8 to 1.2) for atopic eczema (data not shown). Thirty eight of 135 (28%) occupational groups included in the data had four or more children with any of the outcomes. A few of these occupations showed statistically significant ORs (table 2). However, no clear pattern was seen across the different outcome variables.

''No exposure to organic solvents'' was considered most likely in 80.4% of the jobs, while 17.1% were classified with exposure below the TLV, and 2.4% at or above the TLV. The total number of children in the present study who had mothers that worked in solvent related occupations during gestation was 490, of which 470 (7.4%) were considered exposed below TLV and 20 (0.3%) at or above TLV. Exposure at or above TLV gave crude ORs of 1.2 (CI 0.3 to 4.1) for wheezing, 2.0 (CI 0.7 to 6.1) for asthma, 2.6 (CI 1.0 to 6.9) for hay fever, and 0.3 (CI 0.0 to 2.2) for eczema. These estimates were only slightly changed by confounder adjustments (table 3). Additional analyses, according to the lowest rate recording (children was considered exposed below TLV only if all three raters had assigned any degree of exposure, and at or above TLV only if all raters agreed), gave ORs similar to those presented above. When children, on the other hand, were considered exposed to the highest rate recording (by at least one of the raters), the following ORs were obtained for exposure below TLV: wheezing 1.3 (CI 1.0 to 1.6), asthma 1.0 (CI 0.7 to 1.2), hay fever 0.6 (CI 0.5 to 0.8), atopic eczema 1.1 (CI 0.9 to 1.3); and for exposure at or above TLV: wheezing 0.9 (CI 0.5 to 1.5), asthma 1.2 (CI 0.7 to 2.0), hay fever 1.3 (CI 0.8 to 2.0), atopic eczema 1.3 (CI 0.9 to 2.1). Stratification by gender showed no clear gender differences in any of the analyses.

The statistical precision was low in analyses based on the hospitalisation data concerning bronchitis, asthma, allergic rhinitis, and atopic eczema, since the total numbers of affected cases were 50, 349, 11, and 160, respectively. The estimates for shift work were not considerably different, except for allergic rhinitis (OR 2.9, CI 0.7 to 11.5, 3 cases). Furthermore, the crude estimate for hospitalisation with asthma and exposure to organic solvents at or above TLV was 5.2 (CI 1.7 to 15.7) and OR for hospitalisation with bronchitis was 3.5 (CI 1.6 to 7.6) for solvent exposure below TLV (table 4). These analyses also showed significant odds ratios between the following occupational categories: ''physicians'', ''other professional, technical, and related workers'', ''other cooks, waiters, bartenders, maids, and related housekeeping service workers'', and asthma, and between ''philologists, translators, and interpreters'' and atopic eczema.

DISCUSSION

Maternal shift work during pregnancy was marginally associated with asthma in the children and there was a tendency towards an increased risk for asthma and hay fever in association with high solvent exposure in pregnancy. Furthermore, we found elevated risk estimates for certain occupational groups such as bakers, dental assistants, electrical assemblers, sewers, and bookbinders. However, there was no consistent pattern across the different outcome variables for these occupations and the findings are not supported by prior evidence.

The study was based on the reports of actually held job (job titles) as they were stated in the questionnaire by the mothers in the third trimester. Unemployed women were excluded from the analyses to reduce differences in socio-demographic and behavioural risk factors. Some of the reported associations could be due to chance driven by multiple comparisons. In order to assess exposure we used occupational groups. This probably results in potential non-differential misclassification of job exposure due to

Table 2 Odds ratios (OR) with 95% confidence intervals (CI) for atopic diseases by age 14–18 according to maternal occupational categories in pregnancy

		Wheezing				Asthma diagnosis				Hay fever diagnosis				Atopic eczema diagnosis			
Occupational group	**N**	**n**	**OR**	**OR***	**CI***	**n**	**OR**	**OR***	**CI***	**n**	**OR**	**OR***	**CI***	**n**	**OR**	**OR ***	**CI***
Clerical workers	286	42	ref	ref		23	ref	ref		37	ref	ref		41	ref	ref	
Life sciences technicians‡	123	18	1.0	1.1	0.6–1.9	11	1.1	1.2	0.6–2.6	14	0.9	1.0	0.5–1.9	23	1.4	1.4	0.8–2.5
Surveyors	41	8	1.3	1.4	0.6–3.2	NA	NA	NA	NA	4	0.7	0.8	0.3–2.3	NA	NA	NA	NA
Engineering technicians NEC†	78	10	0.9	0.9	0.4–1.9	12	2.1	2.4	1.1–5.1	9	0.9	0.9	0.4–2.0	NA	NA	NA	NA
Medical doctors	70	8	0.8	0.8	0.3–1.9	7	1.3	1.1	0.4–2.9	10	1.1	1.2	0.5–2.8	10	1.0	1.0	0.4–2.2
Medical assistants	956	154	1.1	1.3	0.9–1.9	101	1.3	1.4	0.8–2.2	142	1.2	1.3	0.9–1.9	136	1.0	1.1	0.7–1.6
Dental assistants‡	106	29	2.3	2.4	1.4–4.2	13	1.6	1.8	0.9–3.7	15	1.1	1.1	0.6–2.2	20	1.4	1.4	0.8–2.6
Physiotherapists and occupational therapists	113	11	0.6	0.8	0.4–1.6	9	1.0	1.0	0.4–2.3	15	1.0	1.3	0.7–2.5	11	0.7	0.8	0.4–1.6
Dieticians and public health nutritionists	26	NA	NA	NA	NA	NA	NA	NA	NA	4	1.2	1.3	0.4–4.1	NA	NA	NA	NA
Medical, dental, veterinary, and related workers NEC†	76	12	1.1	1.2	0.6–2.4	6	1.0	1.0	0.4–2.7	17	1.9	2.1	1.1–4.1	10	0.9	0.9	0.4–1.9
Social workers	634	98	1.1	1.2	0.8–1.9	78	1.6	1.6	1.0–2.7	93	1.2	1.4	0.9–2.1	118	1.4	1.6	1.1–2.4
Other professional, technical, and related workers	69	8	0.8	0.9	0.4–2.1	7	1.3	1.2	0.5–3.0	10	1.1	1.4	0.6–3.0	10	1.0	1.2	0.5–2.6
Systems analysts	30	5	1.2	1.1	0.4–3.1	5	2.3	2.4	0.8–7.0	NA	NA	NA	NA	NA	NA	NA	NA
Philologists, translators, and interpreters	62	8	0.9	0.8	0.3–1.8	5	1.0	1.0	0.4–2.8	8	1.0	1.1	0.5–2.6	8	0.9	1.0	0.4–2.3
Teachers	473	69	1.0	1.2	0.8–2.0	39	1.0	1.0	0.6–1.8	55	0.9	1.1	0.7–1.8	91	1.5	1.7	1.1–2.7
Librarians, archivists, and curators	68	11	1.2	1.5	0.7–3.1	10	1.9	2.2	1.0–5.1	9	1.0	1.2	0.6–2.8	12	1.3	1.6	0.8–3.3
Bookkeepers and cashiers	106	21	1.5	1.5	0.9–2.8	12	1.5	1.5	0.7–3.3	16	1.2	1.3	0.7–2.5	13	0.8	0.9	0.5–1.8
Bookkeepers and cashiers and related workers NEC†	195	30	1.1	1.2	0.7–2.0	21	1.4	1.5	0.8–2.8	31	1.3	1.3	0.8–2.3	35	1.3	1.3	0.8–2.2
Bookkeeping and calculating machine operators	16	NA	NA –	NA	NA	NA	NA	NA	NA	5	3.0	3.2	1.0–9.9	5	2.7	3.2	1.0–9.9
Transport and communications supervisors NEC†	114	23	1.5	1.6	0.9–2.8	13	1.5	1.7	0.8–3.5	22	1.6	1.8	1.0–3.3	10	0.6	0.6	0.3–1.3
Working proprietors (wholesale and retail trade)	419	42	0.7	0.6	0.4–1.0	55	1.7	1.8	1.1–3.1	73	1.4	1.5	0.9–2.3	73	1.3	1.4	0.9–2.2
Working proprietors (wholesale and retail trade) NEC†	41	7	1.2	1.4	0.6–3.3	4	1.2	1.3	0.4–3.9	5	0.9	1.0	0.4–2.7	4	0.6	0.7	0.2–2.1
Cooks	146	22	1.1	1.0	0.6–1.9	15	1.3	1.4	0.7–2.8	17	0.9	1.0	0.5–1.9	27	1.4	1.5	0.8–2.6
Waiters, bartenders, and related workers	29	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6	1.6	2.1	0.8–5.5
Maids and related housekeeping service workers NEC†	18	4	1.6	1.4	0.4–4.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Other cooks, waiters, bartenders, maids, and related housekeeping service workers	272	40	1.1	1.0	0.6–1.7	35	1.7	1.5	0.8–2.8	35	1.0	1.2	0.7–2.1	39	1.0	1.2	0.7–2.1
Charworkers, cleaners, and related workers	132	26	1.5	1.4	0.8–2.5	14	1.3	1.2	0.6–2.6	15	0.9	1.0	0.5–2.0	21	1.1	1.5	0.8–2.7
Hairdressers, barbers, beauticians	60	11	1.4	1.4	0.7–3.1	8	1.8	1.9	0.8–4.6	6	0.8	0.8	0.3–2.1	9	1.1	1.2	0.5–2.6
Nursery workers and gardeners	89	12	0.9	0.9	0.4–1.8	12	1.8	1.7	0.8–3.7	7	0.6	0.7	0.3–1.6	15	1.2	1.5	0.8–2.9
Butchers and meat preparers	23	5	1.8	1.6	0.5–4.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bakers, pastry cooks, and confectionary makers	10	NA	NA	NA	NA	4	7.5	11.7	2.6–51.5	NA	NA	NA	NA	NA	NA	NA	NA
Sewers and embroiders	47	11	1.8	1.7	0.8–3.8	4	1.1	1.0	0.3–3.2	7	1.2	1.4	0.6–3.5	13	2.4	3.1	1.4–6.6
Electrical and electronic assemblers‡	28	6	1.7	1.8	0.6–4.8	NA	NA	NA	NA	NA	NA	NA	NA	7	2.0	2.5	1.0–6.3
Bookbinders and related workers‡	11	5	5.4	5.1	1.4–18.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Other production and related workers‡	120	17	1.0	0.9	0.4–1.7	15	1.6	1.5	0.7–3.2	8	0.5	0.6	0.3–1.3	17	1.0	1.2	0.6–2.4
Dockers and freight handlers	47	9	1.4	1.2	0.5–2.8	4	1.1	1.0	0.3–3.0	5	0.8	0.9	0.3–2.5	6	0.9	1.1	0.4–2.7
Other dockers and freight handlers	13	4	2.7	2.2	0.6–7.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Labourers NEC†‡	72	7	0.7	0.7	0.3–1.7	10	1.8	1.7	0.8–4.0	15	1.7	2.3	1.2–4.7	14	1.4	1.8	0.9–3.6

NA, not applicable (number of cases <4; odds ratios and confidence intervals not calculated).
*Adjusted for socioeconomic group, maternal education, maternal age, gender, parity, maternal smoking in pregnancy, postnatal smoking by parents, and breast feeding.
†NEC, not elsewhere classified.
‡Includes one or more occupational categories considered exposed to solvents <TLV.

Table 3 Odds ratios (OR) with 95% confidence intervals (CI) for atopic diseases by age 14–18 according to maternal organic solvent exposure in pregnancy

Solvent exposure	N	Wheezing				Asthma diagnosis				Hay fever diagnosis				Atopic eczema diagnosis			
		n	OR	OR*	CI*	n	OR	OR*	CI*	n	OR	OR*	CI*	n	OR	OR*	CI*
Not exposed	5851	891	ref	ref		636	ref	ref		812	ref	ref		907	ref	ref	
Below TLV†	470	83	1.2	1.1	0.9–1.5	51	1.0	1.0	0.7–1.3	53	0.8	0.8	0.6–1.1	87	1.2	1.2	0.9–1.6
At or above TLV†	20	3	1.2	1.1	0.3–4.1	4	2.0	1.8	0.6–5.6	6	2.6	2.8	1.1–7.5	1	0.3	0.3	0.0–2.3

*Adjusted for socioeconomic group, maternal educational level, maternal age, parity, maternal smoking, gender, postnatal parental smoking, and breast feeding.
†TLV, threshold limit value.

differences in work tasks within the groups. Occasionally, a job exposure matrix can be a useful alternative to expert assessment of exposure in large epidemiological studies. However, job exposure matrices usually have low sensitivity and substantial exposure misclassification, especially when used in another country or for purposes other than those originally designed for.[26] A classification of occupations according to allergen exposure would have been of interest, but occupational grouping by allergen exposure was not feasible. An asthma specific job exposure matrix including assessment of allergen exposure as well as job exposure matrices that include exposure to organic solvents have been developed, but no exposure matrix was available for use with Danish Fagkode that is fully adapted to the Danish setting.[27]

Although parental report of physician diagnoses of asthma has been shown to be accurate,[28] the access to medical care may differ leading to potential differential misclassification of medical diagnoses. To avoid this problem we adjusted for socioeconomic groups. Misclassification by inaccurate recall of wheezing episodes is also possible. But in order for this latter misclassification to be differential the mothers should have related the diseases at follow up with their occupation during pregnancy (more than 10 years ago), which is unlikely. A classification of wheezing into transient, non-atopic wheezing, and atopic wheezing/asthma has been proposed.[29] These different phenotypes may have different aetiology. Unfortunately, we did not have information about the atopic status, or if wheezing symptoms were transient or persistent. It is likely, however, that children with wheezing before 3 years of age, who had not received an asthma diagnosis by age 14–18, represent children with transient symptoms. We also lacked data on family history of atopy/allergy. Mothers with allergic diseases may avoid certain types of occupations, which will lead to negative confounding by genetic factors. Furthermore, employees with work related asthma or allergy are generally advised to avoid or reduce occupational exposure, especially during pregnancy since uncontrolled asthma is associated with both adverse maternal and fetal health conditions.[30] If the maternal disease is manifested in pregnancy, it might be associated with transfer of antibodies and cytokines to the offspring, possibly influencing immune development/response.[31] It has also been suggested that newborns with a deficient production of interferon gamma and with an allergic mother who is exposed to allergens that trigger the disease, are less likely to counteract the effect of the Th2 skewed immune response in pregnancy.[32] A tendency to avoid exposures among allergic mothers would probably underestimate any true associations.

Many occupational exposures are well established causes of atopic diseases such asthma and rhinitis in adults.[33] High molecular allergens such as flour dust, castor beans, rodent and insect proteins, natural rubber (latex), and some low molecular compounds that bind to haptens may induce asthma through IgE immunological mechanisms. However, most low molecular industrial chemicals act through immunological mechanisms that are not related to IgE antibodies or by non-immunological mechanisms. Interestingly, we observed elevated ratios in the children for several occupational groups such as bakers, sewers, and dental assistants that may be exposed to agents commonly associated with occupational asthma. Sensitisation to allergens is known to occur already in utero, possibly even in the absence of maternal sensitisation.[34] A few recent studies also report associations between prenatal exposure to certain environmental chemicals and respiratory symptoms and asthma.[35 36] It is conceivable that maternal exposure to and/or transplacental transfer of occupational agents might contribute to a Th1/Th2 imbalance in pregnancy and development of atopic diseases.[37] Concerning organic

Table 4 Odds ratios (OR) with 95% confidence intervals (CI) for hospitalisation diagnoses of atopic disease according to maternal organic solvent exposure in pregnancy

		Asthma			Allergic rhinitis			Atopic eczema			Bronchitis		
Solvent exposure	N	n	OR	CI	n	OR	CI	n	OR	CI	n	OR	CI
Not exposed	5851	267	ref		9	ref		128	ref		29	ref	
Below TLV*	470	21	1.0	0.6–1.5	0	–	–	7	0.7	0.3–1.5	8	3.5	1.6–7.6
At or above TLV*	20	4	5.2	1.7–15.7	0	–	–	0	–	–	0	–	–

*TLV, threshold limit value.

solvents, fetal exposure has been associated with pregnancy outcomes.[38] Moreover, a recent study showed later functional deficits such as poorer intellectual, language, motor, and neurobehavioural functioning.[39] It could be hypothesised that prenatal exposure to organic solvents also confer immune modulation or ''programme'' the immune function such as showed by Lehmann *et al* for volatile organic compounds, and thereby increase the risk for allergic manifestations.[11]

Our results suggest that certain occupational exposures in pregnancy may increase the risk of atopic diseases in the offspring, although no consistent pattern across the different outcome variables was observed. Associations between mothers' work and atopic diseases among the offspring have not been reported earlier, and thus merit further investigation. If confirmed, further challenges are to find the exposures responsible for these associations as well as potential mechanisms.

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Main messages

- Maternal work in a few specific occupations during pregnancy such as bakers, dental assistants, electrical assemblers, sewers, and bookbinders was associated with moderately elevated risk estimates for atopic diseases in childhood.
- Exposure to organic solvents during pregnancy may be one of several risk factors.
- Associations between mother's work and atopic disease among the offspring have not previously been reported and mechanisms are unknown.

Policy implications

- These findings merit further investigation.
- If the findings are confirmed, a broader set of potential long term health effects of maternal occupational exposures in pregnancy need to be considered.

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