

Original research

Prenatal occupational disinfectant exposure and childhood allergies: the Japan Environment and Children's study

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ABSTRACT

Background Disinfectants are widely used in the medical field, particularly recently because of the coronavirus pandemic, which has led to an increase in their use by both medical professionals and the general population. The objective of this study was to examine whether occupational disinfectant use during pregnancy was associated with the development of allergic disease in offspring at 3 years.

Methods We used data from 78 915 mother/child pairs who participated in the Japan Environment and Children's Study, which is a prospective birth cohort recruited between January 2011 and March 2014. We examined the associations between maternal disinfectant use during pregnancy and allergic diseases (asthma, eczema and food allergies) in children after adjustment for covariates including maternal postnatal return to work when the child was 1 year old by multivariate logistic regression.

Results Compared with those who never used disinfectants, participants who used disinfectant every day had a significantly higher risk of asthma in their offspring (adjusted OR 1.18, 95% CI 1.05 to 1.33 for 1–6 times a week; adjusted OR 1.26, 95% CI 1.05 to 1.52 for every day). The associations between disinfectant exposure and eczema were similar to those of asthma (adjusted OR 1.16, 95% CI 1.02 to 1.31 for 1–6 times a week; adjusted OR 1.29, 95% CI 1.06 to 1.57 for every day). We found a significant exposure-dependent relationship (p for trend <0.01). There were no significant associations between disinfectant use and food allergies.

Conclusion Disinfectant use by pregnant women may be a risk factor for asthma and eczema in offspring. As disinfectants are an effective tool in the prevention of infectious diseases, replication of this study and further research into the mechanisms are warranted.

INTRODUCTION

Allergic diseases are common chronic conditions in children and are caused by a combination of environmental and genetic factors.¹ Multiple factors have been reported to contribute to the development of allergic diseases in children,^{1–3} including prenatal exposure to secondhand smoke, chemicals, mould and ambient air pollutants.^{1,2}

Key messages

What is already known about this subject?

- Disinfectants are widely used in the medical field, particularly recently because of the coronavirus pandemic, which has led to an increase in their use by both medical professionals and the general population.
- Exposure to disinfectants has been reported to cause asthma and dermatitis in occupational settings.

What are the new findings?

- Disinfectant use during pregnancy appears to be a risk factor for asthma and eczema in offspring.
- An exposure-dependent association was found between disinfectant exposure and both asthma and eczema.
- After adjusting for maternal postnatal return to work, the association remained significant.

How might this impact on policy or clinical practice in the foreseeable future?

- Although disinfectants are an effective tool in the prevention of infectious diseases, more attention should be paid to the adverse effects of disinfectants on the health of offspring.

Disinfectants (eg, alcohol, chlorhexidine and quaternary ammonium salts) are widely used in the medical field, and the coronavirus pandemic has led to an increase in their use by both medical professionals and the general population.⁴ Exposure to disinfectants has been reported to cause asthma^{5–7} and dermatitis⁴ in occupational settings.^{8,9} A cross-sectional study of US nurses found an association between disinfectant use and asthma control.⁶ A later prospective cohort study by the same research group did not find an association between disinfectant use and asthma development in nurses,⁵ but the participants in that study were relatively late-career nurses, and the authors noted the need to examine this in early-career nurses. To date, there have been few studies that focused on disinfectant use during pregnancy and the development of allergic disease in the offspring, even though healthcare

Table 1 Characteristics of study participants (n=78 915)

	Number	Percentage
Maternal history of allergy		
Yes	38 016	48.3
No	40 622	51.7
Paternal history of allergy		
Yes	17 426	22.1
No	24 229	30.7
Missing	37 260	47.2
Pre-pregnancy body mass index (kg/m²)		
<18.5	12 763	16.2
≥18.5–<25	58 230	73.8
≥25	7 885	10.0
Maternal age at pregnancy (years)		
<25	9 063	11.5
≥25–<30	22 673	28.7
≥30–<35	27 764	35.2
≥35	19 415	24.6
Household income (million Japanese yen/year)*		
<4	28 684	36.4
≥4–<8	37 120	47.0
≥8	8 312	10.5
Unknown	4 799	6.1
Indoor cigarette smoke during pregnancy†		
No	61 688	79.1
Yes	16 309	20.9
Maternal history of alcohol consumption in early pregnancy		
Never	27 415	35.0
Previously did but quit	43 004	54.9
Currently consuming alcohol	7 933	10.1
Number of night shifts‡		
<3 days per month	75 503	95.7
≥3 days per month	3 412	4.3
Maternal stress (Kessler Psychological Distress Scale, version K6)		
<5 (not experiencing stress)	56 860	72.5
≥5 (experiencing stress)	21 544	27.5
Maternal occupations at the time of pregnancy		
Non-healthcare professional	61 853	79.3
Healthcare professional§	16 195	20.8
Disinfectant exposure during pregnancy		
Never	69 387	87.9
1–3 times a month	4 103	5.2
1–6 times a week	4 064	5.2
Every day	1 361	1.7
Postnatal return to work at 1 year		
Yes	34 663	45.5
No	41 598	54.6
Mode of delivery		
Caesarean section	15 429	19.6
Vaginal	63 160	80.4
Preterm delivery		
Yes (<37 weeks gestation)	4 092	5.2
No (≥37 weeks gestation)	74 682	94.8
Birth weight		
<2500 g	6 960	8.8
≥2500 g	71 773	91.2
Child's sex		
Male	40 392	51.2

continued

Table 1 continued

	Number	Percentage
Female		
	38 523	48.8
Older siblings		
Yes	42 141	53.6
No	36 497	46.4
Duration of exclusive breastfeeding		
Fewer than 6 months	46 202	59.8
At least 6 months	31 109	40.2
Child attended daycare at 1 year		
Yes	20 093	26.1
No	56 895	73.9
Physician-diagnosed allergy		
Asthma at 3 years	6 081	7.7
Eczema at 3 years	5 780	7.3
Food allergy at 3 years	4 970	6.3

*An income of less than 2 million yen per year (approximately US\$18 000) is considered poverty in Japan, while an income of 4–6 million yen is considered average.

†The presence of one or more individuals smoking at home in the presence of a pregnant woman.

‡Work except day shifts (approximately morning to evening).

§Respondents who selected the following; medical doctors, dentists, veterinarians, pharmacists, public health nurses, midwives, nurses, medical technicians, other health workers, social welfare professionals (social workers), other health professionals, nursing care service workers and healthcare service workers.

professionals, the main users of disinfectants, include many women of reproductive age.

Several studies have been published that focused on occupational chemical exposure during pregnancy and allergic diseases in offspring, but few of these studies involved disinfectants. There are reports of increased risk of offspring allergic disease in occupational groups working with low molecular weight agents¹⁰ and solvents.^{11 12} In some of these reports the exposure group includes healthcare professionals¹¹ and in others it does not.¹² Occupational exposure to chemicals, including disinfectants, has been reported to increase the risk of asthma in offspring,¹³ but the occupational category of chemicals in this study was a mix of disinfectants and chemicals such as isocyanates, and disinfectants alone were not assessed.¹³ Occupational exposure to latex and disinfectants has been reported to increase the risk of asthma in offspring,¹⁴ but the occupation was used to estimate disinfectant exposure and the actual frequency of disinfectant use was not measured. Thus, the association between disinfectant use during pregnancy and the development of allergic disease in offspring is not well studied.

Given the current increased use of disinfectants to prevent new coronavirus infections, it is of great public health importance to consider whether prenatal disinfectant exposure is a risk for the development of allergic diseases. Therefore, the current study examined whether prenatal disinfectant exposure was associated with an increased risk of allergic diseases at 3

Table 2 Disinfectant use by healthcare professionals

	Non-healthcare professional (n=61 853)		Healthcare professional (n=16 195)	
	Number	Percentage	Number	Percentage
Disinfectant use				
Never	57 672	93.2	10 947	67.6
1–3 times a month	2 678	4.3	1 377	8.5
1–6 times a week	1 161	1.9	2 862	17.7
Every day	342	0.6	1 009	6.2

Table 3 ORs of physician-diagnosed allergy at 3 years in relation to prenatal disinfectant exposure by frequency

	Model 1		Model 2		Model 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Asthma (n=6081)						
Disinfectant exposure						
Never	Ref		Ref		Ref	
1–3 times a month	1.11	0.99 to 1.25	1.03	0.91 to 1.16	1.02	0.91 to 1.16
1–6 times a week	1.38	1.24 to 1.53	1.19	1.06 to 1.34	1.18	1.05 to 1.33
Every day	1.50	1.26 to 1.78	1.30	1.08 to 1.56	1.26	1.05 to 1.52
p for trend	<0.01		<0.01		<0.01	
Eczema (n=5780)						
Disinfectant exposure						
Never	Ref		Ref		Ref	
1–3 times a month	1.03	0.92 to 1.16	1.01	0.89 to 1.15	1.01	0.89 to 1.15
1–6 times a week	1.16	1.03 to 1.3	1.15	1.02 to 1.31	1.16	1.02 to 1.31
Every day	1.36	1.13 to 1.63	1.31	1.08 to 1.59	1.29	1.06 to 1.57
p for trend	<0.01		<0.01		<0.01	
Food allergy (n=4970)						
Disinfectant exposure						
Never	Ref		Ref		Ref	
1–3 times a month	1.11	0.98 to 1.26	1.07	0.94 to 1.22	1.07	0.94 to 1.22
1–6 times a week	1.15	1.02 to 1.30	0.99	0.87 to 1.13	0.99	0.87 to 1.14
Every day	1.10	0.88 to 1.36	0.98	0.78 to 1.22	0.98	0.79 to 1.23
p for trend	0.01		0.95		0.89	

Model 1: crude. Model 2: adjusted for maternal and paternal history of allergy, maternal body mass index, maternal exposure to indoor cigarette smoke, maternal alcohol consumption during pregnancy, maternal age at pregnancy, household income, mode of delivery, preterm birth, child birth weight, child sex, older siblings, exclusive breastfeeding, child daycare attendance at 1 year, maternal occupation. Model 3: Model 2+adjusted for maternal postnatal return to work when the child was 1 year old. Bold type indicates statistical significance ($p < 0.05$).

years, using samples and data from a longitudinal prospective large birth cohort, the Japan Environment and Children's Study (JECS).

METHODS

Study population

The participants of this study were mother/child pairs who participated in the JECS nationwide birth cohort study funded by the Ministry of the Environment, Japan. The JECS protocol and baseline data have been described elsewhere.^{15,16} Briefly, the JECS is an ongoing nationwide birth cohort study which recruited more than 100 000 pregnant women who lived in one of 15 study areas covering a wide geographical area between January 2011 and March 2014. Participants were recruited via cooperating healthcare providers and/or local government offices issuing Maternal and Child Health Handbooks. The JECS covered approximately half of the births in the study area. The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (IRB number: 100910001) and by the ethics committees of all participating institutions. Written informed consent was obtained from all participants.

This study was based on the jecs-ta-20190930 dataset released in October 2019. The dataset included 104 062 fetal records. There were 5637 mothers of two children who participated in the study and 52 mothers of three children. Of these, we excluded stillbirths and miscarriages ($n=3758$), as well as subjects for whom data were missing for disinfectant use ($n=5733$) and allergic diseases in the children at 3 years ($n=15 656$). The final study population included 78 915 mother/child pairs.

Variables

Outcomes

The outcomes of the present study were physician-diagnosed allergic diseases (asthma, eczema and food allergies) in children at 3 years. Information about the outcomes was self-reported by the mothers and collected using self-administered questionnaires.¹⁷ Allergic disease (asthma, eczema and food allergies) diagnosed by a physician at 3 years was defined as a positive response to the question, "Has your child ever been diagnosed by a physician as having one or more allergic disease(s) in the past 12 months or been treated for such a disease?"

Exposure

In the present study the exposure was disinfectant use. All pregnant women in the second/third trimesters (22–28 weeks gestation) were asked about their disinfectant use by self-administered questionnaires.¹⁸ Participants were asked the "frequency of using or handling following materials during work for more than half a day." 'Medical disinfectant' was one of the materials specified, and no specific disinfectant (eg, alcohol, chlorhexidine and quaternary ammonium salts) was indicated. The response options were 'never', '1–3 times a month', '1–6 times a week' and 'every day'.

Covariates

We selected the following covariates for modelling from previous studies about factors related to development of allergic diseases during gestation and early infancy^{2,3,19–21} and directed acyclic graphs (online supplemental figure A-1).²² Information on maternal and paternal history of allergies (asthma, eczema, food allergies and allergic rhinitis), exposure to indoor cigarette smoke during pregnancy, maternal alcohol consumption during

Table 4 Adjusted ORs of allergy at 3 years of age in relation to disinfectant exposure with or without postnatal return to work

	Without return to work (n=41 598)		With return to work (n=34 663)	
	Adjusted OR*	95% CI	Adjusted OR*	95% CI
Asthma				
Disinfectant exposure				
Never	Ref		Ref	
1–3 times a month	1.02	0.87 to 1.20	1.02	0.85 to 1.23
1–6 times a week	1.13	0.99 to 1.31	1.29	1.05 to 1.60
Every day	1.30	1.05 to 1.60	1.16	0.78 to 1.71
p for trend	<0.01		0.04	
Eczema				
Disinfectant exposure				
Never	Ref		Ref	
1–3 times a month	0.91	0.75 to 1.10	1.12	0.94 to 1.32
1–6 times a week	1.38	1.12 to 1.70	1.06	0.91 to 1.24
Every day	1.28	0.88 to 1.87	1.30	1.04 to 1.64
p for trend	0.02		0.03	

Bold type indicates statistical significance ($p < 0.05$).

P value for interaction (disinfectant exposure and postnatal return to work): asthma, 0.45; eczema, 0.24.

*Adjusted for maternal and paternal history of allergy, maternal body mass index, maternal exposure to indoor cigarette smoke, maternal alcohol consumption during pregnancy, maternal age at pregnancy, household income, mode of delivery, preterm birth, child birth weight, child sex, older siblings, exclusive breastfeeding, child daycare attendance at 1 year, maternal occupation.

pregnancy, maternal stress, night shift work and occupation (healthcare worker or not) during pregnancy, annual household income, the presence of older siblings, exclusive breastfeeding, daycare attendance at 1 year and maternal postnatal return to work when the child was 1 year old was ascertained using self-administered questionnaires during pregnancy, at 1 year and 3 years. Information on age at pregnancy, mode of delivery, gestational age at delivery, pre-pregnancy body mass index, child birth weight and sex of the child was collected from transcriptions from physicians, midwives/nurses or research coordinators.

Statistical analyses

We calculated summary measures of the characteristics of study participants and outcomes. A logistic regression model was used to examine the association of maternal disinfectant use with diagnosed allergies at 3 years and 'never' was used as the reference for the analysis. Model 1 was a crude model. Model 2 was adjusted for maternal and paternal history of allergies, pre-pregnancy body mass index, maternal age at pregnancy, maternal exposure to indoor cigarette smoke during pregnancy, maternal alcohol consumption during pregnancy, mode of delivery, annual household income, birth weight, gestational age at delivery, sex of the child, the presence of older siblings, exclusive breastfeeding, daycare attendance at 1 year and maternal occupation. Model 3 was adjusted further for maternal postnatal return to work when the child was 1 year old. For the trend test on the frequency of disinfectant use, the linear trend was tested by transforming the use of four categories of disinfectant use as continuous variables. Moreover, to examine modification of effect of disinfectant use by maternal postnatal return to work and occupation, subgroup analyses were performed by maternal postnatal return to work and occupation (healthcare professional or not). All analyses were conducted in SAS 9.4 (SAS Institute, Cary, North Carolina, USA). $p < 0.05$ was considered significant.

RESULTS

Table 1 shows the characteristics of the study participants. The prevalence of occupational disinfectant use was 5.2% (1–3 times a month), 5.2% (1–6 times a week) and 1.7% (every day). The prevalence of physician-diagnosed allergies at 3 years was 7.7% for asthma, 7.3% for atopic dermatitis and 6.3% for food allergies. **Table 2** shows disinfectant use stratified by occupation; healthcare professionals used disinfectants more frequently than non-healthcare professionals.

Table 3 shows the results of logistic regression evaluating the associations between disinfectant exposure and physician-diagnosed asthma at 3 years grouped by frequency of exposure. Participants who used disinfectant were more likely to have children with asthma than those who never used disinfectant (Model 1, **Table 3**; OR 1.38, 95% CI 1.24 to 1.53 for 1–6 times a week; OR 1.50, 95% CI 1.26 to 1.78 for every day; p for trend < 0.01). Adjusting for potential confounders slightly reduced the effect of disinfectant use on asthma in offspring (Model 2, **Table 3**; OR 1.19, 95% CI 1.06 to 1.34 for 1–6 times a week; OR 1.30, 95% CI 1.08 to 1.56 for every day; p for trend < 0.01). In the final model, adjusting for maternal postnatal return to work when the child was 1 year old, the effect remained significantly and positively associated with offspring asthma at 3 years (Model 3, **Table 3**; OR 1.18, 95% CI 1.05 to 1.33 for 1–6 times a week; OR 1.26, 95% CI 1.05 to 1.52 for every day; p for trend < 0.01). There was a significant exposure-dependent association between disinfectant exposure and asthma. The associations between disinfectant exposure and physician-diagnosed eczema at 3 years were similar to those of asthma (**Table 3**). However, there were no significant associations between disinfectant exposure and physician-diagnosed food allergy at 3 years.

Table 4 shows the results stratified by whether the mother returned to work when the child was 1 year old. Regardless of whether the mother returned to work at that time, prenatal occupational exposure to disinfectants was associated with an increased risk of asthma and eczema in offspring. Interactions between disinfectant exposure and postnatal return to work were not significant for asthma or eczema (**Table 4**). Interactions between disinfectant exposure and healthcare professionals were not significant for asthma or eczema (online supplemental Table A2).

DISCUSSION

We found that prenatal occupational disinfectant exposure was a risk factor for physician-diagnosed asthma and eczema and exhibited an exposure-dependent pattern. Subgroup analysis showed that, regardless of whether the mother returned to work when the child was 1 year old, prenatal occupational exposure to disinfectants was associated with an increased risk of asthma and eczema in offspring.

The association between maternal use of disinfectants and the development of allergic disease in children has not been well studied. However, some associations between occupational exposure to chemicals in pregnant women and allergic diseases in offspring have been reported.^{10–14 23} Most published papers on occupational disinfectant exposure use a job-exposure matrix to assess exposure and report concomitant exposure to disinfectants and industrial chemicals. Maternal perinatal exposure to chemicals has been shown to be a risk factor in asthma and allergies in offspring.^{10 11 13 14 23} However, in the studies classified by a job-exposure matrix, findings are inconsistent regarding whether this exposure is a risk factor in healthcare professionals, including nurses.^{10 12 14} There are several studies on exposure to

household chemicals, including indoor cleaning agents,^{24–27} and the development of allergies in offspring. Most of these studies conclude that such an exposure can indeed lead to asthma in offspring. Some studies assessed household chemicals using a chemical exposure score and did not specifically focus on disinfectants.^{25–27} The present study is the first to examine occupational exposure to disinfectants alone and to demonstrate an association of disinfectant exposure in pregnancy with asthma and eczema in offspring in an exposure-response relationship.

For the question of when the effects of perinatal exposure to chemicals, including disinfectants, on the development of allergy in offspring are greater, both prenatal and postnatal exposures have been studied.^{10–11, 13–14, 23} Most papers reported a greater effect for postnatal exposure than for prenatal exposure.^{10–11, 13–14} However, a recent report by Tjalvin *et al* found an effect of occupational exposure to cleaning agents on asthma in offspring that was both prenatal and postnatal but not postnatal alone.²³ Our findings indicate that exposure during pregnancy exerts an effect on allergies in offspring regardless of whether the mother returns to work when the child is 1 year old, and suggest an effect by exposure during pregnancy alone. However, whether the frequency of maternal exposure was similar prenatally and postnatally is unknown, requiring a future study with a design that permits a separate evaluation of prenatal and postnatal effects.

There are several possible explanations for the findings of this study. The first is a microbiome-mediated mechanism.^{28–29} Frequent use of disinfectants during pregnancy may alter the dermal flora. The establishment of a newborn's gut microbiota has been reported to be influenced by the mother's flora (intestinal, vaginal and dermal).³⁰ It has also been reported that the intestinal microflora in early life is associated with the development of allergic diseases in later life,^{31–33} and that dysregulation of the mother's skin microflora may contribute to the development of allergic diseases in the child. Antibiotic use during pregnancy has been reported to be associated with the development of allergic disease in the child,³⁴ and only endocrine-disrupting chemicals with antimicrobial activity such as triclosan have been reported to be associated with aeroallergen sensitisation,³⁵ supporting the microbiome-mediated explanation. However, whether disinfectants change the dermal flora has not been fully investigated. In addition, postnatal exposure must also be taken into account. Those who use more disinfectants at work may also use more disinfectants at home, exposing children directly to these chemicals, which may reduce the frequency of common colds and other infections, as the hygiene hypothesis suggests.³⁶ The second is transplacental modification of the fetal immune system. The immune system in fetuses is vulnerable to programming,³⁷ and exposure to volatile organic compounds during pregnancy has been reported to distort the Th1/Th2 immune response in the fetus and may make it more susceptible to asthma later in life.³⁸ Disinfectants may be transferred transplacentally to the fetus and influence the development of the immune system towards an allergic disposition.^{39–40} This mechanism has been reported as an explanation for the development of allergic diseases in children with prenatal exposure to other chemicals,^{38–40} but requires verification for disinfectants by basic research, including animal experiments. Moreover, it is possible that the asthma and eczema reported in this study developed from direct postnatal exposure and sensitisation, as the children inhaled or touched the molecules of disinfectant on the skin of their mothers without involvement of the microbiome. Finally, it is possible that the findings of this study are simply the result of bias; populations that use medical disinfectants frequently

are likely to be more medically knowledgeable and have better access to healthcare than those that do not, and therefore may have reported the development of allergic disease in their children more frequently.¹⁴ However, the finding of a significant association between prenatal exposure to disinfectant and the development of allergic diseases remained after adjustment for maternal occupation.

The strength of this study is that it is the first to examine occupational exposure to disinfectants alone and to show the association of disinfectants with asthma and eczema in children in an exposure-response relationship. Other strengths are the size of the cohort (78 915 mother/child pairs) and the adjustment for a wide range of confounders. However, some limitations should also be noted. The information obtained on disinfectant use, which was the exposure in this study, was self-reported and the specific disinfectants were not identified. Although respondents were asked about medical disinfectants used at work, there was a wide variation in what they perceived as a 'medical disinfectant', which may have led to misclassification of the exposure. However, as exposure information was obtained prior to the outcome, this is likely to be a non-differential misclassification, and the association between disinfectant use during pregnancy and allergic disease in offspring is likely to have been underestimated. Second, the outcome was self-reported by parents from a physician diagnosis. As noted above, disinfectants (the exposure in this study) were used more frequently by healthcare providers, who have more medical knowledge and access to healthcare than the general population and therefore may be more likely to observe and follow-up on allergic reactions in their children.¹⁴ Moreover, the outcome of the present study was physician-diagnosed asthma at 3 years, but this included transient wheezing which may cause an overestimation. Future studies should monitor asthma symptoms over a longer duration. Third, residual confounding is possible, although we adjusted for confounding by factors reported in previous studies. It is possible that the use of disinfectants is distorting and representative of the effects of other factors rather than the effects of their ingredients, and this hypothesis should be tested in other populations.

CONCLUSION

Disinfectant use during pregnancy appears to be a risk factor for asthma and eczema in offspring. There was a significant exposure-dependent association between disinfectant exposure and asthma and eczema. As disinfectants are an effective tool in the prevention of infectious diseases, further research into the underlying mechanisms is warranted.

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Contributors RK contributed to the conception and design of the study, performed the statistical analysis and drafted the manuscript. MK, SO, HY, YA, TO, KM and SH critically reviewed the manuscript. RS and ZY critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript. Guarantor: ZY.

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