# Maternal preconception occupational exposure to cleaning products and disinfectants and offspring asthma



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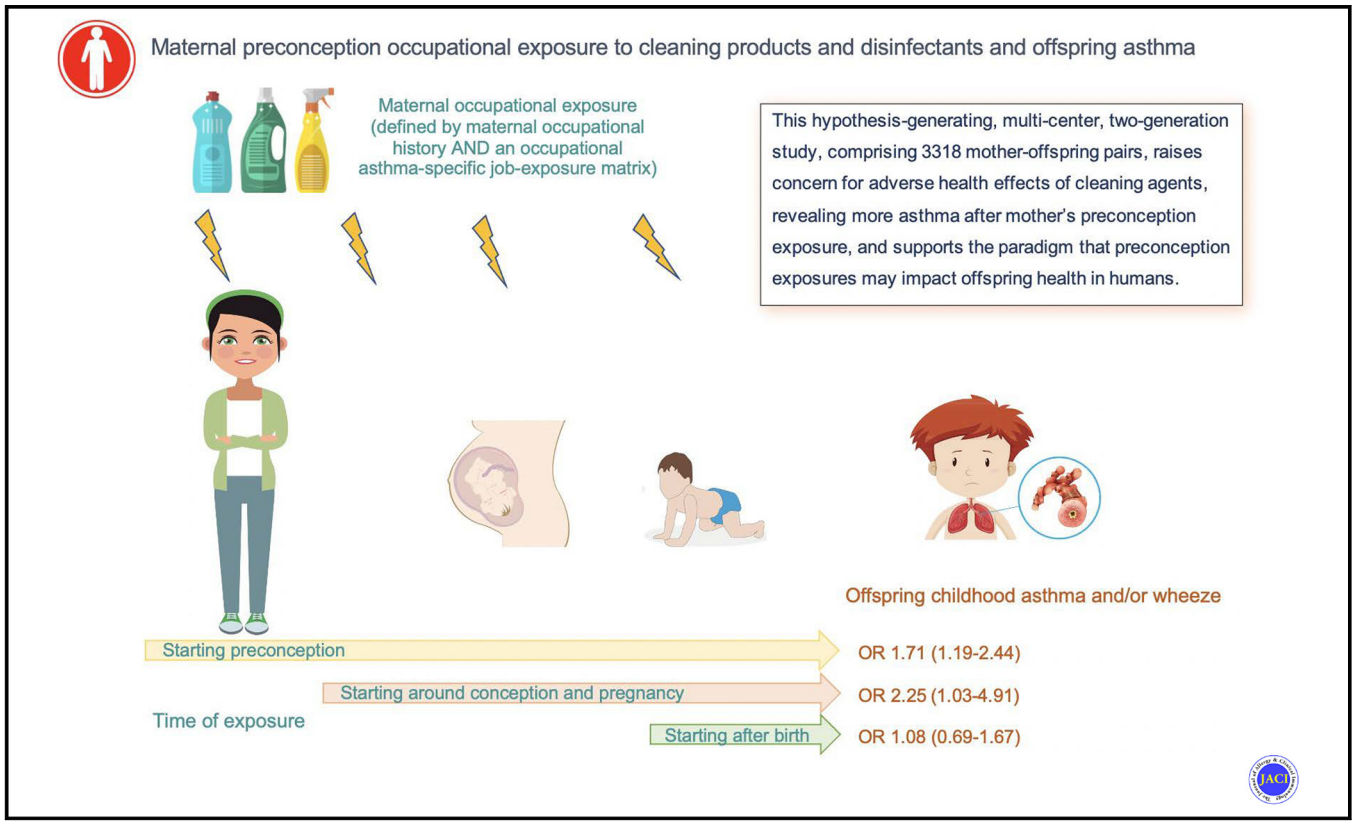
## GRAPHICAL ABSTRACT

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**Background: Emerging research suggests health effects in offspring after parental chemical exposures before conception. Many future mothers are exposed to potent chemicals at work, but potential offspring health effects are hardly investigated.**
**Objective: We sought to investigate childhood asthma in relation to mother's occupational exposure to cleaning products and disinfectants before conception.**
**Methods: The multicenter Respiratory Health In Northern Europe/Respiratory Health In Northern Europe, Spain and Australia generation study investigated asthma and wheeze starting at age less than 10 years in 3318 mother-offspring pairs. From an asthma-specific Job-Exposure Matrix and mothers' occupational history, we defined maternal occupational exposure to indoor cleaning agents (cleaning products/detergents and disinfectants) starting before conception, in the 2-year period around conception and pregnancy, or after birth. Never-employed mothers were excluded. Exposed groups include cleaners, health care workers, cooks, and so forth. Associations were analyzed using mixed-effects logistic regression and ordinary logistic regression with clustered robust SEs and adjustment for maternal education.**
**Results: Maternal occupational exposure to indoor cleaning starting preconception and continuing (n = 610) was associated with offspring's childhood asthma: odds ratio 1.56 (95% CI, 1.05-2.31), childhood asthma with nasal allergies: 1.77 (1.13-2.77), and childhood wheeze and/or asthma: 1.71 (95% CI, 1.19-2.44). Exposure starting around conception and pregnancy (n = 77) was associated with increased childhood wheeze and/or asthma: 2.25 (95% CI, 1.03-4.91). Exposure starting after birth was not associated with asthma outcomes (1.13 [95% CI, 0.71-1.80], 1.15 [95% CI, 0.67-1.97], 1.08 [95% CI, 0.69-1.67]).**
**Conclusions: Mother's occupational exposure to indoor cleaning agents starting before conception, or around conception and pregnancy, was associated with more childhood asthma and wheeze in offspring. Considering potential implications for vast numbers of women in childbearing age using cleaning agents, and their children, further research is imperative. (J Allergy Clin Immunol 2022;149:422-31.)**

***Key words:*** *Occupational exposures, preconception exposures, Job-Exposure Matrix (JEM), disinfectants, cleaning products, mother, childhood asthma, generation study, RHINESSA*

In many countries, the prevalence of childhood asthma has increased substantially since the 1980s.[1] The reason remains largely unknown; however, numerous mechanisms have been proposed, including events occurring early in life, both before and after birth.[1,2]

*Abbreviations used*

| | |
|---|---|
| ISCO: | The International Standard Classification of Occupations |
| JEM: | Job-Exposure Matrix |
| OAsJEM: | Occupational Asthma-specific Job-Exposure Matrix |
| RHINE: | Respiratory Health In Northern Europe |
| RHINESSA: | Respiratory Health In Northern Europe, Spain and Australia |

It is well established that workers who are directly exposed to cleaning products and disinfectants are at risk for respiratory symptoms and asthma.[3-9] In addition, it has been suggested that exposures related to cleaning activities may constitute a risk to long-term respiratory health.[10] A dose-response pattern with increased risk of respiratory symptoms and diseases by increased dose and duration of exposure has been reported.[5,6,9]

Cleaning products and disinfectants comprise a wide range of ingredients that are irritants and/or potential sensitizers.[5,7,9] Furthermore, the use of spray devices results in a substantial airborne exposure to nonvolatile aerosolized agents in the lower airways.

The biological mechanisms by which these products affect respiratory health are not fully understood but include both irritant and allergic mechanisms.[5,7,9,11] Moreover, recent evidence suggests that predisposition to adult-onset asthma may be related to the interaction between genes and occupational exposure to low-molecular-weight agents/irritants.[5] Genes potentially involved in adult asthma by interaction with occupational exposure play a role in the nuclear factor kappa B pathway, which is involved in inflammation.[12]

When future parents are exposed to chemicals, both their somatic and germ cells may be affected.[13] Emerging evidence from human and animal models suggests that preconception parental exposures may influence the health of future generations.[14-24] Previous studies on maternal occupational exposure and respiratory health in offspring are scarce.[25-27] However, a registry study found that several parental occupations were associated with increased hospitalization for childhood asthma among offspring.[26]

We hypothesize that preconception occupational exposures might impact offspring's health through germline cell exposure. Furthermore, occupational exposure in a pregnant woman might directly affect the fetus at critical time windows during the fetal growth and development.[28] Finally, a shared home environment influenced by maternal occupational habits might influence the health of the child after birth.[29] A theoretical model is summarized in Fig 1.

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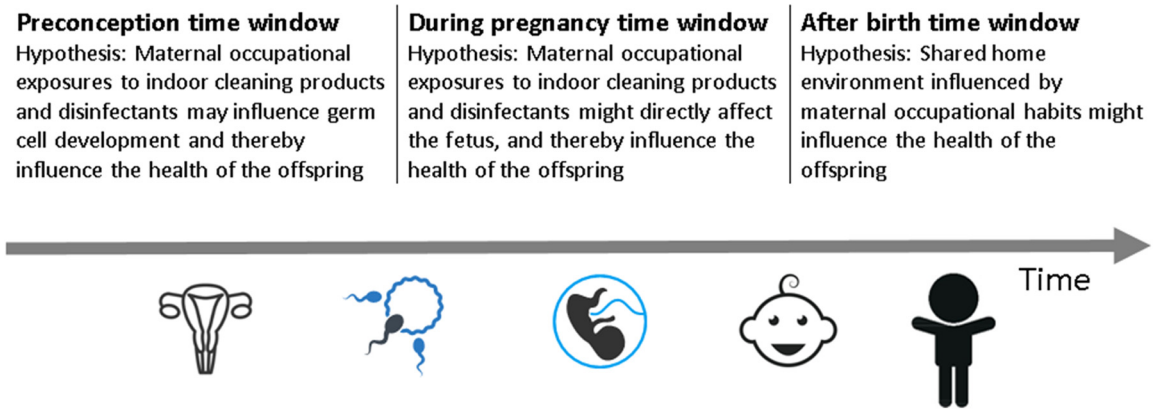


**FIG 1.** Theoretical model of time windows in which maternal occupational exposure to indoor cleaning products and disinfectants could have an impact on their offspring's health outcomes. When a future mother is exposed to chemicals before conception, even her germ cells will be exposed. Hence, the exposure might influence the health of her future offspring. In a pregnant woman, the exposure might directly affect the fetus, whereas shared home environment influenced by maternal occupational habits might influence the health of the child after birth.

The aim of our study was to investigate asthma risk in children whose mother had been occupationally exposed to indoor cleaning products and disinfectants before conception or around the time of conception and pregnancy.

## METHODS

### Study population

Two linked cohorts were used: the population-based RHINE (Respiratory Health In Northern Europe) study and the RHINESSA (Respiratory Health In Northern Europe, Spain and Australia) study of their offspring (www.rhinessa.net).[18,30] The present analysis includes data from 3318 RHINESSA study participants (offspring born 1962-1998) and their mothers who participated in the RHINE study (Fig 2). RHINE II included questionnaire-based data on persons born 1945 to 1973 from 7 centers in Northern Europe (Bergen in Norway, Umeå, Gothenburg, and Uppsala in Sweden, Aarhus in Denmark, Reykjavik in Iceland, and Tartu in Estonia). The survey was conducted from 1999 to 2001, and comprised a full occupational history for individual mothers within the time span 1963 to 1998.

The studies were approved by regional ethics committees, and all participants signed written informed consents.

### Mother's exposure

Maternal occupational history, including job titles with start-year and stop-year for each job, was coded by an expert group according to the International Standard Classification of Occupations-1988 (ISCO-88).[31] Subsequently, each mother's ISCO job codes were combined with an Occupational Asthma-specific Job-Exposure Matrix (OAsJEM). The OAsJEM considers exposure to 30 specific sensitizers/irritant agents for all job codes in ISCO-88. The Job-Exposure Matrix (JEM) category "indoor cleaning" defines occupational exposure to indoor cleaning agents (=cleaning products/detergents and low/intermediate-level disinfectants).[32] Such exposures were present in 21 ISCO-88 job codes (see Table E1 in this article's Online Repository at www.jacionline.org).

In the present study, maternal occupational exposure to indoor cleaning agents was defined according to the OAsJEM as having had at least 1 ISCO job code with high (high probability and moderate to high intensity) or medium (low to moderate probability or low intensity) exposure to indoor cleaning agents for 6 months or longer. The reference category included mothers who had held at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents according to ISCO job code in combination with the OAsJEM.

Time windows of exposure were defined on the basis of when the first exposed job *started* (Fig 3); (1) Exposure only before conception (2 years or more before the child's birth year), (2) Exposure starting before conception and continuing around conception and pregnancy and/or after birth, (3) Exposure starting around conception and pregnancy, and (4) Exposure only after birth (starting the year after the child's birth year, or later). Because of the 1-year time resolution, the time window around conception and pregnancy covers 2 years, including approximately 3 to 15 months preconception, 9 months pregnancy, and 0 to 12 months infancy. In sensitivity analyses with smaller numbers, categories 1 to 3 were merged.

### Offspring health outcomes

Three asthma outcomes, all starting before age 10 years, were defined on the basis of questionnaire data from RHINESSA adult offspring (wording given in this article's Online Repository at www.jacionline.org): childhood asthma, childhood asthma with nasal allergies, and childhood wheezing and/or asthma. Age 10 years was set as cutoff to distinguish childhood asthma and wheeze from asthma with onset in puberty or in adulthood.

### Covariates

Potential confounders were identified on the basis of previous studies[2,17,33-36] and directed acyclic graphs.[33,37] Variables that had the potential to be associated with maternal occupational exposure and to cause childhood asthma/wheeze, and were not on the causal pathway between the exposure and outcome, were considered for inclusion in the model.[33] The minimal sufficient adjustment set included maternal education only[33,37] (see Fig E1 in this article's Online Repository at www.jacionline.org). Sensitivity analyses included adjustment for additional variables (offspring sex, nonsmoking mother, birth cohort).

### Statistical methods

For the main analysis, associations between maternal exposure to indoor cleaning agents and offspring outcomes were analyzed using mixed-effects logistic regression with random intercept for study center and mother. In analyses stratified on offspring's birth cohort (1962-1979 and 1980-1998), offspring's sex, and mother's smoking habits, such models did not converge because of few exposed in some categories, and we used ordinary logistic regression with adjustment for study center as a covariate and clustered robust SEs to account for clustering of siblings within mothers. Association between the 5-category variable with level and timing of exposure and risk of asthma before age 10 years in the offspring was analyzed using mixed-effects logistic regression with random intercept for study center and mother.

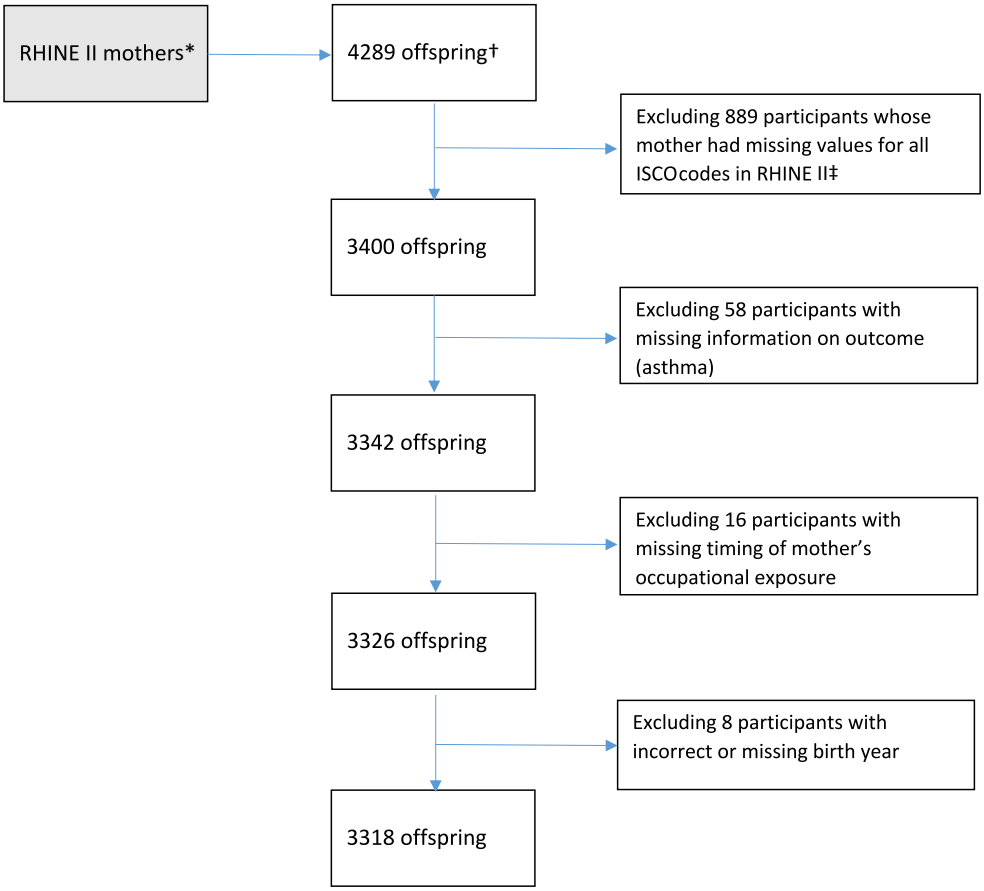


**FIG 2.** Definition of study population. *Female participants in the RHINE II study. †RHINE II offspring 18 years or older who had participated in the RHINESSA study. ‡Mothers who had missing values for all ISCO job codes included mothers who did not report any jobs, that is, those who never were employed, and those who failed to respond to this question in the questionnaire.

Two-sided tests and significance level of 5% were used. Analyses were performed in STATA15 (StataCorp LLC, College Station, Tex).

## RESULTS

Of 3318 offspring, 1307 had a mother who had been employed for at least 6 months in a job that involved exposure to indoor cleaning agents, whereas 2011 had a mother who had held at least 1 job for 6 months or more, but no occupational exposure to such agents. Exposed mothers were slightly younger, had lower education, and smoked slightly more (Table I).

For 150 offspring (11.5% of the exposed), the mother had been exposed to indoor cleaning agents only before conception (scenario 1 in Fig 3); on average, this exposure stopped 7 years before the offspring was born (mean, 7.8 years; median, 7 years). In 610 persons (46.7%), maternal exposure had started before conception and continued (scenario 2), whereas maternal exposure started around the time of conception and pregnancy for 77 persons (5.9%) (scenario 3). Finally, in 470 persons (36%), the maternal exposure started after the offspring were born (scenario 4).

Offspring asthma outcomes appeared to be higher if the mother had been occupationally exposed to indoor cleaning agents only before conception. Maternal exposure starting before conception and continuing was associated with offspring's childhood asthma: odds ratio 1.56 (95% CI, 1.05-2.31), childhood asthma with nasal allergies: 1.77 (95% CI, 1.13-2.77), and childhood wheeze and/or asthma: 1.71 (95% CI, 1.19-2.44). Exposure starting around conception and pregnancy was associated with increased childhood wheeze and/or asthma: 2.25 (95% CI, 1.03-4.91). Exposure only after birth of the child was not associated with offspring asthma outcomes (Table II). Sensitivity analyses with adjustment for maternal smoking during pregnancy or offspring's childhood, and maternal asthma, slightly weakened the associations, but did not substantially alter the estimates (Table II).

Maternal exposure before conception or around conception and pregnancy appeared to be more strongly associated with offspring asthma if the exposure level had been high than if the exposure level had been medium (Table III). The magnitude of the associations of maternal exposure to indoor cleaning agents during preconception/pregnancy and childhood asthma appeared to be similar in male and female offspring (Table IV). The association was also consistent among offspring with a mother who did not smoke when she was pregnant or during their childhood (Table IV). Few cases in some exposure groups prevented detailed categorization in these sensitivity analyses. Sensitivity analyses stratified by birth cohort (1962-1979 and 1980-1998) suggested stronger associations for exposure back in time even though the CIs were overlapping (see Table E2 in this article's Online Repository at www.jacionline.org).

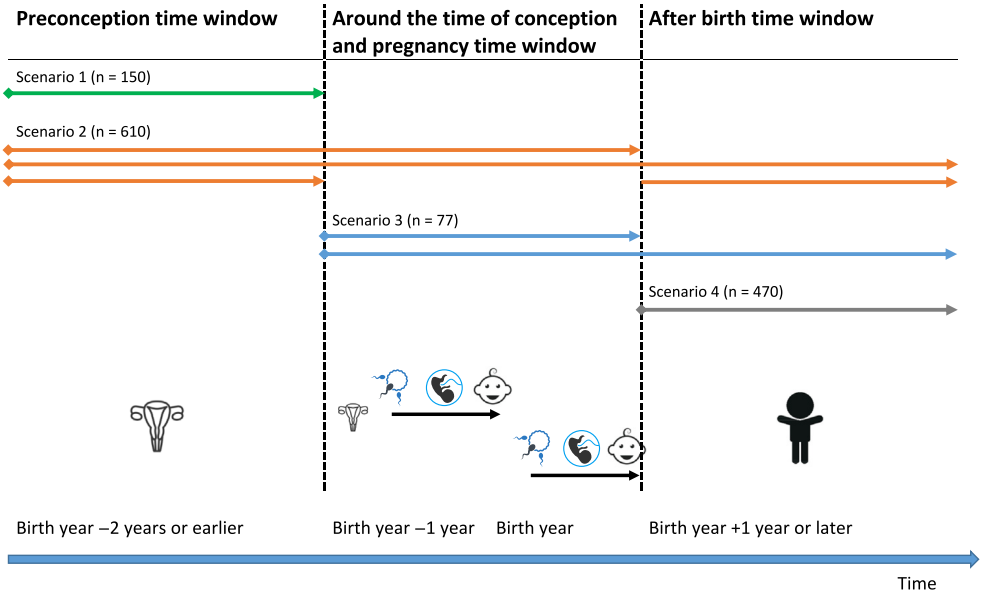


**FIG 3.** Real-life scenarios of time windows in which maternal occupational exposure to indoor cleaning products and disinfectants could have an impact on offspring health outcomes. Within each time window, the mother could have several consecutive jobs. Four exposure scenarios were defined on the basis of when mother's exposure started: (1) Exposure only before conception; (2) Exposure starting before conception and continuing into different time windows, around the time of conception and pregnancy, and/or after birth; (3) Exposure starting around the time of conception and pregnancy; and (4) Exposure only after birth. The time window around conception and pregnancy covers 2 years, including approximately 3 to 15 months preconception, 9 months pregnancy, and 0 to 12 months infancy.

**TABLE I.** Characteristics of the study population, according to mother's occupational exposure status

| Characteristic | Total study sample | No jobs with exposure to indoor cleaning agents* | At least 1 job with exposure to indoor cleaning agents† | *P* value‡ |
|---|---|---|---|---|
| n | 3318 | 2011 | 1307 | |
| Sex: female, n (%) | 1900 (57.3) | 1157 (57.5) | 743 (56.9) | .69 |
| Birth year, n (%) | | | | |
| 1962-1969 | 161 (4.9) | 108 (5.4) | 53 (4.1) | .21 |
| 1970-1979 | 907 (27.3) | 534 (26.6) | 373 (28.5) | |
| 1980-1989 | 1318 (39.7) | 789 (39.2) | 529 (40.5) | |
| 1990-1998 | 932 (28.1) | 580 (28.8) | 352 (26.9) | |
| Asthma before age 10 y, n (%) | 234 (7.1) | 127 (6.3) | 107 (8.2) | .045 |
| Mother's age at birth, mean ± SD | 27.3 ± 4.9 | 27.5 ± 4.9 | 27.0 ± 5.0 | .007 |
| Mother's educational level, n (%) | | | | |
| Primary | 514 (15.5) | 257 (12.8) | 257 (19.7) | <.001 |
| Secondary | 1158 (34.9) | 656 (32.6) | 502 (38.4) | |
| College/university | 1629 (49.1) | 1090 (54.2) | 539 (41.2) | |
| Missing | 17 (0.5) | 8 (0.4) | 9 (0.7) | |
| Mother's smoking, n (%) | | | | |
| No smoking during childhood | 2143 (64.6) | 1355 (67.4) | 788 (60.3) | .01 |
| Smoking during childhood | 837 (25.2) | 574 (23.7) | 361 (27.6) | |
| Smoking during pregnancy | 289 (8.7) | 189 (7.7) | 134 (10.3) | |
| Missing | 49 (1.5) | 25 (1.2) | 24 (1.8) | |
| Asthma in mother, n (%) | | | | |
| Yes | 363 (10.9) | 198 (9.9) | 165 (12.6) | .07 |
| Missing | 149 (4.5) | 99 (4.9) | 50 (3.8) | |

Information on mother's education and smoking during pregnancy and/or childhood was reported by the offspring in the RHINESSA study. Information on mother's asthma and occupational history was reported by the mother in the RHINE II study.

*Mothers with at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents according to the ISCO-88 job code and the OAsJEM.

†According to the ISCO-88 job code and the OAsJEM.

‡Differences in characteristics between offspring of exposed and nonexposed mothers were tested using bivariate linear regression for continuous outcomes, bivariate logistic regression for binary outcomes, and bivariate multinomial logistic regression for categorical outcomes. Clustered robust SEs were used to account for clustering of siblings within the same mother.

**TABLE II.** Associations between timing of mother's occupational exposure to indoor cleaning agents* and asthma, asthma with nasal allergies, and wheezing and/or asthma before age 10 years in the offspring†

| Exposure time categories for offspring outcomes | n outcome/ n total (%) | OR (95% CI) Crude model‡ | Model 2§ | Model 3‖ | Model 4¶ |
|---|---|---|---|---|---|
| **Asthma before age 10 y in the offspring** | | | | | |
| n | 234/3318 (7.0) | 3318 | 3301 | 3254 | 2906 |
| Timing of mother's occupational exposure | | | | | |
| No jobs with exposure to indoor cleaning agents# | 127/2011 (6.3) | 1 | 1 | 1 | 1 |
| Exposure only before conception | 12/150 (8.0) | 1.29 (0.64-2.61) | 1.26 (0.63-2.54) | 1.29 (0.64-2.62) | 1.31 (0.63-2.74) |
| Exposure started before conception and continued | 55/610 (9.0) | **1.55 (1.05-2.29)** | **1.56 (1.05-2.31)** | **1.50 (1.00-2.24)** | 1.46 (0.97-2.21) |
| Exposure started around the time of conception or pregnancy | 9/77 (11.7) | 2.26 (0.98-5.21) | 2.30 (1.00-5.28) | 2.27 (0.98-5.26) | 2.32 (1.00-5.39) |
| Exposure only after year of birth | 31/470 (6.6) | 1.04 (0.66-1.64) | 1.13 (0.71-1.80) | 1.10 (0.68-1.76) | 1.13 (0.69-1.87) |
| **Asthma before age 10 y in the offspring, with nasal allergies**** | | | | | |
| n | 169/3253 (5.2) | 3253 | 3236 | 3190 | 2852 |
| Timing of mother's occupational exposure | | | | | |
| No jobs with exposure to indoor cleaning agents# | 86/1970 (4.4) | 1 | 1 | 1 | 1 |
| Exposure only before conception | 11/149 (7.4) | 1.75 (0.84-3.65) | 1.72 (0.82-3.60) | 1.78 (0.85-3.71) | 1.71 (0.77-3.78) |
| Exposure started before conception and continued | 43/598 (7.2) | **1.77 (1.14-2.75)** | **1.77 (1.13-2.77)** | **1.72 (1.09-2.69)** | **1.62 (1.00-2.61)** |
| Exposure started around the time of conception or pregnancy | 7/75 (9.3) | 2.49 (0.99-6.27) | 2.52 (1.00-6.36) | 2.48 (0.98-6.26) | 2.44 (0.94-6.37) |
| Exposure only after year of birth | 22/461 (4.8) | 1.07 (0.63-1.81) | 1.15 (0.67-1.97) | 1.09 (0.63-1.88) | 1.08 (0.60-1.95) |
| **Wheezing and/or asthma before age 10 y in the offspring** | | | | | |
| n | 267/3311 (8.1) | 3311 | 3294 | 3247 | 2900 |
| Timing of mother's occupational exposure | | | | | |
| No jobs with exposure to indoor cleaning agents# | 143/2006 (7.1) | 1 | 1 | 1 | 1 |
| Exposure only before conception | 15/150 (10.0) | 1.50 (0.80-2.81) | 1.46 (0.78-2.74) | 1.49 (0.79-2.81) | 1.52 (0.77-2.59) |
| Exposure started before conception and continued | 66/610 (10.8) | **1.69 (1.18-2.40)** | **1.71 (1.19-2.44)** | **1.64 (1.14-2.37)** | **1.59 (1.08-2.34)** |
| Exposure started around the time of conception or pregnancy | 10/77 (13.0) | **2.22 (1.02-4.83)** | **2.25 (1.03-4.91)** | **2.23 (1.02-4.89)** | 2.01 (0.87-4.63) |
| Exposure only after year of birth | 33/468 (7.1) | 0.99 (0.64-1.53) | 1.08 (0.69-1.67) | 1.00 (0.64-1.58) | 1.03 (0.63-1.68) |

Boldface indicates statistical significant associations at significance level 0.05.
*OR*, Odds ratio.
*According to the ISCO-88 job code and the OAsJEM.
†Analyzed using mixed-effects logistic regression with random intercept for study center and mother.
‡Crude estimates with random intercept for study center and clustering by family in case of multiple offspring from the same mother.
§Adjusted for mother's level of education (primary, secondary, and college/university). Fully adjusted model identified by directed acyclic graphs.
‖Adjusted for mother's level of education and maternal smoking in 3 categories (no smoking, during pregnancy and/or childhood, during childhood).
¶Adjusted for mother's level of education, maternal smoking in 3 categories (no smoking, during pregnancy and/or childhood, during childhood) and maternal ever asthma.
#Mothers with at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents according to the ISCO-88 job code and the OAsJEM.
**Excluding 65 offspring with asthma without nasal allergies.

**TABLE III.** Level of maternal occupational exposure to indoor cleaning agents* and risk of asthma before age 10 years in offspring†

| Exposure time categories for levels of exposure | n asthma/n total | Adjusted model,‡ OR (95 % CI) |
|---|---|---|
| **Maternal occupational exposure** | | |
| n | 234/3318 | 3301 |
| **Medium exposure**§ | | |
| Timing of exposure‖ | | |
| No jobs with exposure to indoor cleaning agents¶ | 127/2011 | 1 |
| Exposure started the year of offspring's birth or before | 34/415 | 1.32 (0.84-2.08) |
| Exposure only after offspring's year of birth | 12/239 | 0.81 (0.42-1.58) |
| **High exposure**# | | |
| Timing of exposure‖ | | |
| No jobs with exposure to indoor cleaning agents¶ | 127/2011 | 1 |
| Exposure started the year of offspring's birth or before | 42/422 | **1.83 (1.18-2.83)** |
| Exposure only after year of offspring's birth | 19/231 | 1.52 (0.85-2.71) |

Boldface indicates statistical significant associations at significance level 0.05.
*OR*, Odds ratio.
*According to the ISCO-88 job code and the OAsJEM.
†Analyzed using logistic regression with adjustment for study center as a covariate and clustered robust SEs to account for clustering of siblings within mothers.
‡Adjusted for mother's level of education (primary, secondary, and college/university).
§Low to moderate probability or low-intensity exposure to indoor cleaning for each ISCO-88 job code according to the OAsJEM.
‖Few cases in some exposure groups prevented a more detailed timing of exposure categorization than the year of offspring's birth or before vs after offspring's year of birth.
¶Mothers with at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents according to the ISCO-88 job code and the OAsJEM.
#High probability of exposure and moderate- to high-intensity exposure to indoor cleaning for each ISCO-88 job code according to the OAsJEM; with or without medium exposure.

**TABLE IV.** Mother's occupational exposure to indoor cleaning agents* and risk of asthma before age 10 years in subgroups of offspring—male offspring, female offspring, and offspring with nonsmoking mother†

| Exposure time categories for offspring subgroups | n asthma/ n total | Adjusted model,‡ OR (95 % CI) |
|---|---|---|
| **Male offspring** | | |
| n | 121/1418 | 1411 |
| Timing of exposure§ | | |
| No jobs with exposure to indoor cleaning agents | 67/854 | 1 |
| Exposure started the year of offspring's birth or before | 39/366 | 1.38 (0.89-2.13) |
| Exposure only after year of offspring's birth | 15/198 | 1.05 (0.57-1.92) |
| **Female offspring** | | |
| n | 113/1900 | 1890 |
| Timing of exposure§ | | |
| No jobs with exposure to indoor cleaning agents‖ | 60/1157 | 1 |
| Exposure started the year of offspring's birth or before | 37/471 | 1.49 (0.95-2.36) |
| Exposure only after year of offspring's birth | 16/272 | 1.14 (0.62-2.08) |
| **Offspring with nonsmoking mother¶** | | |
| n | 150/2143 | 2137 |
| Timing of exposure§ | | |
| No jobs with exposure to indoor cleaning agents‖ | 83/1355 | 1 |
| Exposure started the year of offspring's birth or before | 51/538 | **1.60 (1.09-2.36)** |
| Exposure after year of offspring's birth | 16/250 | 1.15 (0.64-2.06) |

Boldface indicates statistical associations at significance level 0.05.
*OR*, Odds ratio.
*According to the ISCO-88 job code and the OAsJEM.
†Analyzed in separate models using logistic regression with adjustment for study center as a covariate and clustered robust SEs to account for clustering of siblings within mothers.
‡Adjusted for mother's level of education (primary, secondary, and college/university).
§Few cases in some exposure groups prevented a more detailed timing of exposure categorization than the year of offspring's birth or before vs after offspring's year of birth.
‖Mothers with at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents according to the ISCO-88 job code and the OAsJEM.
¶Mother did not smoke when pregnant with them or during their childhood.

## DISCUSSION

This 2-generation study finds that maternal occupation that involved exposure to indoor cleaning agents (cleaning products/detergents and disinfectants), when starting before conception, was associated with increased risk for childhood asthma in the offspring. This was found consistently for asthma, asthma with nasal allergies, and wheezing and/or asthma, and for offspring of nonsmoking mothers. There was modest evidence of an association with exposure that started around conception and pregnancy. Preconception exposure (suggesting germ cell impact) could not be definitely separated from exposure *in utero* (suggesting a direct effect on the fetus). Our hypothesis-generating results suggest potential impact of preconception exposure, because the estimates for exposure only before conception (small sample) were of crudely similar magnitude as estimates for preconception exposure continuing after conception (large sample). The associations appeared to be stronger with higher *versus* medium maternal exposure. Estimates were similar in male and female offspring, and fairly consistent with adjustment for maternal educational level, maternal smoking, and maternal asthma. Maternal exposure starting after birth of the offspring showed no clear associations with offspring outcomes, giving additional support to a specific role of preconception exposure rather than confounding.

To our knowledge, this is the first study that addresses potential offspring health impact of mother's preconception occupational exposure to cleaning products and disinfectants. Our findings are to some extent supported by a recent article suggesting increased risk for early-onset asthma if the mother had been occupationally exposed to allergens and reactive chemicals both before and after the offspring's year of birth.[38] This analysis of the RHINESSA/RHINE/ European Community Respiratory Health Survey cohorts studied 4 groups of occupational exposures, including 20 of the 30 asthmagens defined by the OAsJEM,[32] but *not* the JEM category "indoor cleaning," which is the focus of the present analysis. Furthermore, a recent analysis found higher asthma risk in offspring if mothers had been exposed to air pollution before age 18 years.[20] A role of preconception occupational exposure through the paternal line was suggested in an analysis of fathers' exposure to welding and metal fumes, showing increased asthma related to preconception exposure but no effect of postnatal exposure.[18] Indirect support to a role of preconception occupational exposure in childhood asthma is provided by a Swedish registry study that found that several occupations, in which the employees most likely would have been exposed to cleaning agents, were associated with an increased risk of hospitalization for childhood asthma in offspring.[26]

Emerging evidence from animal and human studies supports that environmental and occupational exposures might cause epigenetic changes that might be transmissible to offspring.[14-22,39] Such environmentally induced epigenetic alterations must be present in the germline to be transmissible to the next generation.[13,24] Alterations passed through the germline might result in inherited changes in gene expression in offspring in any kind of tissue and hence induce alteration in various tissues and cell types with impact on offspring phenotype.[13,16,40] With regard to cleaning agents, many have lipophilic properties and may accumulate in the future mother's fat tissue; thereby, such agents may constitute a continuous internal source of exposure because the accumulated chemicals subsequently are slowly released into the mother's bloodstream.[41]

Another potential mechanism for our findings could involve the microbiome. We speculate that maternal exposure to cleaning chemicals and disinfectants could influence the maternal microbiome, which in turn could influence her germline cells and thereby future offspring. Alternatively, the exposure could possibly contribute to persistent changes in the mother's microbiome, which may impact gestational biology directly. To our knowledge, there is no relevant literature exploring effects mediated by the microbiome across generations, but it is an interesting question for future research.

The increased risk for offspring asthma related to maternal exposure *during pregnancy* is biologically plausible, and supported by a rich literature showing that an unfavorable intrauterine environment may increase the risk of developing diseases later in life.[42,43] A Danish birth cohort study found that prenatal and postnatal maternal occupational exposure to low-molecular-

weight agents and irritants was associated with asthma in 7-year-old offspring.[25] A British birth cohort study found that maternal exposure to biocides/fungicides during and following pregnancy was associated with higher asthma risk in 7-year-old children.[27] Mother's domestic use of cleaning sprays during pregnancy was associated with increased risk of wheezing and lower respiratory tract infections during offspring's early life in an analysis of 4 Spanish birth cohorts.[44] Because most cleaning agents comprise low-molecular-weight chemicals and are lipophilic, they readily diffuse across the placenta,[28] and it seems plausible that they may affect the prenatal development of the airways.[28,42]

In the present study, the participants were born during the period 1962 to 1998. During this time interval, the chemical content, application devices, and cleaning methods changed considerably. Several studies have identified the use of cleaning sprays as an important risk factor for asthma and wheezing.[7,9,44,45] Unfortunately, our study could not investigate specific chemicals, cleaning methods, or time trends.

A major strength of the present study was the multicenter generational study design, with data from mothers and offspring from 2 separate but linked studies.[30] The mother provided information about her own occupational history in the RHINE II study, more than 15 years before the offspring provided information about their asthma and wheeze in the RHINESSA study. The multicenter design increases the external validity of the findings but may also introduce random error due to random differences between study centers, which would reduce observed associations toward the null.

The exposure assessment in relation to the birth year of the offspring represents another important strength of the study. Data included full parental occupational history comprising up to 10 ISCO job codes[31] for each mother with start- and stop-years, and OAsJEM classification of all these job codes with respect to exposure to indoor cleaning products and disinfectants.[32] These 2 measures, together with the birth year of the offspring, enabled us to model maternal occupational exposure into 4 time windows of interest. This is quite unique in a human study.

An inherent limitation in a human study is the lack of ability to disentangle the immediate preconception from the intrauterine time window. Women starting in a job before conception will often continue into other time windows, and probably few would quit an exposure immediately after conception. The modeling of time windows was also limited by the 1-year time resolution in employment period and offspring year of birth; thus, the category "Exposure started around the time of conception and pregnancy" included 3 to 15 months before conception. However, by defining "Exposure only before conception" as mother's occupational exposure that had ended 2 years or more before year of birth for each child (median, 7 years), this subcategory was well separated from the exposure category *in utero*. Because the association estimates were of similar magnitude for this subcategory and the subcategory in which the exposure started preconception and continued, a preconception effect seems likely.

Defining asthma in epidemiological studies implies some degree of misclassification. We analyzed 3 outcome variables capturing different aspects of asthma: asthma, asthma with nasal allergies, and wheezing and/or asthma. Reassuringly, these outcomes gave consistent results. The retrospective questionnaire data imply an inherited risk of recall bias when reporting childhood asthma back in time. However, both types of misclassification in definition of the outcomes, reported by the offspring themselves, are unlikely to be related to start- and stop-years of a range of different jobs reported by their mother in another survey. Thus, such misclassification is likely to have attenuated observed results but not to have produced spurious results.

The mothers' occupational exposure was based on job title and a JEM, and not self-reported exposure or personal measurements of exposure. This implies both limitations and strengths. Exposure measurements would be impossible in this setting because the exposure is back in time; furthermore, cleaning products and disinfectants constitute a mixed exposure with multiple constituents. We used an asthma-specific JEM[32] specifically designed for this kind of studies, based on an expert evaluation step to define the category "indoor cleaning." The JEM thus defines group averages of exposures, rather than exposure in each individual. Studies using a JEM are prone to a Berkson-type error, which in theory causes nearly unbiased effect estimates, but at the expense of loss of statistical power.[11] Thus, misclassification in exposure is likely to cause less precise results, but it is unlikely that our results are caused by information bias, while they might be underestimated because of nondifferential misclassification bias. Confounding by other occupational exposures that are correlated to exposure to indoor cleaning agents seems unlikely because exposure to cleaning and disinfectants was found in many different occupations (see Table E1). Rest confounding by socioeconomic status is possible. However, the variety in occupations with exposures to cleaning products and disinfectants reduces the chance for such confounding. Together with the adjustment for maternal education, we consider the risk of rest confounding by socioeconomic status to be relatively low. Rest confounding by smoking is unlikely because the results were consistent in offspring of never-smoking mothers.

Defining a reference group is critical in epidemiological studies involving occupational exposure. In this study, we compared offspring whose mother had been occupationally exposed to cleaning products and disinfectants with all other working mothers. Thus, the control group included offspring whose mother might have been occupationally exposed to any other of the 30 asthmagens in the OAsJEM[32] as well as persons with no such exposure. We considered the group of persons exposed to none of the 30 asthmagens more subject to selection bias, for instance, with regard to socioeconomic conditions, and therefore less appropriate as reference category. The group that was exposed only after the offspring's year of birth constitutes a different comparison group, which would have similar characteristics except the onset of exposure in relation to the birth year of a particular offspring. This group showed a null effect, strengthening the interpretation of a preconception/prenatal effect rather than shared environment.

Even though causality cannot be inferred from a single study, we speculate that the associations we observed in this study might possibly be causal.[46] Maternal occupational exposure preceded the onset of offspring disease, and a biological gradient is suggested. In addition, our results are consistent with the emerging understanding of intergenerational inheritance[16,39] and of how an unfavorable intrauterine environment might cause diseases later in life,[42,43] supporting the biological plausibility of our findings. Misclassification error is likely to be nondifferential, but unknown/unmeasured confounding cannot be ruled out.

## Conclusions

We find a consistent association between mother's use of cleaning products and disinfectants at work that started before conception, and offspring asthma, in this 2-generation study. This is the first human study addressing offspring respiratory health effects of maternal preconception occupational exposure to cleaning products and disinfectants. Our hypothesis-generating study adds substantially to the emerging understanding of intergenerational effects. The use of cleaning products and disinfectants is widespread, not least in women of childbearing age. Our findings on adverse health effects of preconception exposure to such products adds a new dimension to the growing concern about health effects of cleaning agents. Because of potentially vast implications of this, there is an urgent need for focused mechanistic research and replication in human studies.

## Data availability statement

The data set is held and managed by the RHINESSA study coordinating center at the Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway. Data cannot be made freely available because they are subject to Norwegian Data Protection regulations, but deidentified data can be made available to researchers on request. Requests for data can be sent to the principal investigator of the RHINESSA study: Cecilie Svanes, cecilie.svanes@helse-bergen.no.

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**Key messages**

- **This study finds more childhood asthma outcomes if the mother had held a job that included exposure to cleaning products/detergents and disinfectants before conception.**
- **The findings appeared to be stronger with higher *versus* medium exposure to indoor cleaning agents, and were consistent for 3 asthma outcomes, in offspring of never-smoking mothers, and on adjustment for potential confounding variables from 2 generations.**
- **The study raises concern for adverse health effects of cleaning products and disinfectants, even in the next generation, and supports the paradigm that exposures before conception may have an impact on offspring phenotype in humans.**

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# METHODS

## Study population

In this study, we used data from 2 linked surveys: (1) RHINE II (www.rhine.nu), a postal questionnaire follow-up of stage I of the European Community Respiratory Health Survey, which included randomly selected population-based samples of participants in more than 30 centers in Europe; and (2) RHINESSA (www.rhinessa.net), a questionnaire survey on offspring of the RHINE participants.[E1]

RHINE II included data on persons born from 1945 to 1973 from 7 centers in Northern Europe (Bergen in Norway, Umeå, Gothenburg, and Uppsala in Sweden, Aarhus in Denmark, Reykjavik in Iceland, and Tartu in Estonia). This survey, which took place from 1999 to 2001, comprised a full occupational history.

Our study population consisted of adult offspring who had participated in the RHINESSA study, but restricted to those who had a mother with at least 1 job lasting for at least 6 months and who had participated in the RHINE II study. The RHINESSA study was conducted in the period 2013 to 2016. In total, there were 4289 adult offspring of female participants in RHINE II, born before 1999. After excluding participants due to missing information on critical variables (Fig 2 in the main article), the final study population comprised 3318 adult offspring, of which 1307 had a mother with at least 1 job that involved exposure to indoor cleaning agents. The control group (n = 2011) included adult offspring whose mother had held at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents.

## Exposure in mother

**Characterization of exposure.** RHINE II comprised a full maternal occupational history, including start- and stop-year for each job, based on the question "List your jobs including branch, your work tasks and the period of employment. Periods shorter than six months need not to be specified. Employment also includes work done by people with their own company." All jobs were coded according to ISCO-88.[E2]

An OAsJEM that considers exposure to 30 specific sensitizers/irritant agents was used to characterize the mothers' occupational exposure to indoor cleaning agents.[E3] In the OAsJEM, an expert group previously assessed the exposure to each of the 30 agents for all job codes in ISCO-88.[E2] The JEM category "indoor cleaning" was defined as exposure to cleaning products/detergents or low/intermediate-level disinfectants.[E3] A total of 21 different job codes in ISCO-88 included exposure to indoor cleaning agents; from cleaners in offices, hotels, and other establishments, building caretakers, domestic helpers and cleaners, health care personnel, institutional-based and home-based personal care workers, and hairdressers, to food handlers such as butchers, cooks, and waiters (Table E1). In the OAsJEM, the job codes were classified into 3 exposure-level categories: (1) "High" (high probability of exposure and moderate to high intensity); (2) "Medium" (low to moderate probability or low intensity); and (3) "Unexposed" (Table E1). For the main analyses, maternal exposure was defined as having held at least 1 job with high or medium exposure to indoor cleaning agents, lasting for 6 months or more.

The control group included offspring whose mother had held at least 1 job for at least 6 months, but not been occupationally exposed to indoor cleaning agents, according to ISCO job code and OAsJEM. However, the mother might have been occupationally exposed to any other of the 30 agents in the OAsJEM.[E3]

**Time windows.** In this observational study, it was impossible to establish mutually exclusive groups for maternal occupational exposure to indoor cleaning agents because most occupationally exposed women had been exposed during more than 1 single time window. Even if the first exposed job ended before conception, there were often later exposed jobs for the same woman. Based on the theoretical model (Fig 1 in the main article) and modeling of different real-life scenarios for maternal lifetime occupational exposure (Fig 3 in the main article), we decided to categorize maternal occupational exposure according to when her first exposed job started. Preconception exposure was defined as mother's occupational exposure to indoor cleaning agents that had started 2 years or more before year of birth for each child. Because we suspected that the mothers whose exposure also stopped within this time window differed from the mothers whose exposure continued, we decided to split the preconception category into 2 subcategories: Exposure only before conception and Exposure starting before conception and continued. This resulted in a total of 5 exposure categories: (a) No occupational exposure to indoor cleaning agents; (b) Exposure only before conception (= scenario 1 in Fig 3 in the main article); (c) Exposure started before conception and continued (= scenario 2); (d) Exposure started around the time of conception and pregnancy (scenario 3); (e) Exposure only after year of birth (= scenario 4). Occupational exposure around the time of conception and pregnancy was crudely assessed as exposure starting during the offspring's birth year or the year before birth for each child, because we only had start- and stop-year and not exact start- and stop-dates for each job. For different women, exposure in this time window included 3 to 15 months preconception exposure and up to 12 months exposure during offspring's infancy. For the Exposure only after birth year category, the mother's exposure to indoor cleaning agents started the year after the child's birth year, or later. In all the exposure groups, the mother could have several consecutive jobs (up to 10) with different exposure levels to indoor cleaning agents, or only 1 single job with such exposure.

To investigate whether level of exposure influenced the outcome, we also made a categorical variable in which we incorporated the level of exposure, according to the OAsJEM, for each woman.[E3] A mother with a combination of jobs with high and medium exposure was categorized as having high exposure, and start of exposure was defined as the start-year for the first exposed job regardless of the level of exposure in this job. Because of few cases, we combined the time windows before conception and time around conception and pregnancy in this variable, giving the following 5 exposure-level categories: (1) No occupational exposure to indoor cleaning agents; (2) Medium exposure starting the year of birth or before; (3) High exposure starting the year of birth or before; (4) Medium exposure, only after year of birth; (5) High exposure, only after year of birth.

## Health outcomes in offspring

The RHINESSA study provided information given by offspring about their own asthma, allergies, and wheeze (www.rhinessa.net).

Childhood asthma was defined as an affirmative answer to the question "Do you have, or have you ever had asthma?" and a self-reported age less than 10 years on the question "How old were you when you first experienced asthma symptoms?" Children with nasal allergies were defined as the above, plus a confirmation to the question "Have you ever experienced nasal symptoms such as nasal congestion, rhinorrhea (runny nose), and/or sneezing attacks without having a cold?"

Childhood wheeze was defined as an affirmative answer to the question "Have you ever had wheezing or whistling in your chest?" and a self-reported age less than 10 years on the question "How old were you when you first noticed wheezing or whistling in your chest?" The outcome "Wheezing and/or asthma before age 10" was defined as an affirmative answer to either childhood asthma, or childhood wheeze, or both.

Age 10 years was set as cutoff to distinguish childhood asthma and wheeze from asthma with onset in puberty or adulthood because the latter 2 may be related to other causes and/or biased by other exposures, such as offspring's own smoking and occupational exposure.

## Statistics

Descriptive statistics for the study population were calculated as mean and SDs for continuous variables, and counts and percentages for categorical variables. Differences in characteristics between offspring of exposed and nonexposed mothers were tested using linear regression for continuous outcomes, logistic regression for binary outcomes, and multinomial logistic regression for categorical outcomes. Clustered robust SEs were used to account for clustering of siblings within mothers.

Association between timing of exposure to indoor cleaning agents and risk of asthma before age 10 years in the offspring was analyzed using mixed-effects logistic regression with random intercept for study center and mother and reported as odds ratios with 95% CIs. The same method was applied for asthma before age 10 years with nasal allergies, and wheezing and/or asthma before age 10 years.

For models with stratification on offspring's birth cohort, offspring's sex, and mother's smoking, the mixed-effect logistic regression failed to converge because of the low number of outcomes within each exposure category, and we therefore applied ordinary logistic regression with adjustment for study center as a covariate and clustered robust SEs to account for clustering of siblings within mothers. In models with stratification on sex and mother's smoking, we also collapsed the 3 exposure categories for exposure before and during pregnancy into 1 category.

Association between the 5-category variable with level and timing of exposure and risk of asthma before age 10 years in the offspring was analyzed using mixed-effects logistic regression with random intercept for study center and mother.

Two-sided tests with a significance level of 5% were used in all analyses. All analyses were performed in STATA version 15 (StataCorp LLC, College Station, Tex).

## Confounders/adjustment

Potential confounders in the association between mother's occupational exposure to indoor cleaning agents and offspring asthma and wheeze were identified a priori on the basis of previous studies,[E4-E10] and by using directed acyclic graphs[E4,E11] in the online tool http://www.dagitty.net/dags.html. Variables that had the potential to be associated with the exposure of interest and to cause childhood asthma/wheeze, such as parental educational level, asthma, and smoking, were considered for inclusion in the model (Fig E1). According to the online tool, which specifies minimal sufficient adjustment sets, the fully adjusted model indicated adjustment for maternal education only.[E4,E11]

Information on mother's educational level was reported by the offspring in the RHINESSA study.

## Ethics

This study was approved by regional committees of medical research ethics in each study center according to national legislations. A written informed consent was obtained from each participant before participation.

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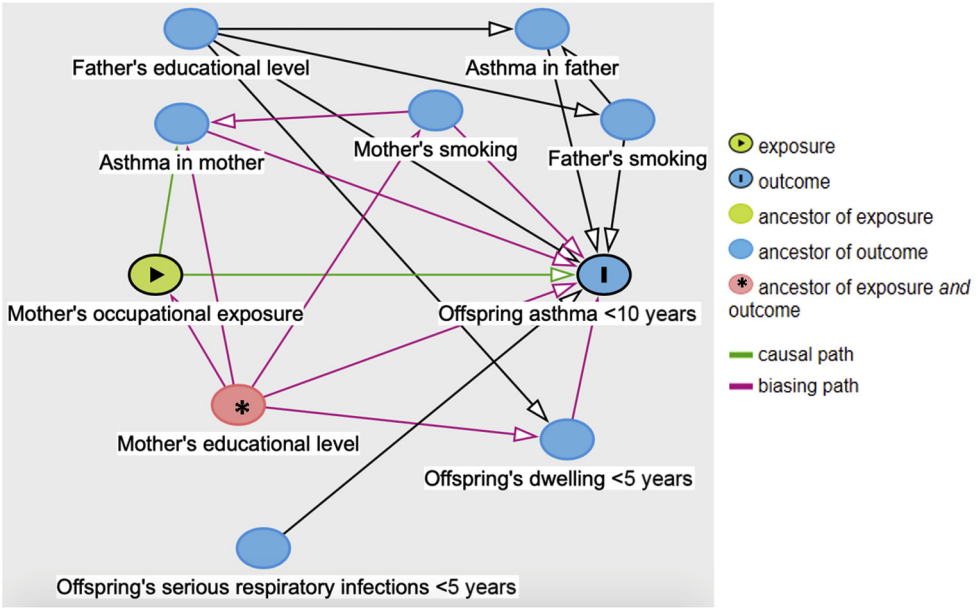


**FIG E1.** Directed acyclic graph (DAG) identifying potential confounders in the association between mother's occupational exposure to indoor cleaning agents and offspring asthma, based on previous studies. The DAG is created by the online DAGitty software, which is available at www.dagitty.net.

**TABLE E1.** ISCO-88 job codes* including exposure to indoor cleaning agents,† and corresponding exposure-level categories†

| 3-digit ISCO code (minor group)* | 4-digit ISCO code (unit group)* | ISCO minor group or unit group description | Exposure level‡ | N |
|---|---|---|---|---|
| | 2230 | Nursing and midwifery professionals | Medium | 172 |
| | 3231 | Nursing associate professionals | Medium | 148 |
| 512 | | Housekeeping and restaurant services workers | Medium | 2 |
| | 5121 | Housekeepers and related workers | Medium | 13 |
| | 5122 | Cooks | Medium | 94 |
| | 5123 | Waiters, waitresses, and bartenders | Medium | 56 |
| 513 | | Personal care and related workers | Medium | 21 |
| | 5131 | Child-care workers | Medium | 267 |
| | 5132 | Institution-based personal care workers | High | 429 |
| | 5133 | Home-based personal care workers | Medium | 170 |
| | 5139 | Personal care and related workers not elsewhere classified | Medium | 17 |
| | 5141 | Hairdressers, barbers, beauticians, and related workers | Medium | 53 |
| | 5143 | Undertakers and embalmers | Medium | 3 |
| | 7411 | Butchers, fishmongers, and related food preparers | Medium | 17 |
| 913 | | Domestic and related helpers, cleaners, and launderers | Medium | 1 |
| | 9131 | Domestic helpers and cleaners | High | 17 |
| | 9132 | Helpers and cleaners in offices, hotels, and other establishments | High | 295 |
| | 9133 | Hand-launderers and pressers | Medium | 7 |
| 914 | | Building caretakers, window and related cleaners | Medium | 0 |
| | 9141 | Building caretakers | Medium | 45 |
| | 9142 | Vehicle, window, and related cleaners | Medium | 5 |

*ISCO-88's hierarchical structure consists of 10 major groups at the top level of aggregation, subdivided into 28 submajor groups, 116 minor groups, and 390 unit groups.
†According to the OAsJEM.
‡High: high probability of exposure and moderate to high intensity. Medium: low to moderate probability or low intensity, both according to the OAsJEM.

**TABLE E2.** Analyses stratified by year of birth for the child: Association* between timing of exposure† and asthma before age 10 years in the offspring (N = 3318)

| Exposure time categories for birth cohorts | n asthma/N total | Crude model,‡ OR (95 % CI) | Model 2,§ OR (95 % CI) |
|---|---|---|---|
| **Year of birth 1963-1979** | | | |
| n | | 1013 | 1004 |
| Timing of mother's occupational exposure | | | |
| No jobs with exposure to indoor cleaning agents‖ | 24/642 | 1 | 1 |
| Exposure only before conception | 0/12 | — | — |
| Exposure started before conception and continued | 7/125 | 1.48 (0.61-3.58) | 1.53 (0.62-3.76) |
| Exposure started around the time of conception or pregnancy | 3/36 | 2.34 (0.67-8.22) | 2.34 (0.67-8.22) |
| Exposure only after year of birth | 11/253 | 1.17 (0.56-2.44) | 1.21 (0.56-2.59) |
| **Year of birth 1980-1998** | | | |
| n | | 2250 | 2242 |
| Timing of mother's occupational exposure | | | |
| No jobs with exposure to indoor cleaning agents‖ | 103/1369 | 1 | 1 |
| Exposure only before conception | 12/138 | 1.10 (0.56-2.13) | 1.10 (0.57-2.14) |
| Exposure started before conception and continued | 48/485 | 1.27 (0.88-1.85) | 1.28 (0.87-1.87) |
| Exposure started around the time of conception or pregnancy | 6/41 | 1.95 (0.80-4.77) | 1.97 (0.81-4.81) |
| Exposure only after year of birth | 20/217 | 1.21 (0.72-2.04) | 1.27 (0.75-2.14) |

*OR*, Odds ratio.

*ORs are estimated using logistic regression with clustered robust SEs to take into account clustering of siblings. Study center is included as an adjustment variable in all models.

†According to the ISCO-88 job code and the OAsJEM.

‡Adjusted for study center.

§Adjusted for mother's level of education (primary, secondary, and college/university). Fully adjusted model identified by directed acyclic graphs.

‖Mothers with at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents according to the ISCO-88 job code and the OAsJEM.