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Daycare use of disinfectants and cleaning products and wheeze among children: Cross-sectional analyses in the French CRESPI cohort

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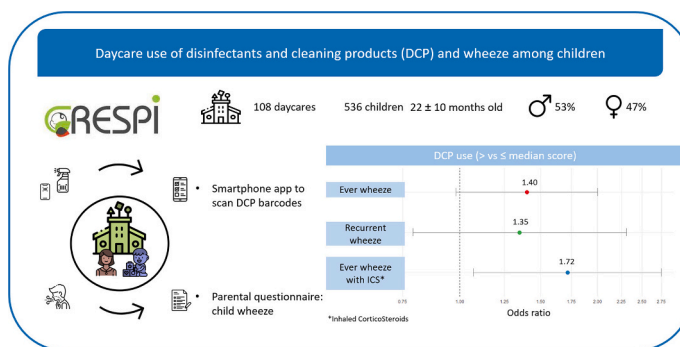
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HIGHLIGHTS

- Disinfectants and cleaning products (DCP) are used widely in daycares
- Exposure to chemicals in DCP is of respiratory health concern for children
- High use of DCP in daycares is associated with increased odds of wheeze with inhaled corticosteroid use in children

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Evidence is mounting that domestic use of disinfectants and cleaning products (DCP), particularly in spray form, is associated with wheezing in children. Beyond the home environment, many children are also exposed to DCP in daycare. The links between daycare exposures to DCP and child respiratory health have never before been studied.

Objectives: Evaluate the associations between daycare DCP use and wheeze among children.

Methods: This cross-sectional study draws upon the data at inclusion for 536 children (mean age: 22.3 months; 47.4 % female) of the French CRESPI cohort (108 daycares in the Paris region, 2019–2022). Exposure to DCP was evaluated using a barcode-scanning smartphone application with an embedded questionnaire. An exposure score was calculated as the sum of frequencies of use of DCP for each daycare. Child wheezing outcomes (ever wheeze since birth, recurrent wheeze (≥ 3 times since birth), and wheeze ever treated with inhaled corticosteroids (ICS))

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were evaluated by parental questionnaire. Associations between daycare DCP exposure and wheezing outcomes were analyzed with Generalized Estimating Equations to account for a possible center effect, and adjusted for child age, parental smoking status, parental educational attainment, and daycare size.

Results: The prevalence of ever wheeze was 32.1 %, that of recurrent wheeze 13.3 %, and that of wheeze ever treated with ICS 14.5 %. Above-median exposure scores (vs. \leq median exposure scores) were associated with higher odds of wheeze ever treated with ICS (Odds Ratio = 1.72, 95 % Confidence Interval: 1.07–2.75) and ever wheeze (1.40, 0.98–2.00), but not with recurrent wheeze (1.35, 0.79–2.31). Relationships between specific DCP application modes and wheezing outcomes did not suggest a predominant role of specific modes.

Discussion: Given the observed association between daycare DCP use and wheeze in children, measures which limit child exposure to DCP in care settings should be considered.

1. Introduction

In France, approximately 11 % of children are affected by asthma, making it the most common chronic disease in children (Delmas et al., 2017). Occurrence of wheeze, in particular recurrent wheeze, is often used as a symptom diagnosis for asthma in early childhood, as pulmonary function tests are often not carried out before the age of 6 (Ducharme et al., 2014). Various European cohorts have found prevalence of wheeze to vary between about 19 %–39 % in children under two (Herr et al., 2012) and between 10 %–55 % at age four (Uphoff et al., 2017). Environmental exposures, such as outdoor air pollution, tobacco smoke, and mold have been consistently identified in association with asthma and asthma-like symptoms in childhood (Beasley et al., 2015; von Mutius and Smits, 2020). Exposures in the indoor environment, such as chemical exposures, receive increasing attention, but their impact on respiratory health remains incompletely characterized (Casas et al., 2023).

In industrially developed countries, children and infants spend a majority of time indoors (Farrow et al., 1997; Conrad et al., 2013), at home and also in daycares. Daycare attendance has in some instances been shown to be predictive of child wheeze, although it has been reported as both a protective and a risk factor (Herr et al., 2012; Beasley et al., 2015; von Mutius, 2016). A number of characteristics could mediate these associations, such as the microbial environment (more diverse bacterial exposures, but also increased risk of viral respiratory infections and exposure to bacterial endotoxin) (von Mutius, 2016), and also chemical exposures, including disinfectants and cleaning products (DCP) (Herr et al., 2012; Casas et al., 2015), which are frequently used in daycares (Wei et al., 2016).

DCP contain a large number of ingredients, including many irritants and sensitizing agents. A recent UK-based occupational study identified 55 respiratory sensitizers and 26 respiratory irritants among cleaning products used by the National Health Service (Lee et al., 2024). Similarly, a median of 12 irritants and 4 sensitizers was found in cleaning products used weekly by French women for domestic cleaning (Lemire et al., 2022). Many chemical ingredients of DCP, such as bleach, quaternary ammonium compounds, and various acids, have been shown to be associated with adult asthma (Dumas et al., 2017; Archangelidi et al., 2021). Mechanistic hypotheses to explain such observations include damage of the airway epithelium due to increased inflammation and oxidative stress (irritants), as well as immunologically-mediated mechanisms (sensitizers) (Dumas et al., 2017; Archangelidi et al., 2021). Studies carried out in the home environment reported adverse effects of pre- and postnatal use of DCP, particularly with a spray application mode, on wheeze and other asthma-related outcomes in children (Casas et al., 2023, 2013a, 2013b; Sherriff et al., 2005; O'Connor et al., 2018; Mikeš et al., 2019; Parks et al., 2020). To our knowledge, no study has been performed on DCP exposure in daycare. In addition, many previously published association studies have used questionnaires to evaluate DCP exposure, which introduces the possibility of both non-differential and differential exposure misclassification (Lemire et al., 2022, 2021). Recently, a barcode-based smartphone application (app) has been proposed as an opportunity to collect more accurate exposure data compared to questionnaires (Lemire et al., 2022, 2021).

The CRESPI (santé RESPIratoire des enfants en Crèche, <https://respi.vjf.inserm.fr>) cohort is the first cohort set up specifically to examine use of DCP in daycare settings and respiratory health effects among children attending daycare (Casas et al., 2023). CRESPI utilizes a barcode-based smartphone app to collect DCP use data in daycares (Casas et al., 2023). In the current study, we aimed to investigate the relationship between daycare worker use of DCP and parent-reported child wheezing outcomes. Based on results from prior studies on home exposures to DCP, we hypothesized that high daycare use of DCP is associated with child wheeze and asthma-related outcomes in the CRESPI cohort.

2. Methods

2.1. Study design and data collection

CRESPI is a cohort designed to include children aged at least 3 months who attend daycare centers in Ile-de-France (Paris Metropolitan area, France). It was conceived in part to examine the associations between DCP use in daycares and the respiratory health of daycare children. Details regarding the study protocol have been described previously (Le Moual et al., 2023). Briefly, 400 daycare centers chosen randomly from an administrative childcare database (curated by the French Caisse d'Allocation Familiale (CAF), a governmental funding body which supports all families with costs from housing to childcare) were progressively contacted until at least 100 accepted to participate, with an acceptance rate of 55 %. Daycares included public and private centers licensed by the CAF. Ultimately, 108 daycares have been included in CRESPI (102 from the random selection, and 6 additional non-randomized volunteer centers). Comparable numbers of daycares were included for each Paris Metropolitan Area administrative department as were expected with a sample size of 100 (Le Moual et al., 2023). Daycares which declined to participate were more frequently located in more socioeconomically advantaged areas compared with daycares which agreed to participate, as measured by the French Deprivation index (Fig. S1) (Rey et al., 2009; Temam et al., 2019). In contrast, daycares in more socioeconomically disadvantaged areas tended to have lower participation rates of families than daycares in higher socioeconomic areas (Fig. S2). Visits to participating daycares were carried out between November 2019 and February 2022, spanning the period before the first Covid-19 pandemic-related lockdown as well as the subsequent period (L'Obs, 2023). There were 101 daycares with both children recruited and daycare DCP use data (Fig. 1). Before March 2020, 16 CRESPI daycares were visited (101 total recruited children), with the remaining 85 daycares visited after the onset of the COVID-19 pandemic (435 total recruited children). Parents of children attending participating daycares were initially invited through the daycare manager, who sent invitations to all registered families. An estimated total of 5790 families of children from participating daycares were invited to participate in the CRESPI study. 922 families (16 %) sent in a positive reply coupon indicating their consent for participation and were sent a standardized questionnaire to be self-administered, with questions pertaining to child health, birth and growth outcomes as well as parental antecedents. After the end of inclusion in December 2022, 551

questionnaires had been completed by parents (60 % of those who sent positive reply coupons) from 101 daycares. Overall response rates per daycare varied from zero for six daycares with no children recruited to 30 %, and the overall response rate was 9.5 %. The cohort thus is composed of individual-level data pertaining to 551 children. The present analysis is cross-sectional in nature.

2.2. Ethical considerations

The CRESPI study, sponsored by the French National Institute for Health and Medical Research (Inserm, references C18-05; ID RCB n° 2018-A02657-48), has been approved by the French ethics committee

“Comité de protection des personnes” (CPP Sud- Est I n°2019-38; May 2019) and the French Data Protection Authority “Commission Nationale de l’Informatique et des Libertés” (CNIL n°919,185; October 2019). The CRESPI protocol was registered in the clinical trials register (NCT n° 04170881). At least one parent or guardian for each child participating in the study signed a written consent form.

2.3. Outcome definition

The main outcome of interest in this study is child wheezing status at inclusion, defined by parental questionnaire response, as in other French and European cohorts (Uphoff et al., 2017). Two non-mutually exclusive

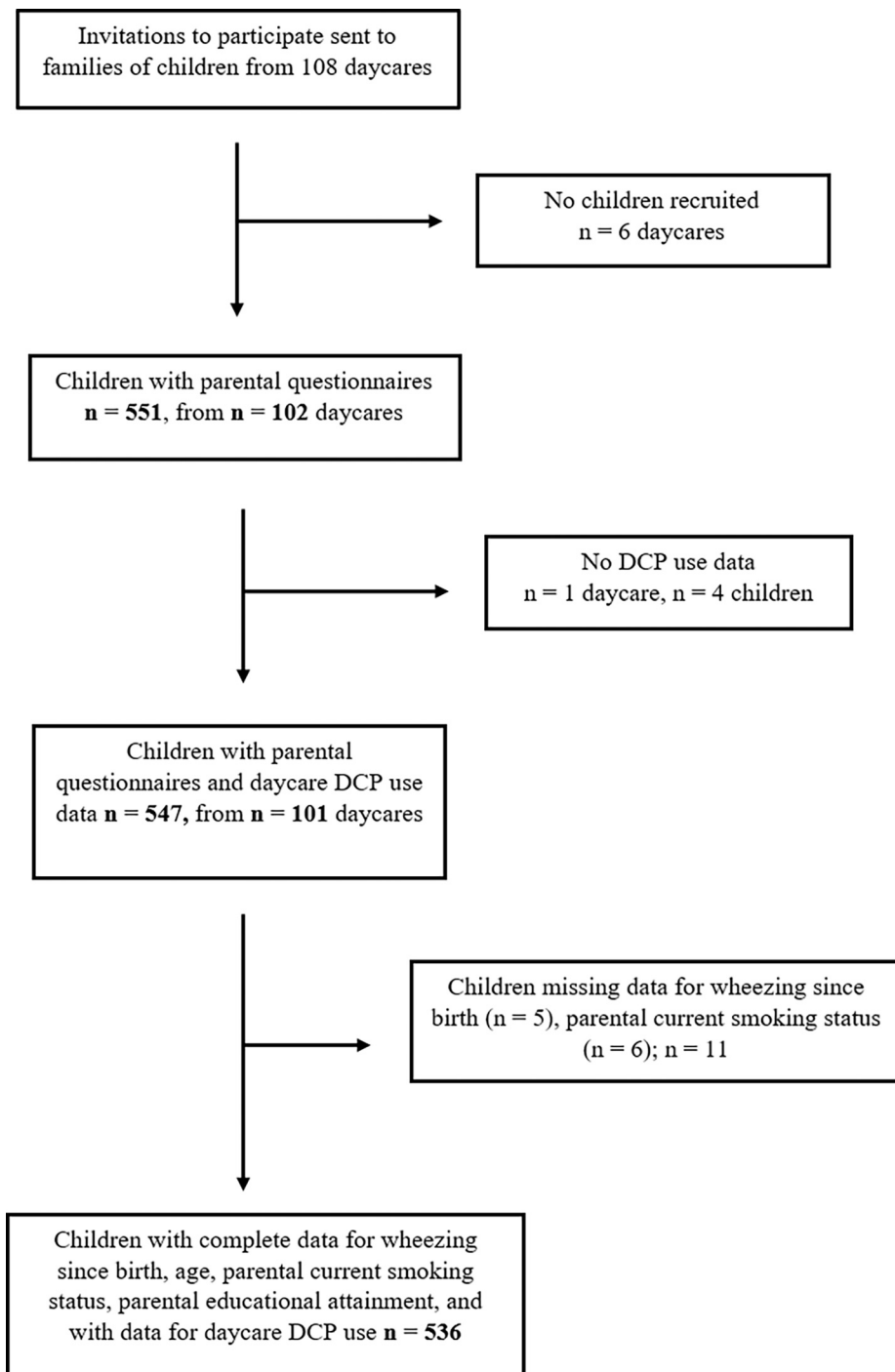


Fig. 1. Main database flow chart.

wheezing outcomes were defined as follows: (i.) ever wheeze since birth, if the inclusion questionnaire indicated that the participating child experienced wheezing in the chest at any point (Uphoff et al., 2017); and (ii.) recurrent wheeze, defined by at least 3 episodes of wheezing since birth (Alvarez-Alvarez et al., 2018). Wheeze ever treated with inhaled corticosteroids (ICS) was considered as at least one episode of wheezing, along with parental reported treatment with ICS. Sensitivity analyses included (i.) a stringent definition of recurrent wheeze, defined as at least 3 episodes of wheezing since birth, in addition to either nighttime wakening and a duration of wheeze of at least one day, or doctor-prescribed treatment indicated by parental questionnaire (Dumas et al., 2019); and (ii.) a definition of ever wheeze based on at least one episode of wheezing, along with ICS and/or hospitalization (Herr et al., 2012). In the questionnaire, hospitalization refers specifically to the child having ever been hospitalized for bronchiolitis, wheezy bronchitis, or an asthma attack. Questionnaire-based wheezing outcomes were compared to data from children's health booklets in a subsample of children (see online supplemental material).

2.4. Exposure assessment

In a face-to-face interview with each daycare worker present during the visit ($n = 1586$), Inseam fieldworkers scanned DCP used in the daycares using a barcode-based smartphone application (app) paired with a questionnaire (Le Moual et al., 2023). All personnel present the day of the daycare visit agreed to the face-to-face interview; an average of 14 staff members were interviewed per facility. Data were collected during visits to 107 of 108 participating daycares, and 9985 products – DCP as well as cosmetic products – were scanned or input. Barcodes of commercial products were scanned, and a questionnaire allowed the inputting of products made by daycare staff as well as those industrially manufactured products lacking barcodes (7.6 % of all products). Data on frequency and purpose of product use, as well as product application mode (e.g., spray, wipe), were collected from daycare personnel via the questionnaire integrated in the app. In addition to the smartphone application, information on the building ventilation system and usual timing of various cleaning tasks (furniture, floors, windows, or toys) was collected by questionnaire.

2.5. Exposure definition

In analyses for the present study, products considered in the definition of DCP use were those used for cleaning/disinfection of surfaces (e.g., kitchen, toilets, floor), furniture (e.g., tables) or instruments. Excluded were products used for the purposes of handwashing and hand moisturizing, dishwashing, diaper change, and laundry, as well as those marked only as “other”. Thus, a database of 3074 products used for cleaning/disinfection purposes was used to construct summary variables of exposure to DCP per daycare. Questions integrated into the application pertained to weekly and daily frequency of use of the input or scanned DCP, and these were aggregated into an overall frequency of use variable, ranging from 0 to 4 (0 = 1 time per day or less; 1 = 2–5 times per day; 2 = 5–10 times per day; 3 = 10–20 times per day; 4 = >20 times per day). The application modes of spray, wipe, liquid, gel, cream or foam, and responses of “other” were retained to define exposure.

To represent daycare DCP use, an exposure score was calculated, inspired by the existing literature (Parks et al., 2020; Weinmann et al., 2017; Bédard et al., 2014). This exposure score was defined per daycare as the sum of the frequencies of use (0 to 4, as defined above) of each product used in the daycare. For the DCP application modes of spray, wipe, and liquid, a separate score was also calculated by summing the frequencies of use of products of only the respective application mode. Scores were then categorized at the daycare level into terciles and binary categories separated at the median. In addition, three application-mode-specific exposure variables were defined as three-category variables, consisting of 1) low (\leq daycare median score) use of DCP, 2) high ($>$

daycare median score) use of DCP and low use of the particular application mode, and 3) high use of DCP and high use of the particular application mode. A single score was calculated for each facility and attributed to all included children attending that facility.

2.6. Potential confounding factors

Child age, parental current smoking status and parental educational attainment were retained a priori in all adjusted models. Age was included as a continuous variable (in months); all others were categorical. Parental current smoking status was considered present if at least one of the child's parents reported being a current smoker. Parental educational attainment was considered as the maximum educational attainment of either parent, classed in three categories: two years of further study after high school or less, high school and three to four years of further study, and high school and five or more years of study.

Adjusted models also included an additional daycare-level variable representing daycare size, defined using the number of children registered in each daycare (11 to 125, median: 55), divided into quartiles. Since the number of products used per daycare (taken into account in the DCP exposure score) was found to be associated with the number of children registered, daycare size was added as a confounder. Indeed, larger daycares are expected to use more products. In addition, larger daycares might also facilitate greater viral transmission.

2.7. Statistical analyses

Associations between exposures and wheezing outcomes were evaluated by logistic regressions with Generalized Estimating Equations (GEE), used to take into account a potential center (daycare) effect. In GEE models, a working correlation matrix is employed to address the lack of independence of observations (Huang, 2022). In this case, an exchangeable correlation structure was specified, due to the hypothesis that the correlation between all children in the same daycare is the same. Exposure was considered in terciles to examine a potential dose-response relationship and in binary categories with cutoffs at the median for comparability with application mode exposure variables. For the overall exposure score, analyses were also conducted with exposure considered as an interquartile range (IQR) increase of the continuous exposure score.

Additionally, analyses stratified by child's sex and age were carried out, with the hypothesis of potential interaction - namely the possibility of a stronger effect in female children than in male children (Parks et al., 2020), and of an exploratory nature by age category. Sensitivity analyses were also performed. These included the restriction of analyses to only those children (i.) from daycares with <15 recruited children (to exclude a potential influence on the results of a few large daycares which might have specific cleaning habits), (ii.) whose first episode of wheeze occurred after the start of daycare attendance, (iii.) whose mother(s) completed the inclusion questionnaire (since there were relatively more children with all three wheezing outcomes whose mothers completed the questionnaire as opposed to those whose fathers completed the questionnaire without the mother), (iv.) having attended daycare for at least 11 months (the median length of attendance in this population), (v.) from daycares visited March 2020 or later (when circulation of the Covid-19-causing SARS-CoV-2 virus drastically increased in Europe and social measures were enacted), (vi.) attending daycare at least five days per week, (vii.) whose mothers did not smoke during pregnancy (as there were too few children whose mothers smoked during pregnancy to adjust for this factor in main models), and (viii.) who were not born preterm (where preterm is defined as <37 weeks gestation). Building characteristics such as visible mold and type of mechanical ventilation system were further taken into account by restriction (excluding six daycares with visible mold) and stratified analyses (daycares with exhaust-only mechanical ventilation vs. those with balanced mechanical ventilation, as only nine daycares reported no ventilation system). All

daycares were in urban (85 %) or peri-urban zones and no daycare reported never opening windows; therefore, these factors were not considered for sensitivity analyses.

Statistical analyses were conducted using SAS version 9.0.

3. Results

3.1. Child-level descriptive statistics

A total of 551 children were recruited, and 547 had DCP use data from daycare visits as well as completed questionnaires. Of these, there were 536 with data for wheezing since birth and all selected covariates (Fig. 1). At the time of questionnaire completion, the average age of participating children was 22.3 months (IQR 13.8–30.1 months) (Table 1). Slightly less than half of the participants were female (47.4 %), and nearly all were born in France. Most often, the mother completed the questionnaire (83.5 %), alone for 70.9 % of children and along with the father for 12.6 %. The average frequency of child presence in daycare was 4.70 days per week, and 76.6 % of parents reported that their child was present in daycare five days per week. On average, children had been attending daycare for 13.6 months at the time of completion of the parental questionnaire. The vast majority of parents (79.9 %) had a diploma equivalent to five years of study post-high school, and 21.5 % reported being current smokers.

The prevalence of ever wheeze was 32.1 %, and that of recurrent wheeze was 13.3 %. A majority of children who were ever wheezers began wheezing after the start of daycare attendance. For 14.5 % of children, wheeze ever treated with inhaled corticosteroids (wheeze ever treated with ICS) was reported. Comparison of questionnaire-based wheezing outcomes to data from children's health booklets in a subsample of children ($n = 46$) suggested high specificity (>95 %) for these

questionnaire-based definitions (see online supplemental material). Children's characteristics according to wheezing outcomes are presented in Table S1. Briefly, children with wheezing outcomes were generally older (23.1 months for ever wheezers compared to 21.9 months for children without wheeze), more often male (33.3 % of male children compared to 30.7 % of female children were ever wheezers), and more often had parental current smoking (39.1 % of children with compared to 30.2 % of children without parental current smoking were ever wheezers), although differences for specific wheezing outcomes were not always significant. Parental education status was not associated with any wheezing outcomes.

3.2. Description of daycare variables

The exposure score calculated from the 3074 products used for cleaning purposes in 101 daycares with children recruited ranged from 4 to 108, with a mean of 43.3, a standard deviation of 22.1, and an IQR of 27–54 (Fig. S3). Sprays were the most common and were the application mode with the highest relative contribution to the exposure score (mean of 24.1 points compared to the second-highest contributor, liquid application mode, with a mean of 8.32 points; Table S2). In terms of usual timing of cleaning tasks, 43.4 % of daycares reported cleaning furniture, floors, windows, or toys at least once a day in the presence of children, 20.8 % during the day but in the absence of children, 15.1 % in the morning, and 20.8 % reported cleaning only in the evening.

As expected, larger daycare size was associated with DCP exposure scores above the median (Table S3). Visits to daycares before March 2020 were associated with more reported ever wheeze, recurrent wheeze, and wheeze ever treated with ICS (Table S4). For example, the prevalence of ever wheeze was higher before March 2020 (41.6 %) compared with March 2020 or later (29.9 %). Children from daycares

Table 1
Characteristics of CRESPI children.

N = 536 unless otherwise stated	Mean \pm SD [min–max]	n (%)
Age of child (months) at time of questionnaire completion	22.3 \pm 10.3, 13.8–30.1 ^a [3.55–57.0]	
Age of child (months) at daycare visit	19.7 \pm 10.2 [–13.3–55.0]	
Sex of child, female		254(47.4)
Child born in France ^b		527 (98.5)
Child born preterm (<37 weeks gestation) ^b		32 (6.34)
Days per week child present in daycare ^b	4.70 \pm 0.64 [1–6]	
Duration of child daycare attendance (months) at questionnaire completion ^b	13.6 \pm 9.62 [0.33–53.0]	
Person completing questionnaire ^b		
Mother		372 (70.9)
Father		85 (16.2)
Both mother and father		66 (12.6)
Another person		2 (0.38)
Maternal smoking during pregnancy ^b		27 (5.17)
Parental current smoking		115 (21.5)
Parental educational attainment		
2 years of study after high school or less		31 (5.78)
High school and 3 to 4 years of further study		77 (14.4)
High school and at least 5 years of further study		428 (79.9)
Child asthma-related outcomes		
Ever wheeze (at least one episode of wheeze since birth)		172 (32.1)
Age (months) at first wheezing episode ($n = 157$ of 172 wheezers)	7.90 \pm 4.39 [0–26]	
Difference in age at first wheezing episode and at the start of daycare attendance ($n = 156$ of 172 wheezers)	–0.83 \pm 7.47 [–26.1–16.0]	
Recurrent wheeze (≥ 3 episodes of wheeze since birth) ^b		71 (13.3)
Stringent definition of recurrent wheeze ^{b,c}		62 (11.8)
Wheeze ever treated with ICS ^b		77 (14.5)
Wheeze ever treated with ICS and/or hospitalization		84 (15.7)

^a IQR.

^b Some missing values (minimum 1 to maximum 35 (child born in France)).

^c Defined as (≥ 3 episodes of wheezing) and ([nighttime waking & duration ≥ 1 day] or [doctor-prescribed treatment]); ICS: inhaled corticosteroids.

Table 2
Associations between DCP use score and child wheeze.^a

	Ever wheeze (n = 536)			Recurrent wheeze (n = 435)			Wheeze ever treated with ICS (n = 441)		
	Ever wheeze, n (%)	OR (95% CI)	p	Recurrent wheeze, n (%)	OR (95% CI)	p	Wheeze ever treated with ICS, n (%)	OR (95% CI)	p
DCP use score in tertiles	n = 172		0.29	n = 71		0.55	n = 77		0.05
First tertile	48 (30.2)	1		21 (15.9)	1		19 (14.6)	1	
Second tertile	54 (29.0)	0.85 (0.50–1.44)	0.55	22 (14.3)	0.98 (0.42–2.29)	0.96	23 (14.8)	1.24 (0.56–2.76)	0.59
Third tertile	70 (36.7)	1.28 (0.78–2.09)	0.33	28 (18.8)	1.27 (0.54–2.99)	0.58	35 (22.4)	2.09 (0.92–4.76)	0.08
DCP use score in binary categories									
≤Median	83 (28.7)	1		35 (14.5)	1		34 (14.2)	1	
>Median	89 (36.0)	1.40 (0.98–2.00)	0.07	36 (18.6)	1.35 (0.79–2.31)	0.27	43 (21.4)	1.72 (1.07–2.75)	0.02
Interquartile range (IQR) increase of DCP use score		1.22 (0.97–1.52)	0.09		1.23 (0.86–1.75)	0.26		1.51 (1.11–2.05)	0.01

^a Models adjusted for child age (months), parental smoking status, parental educational attainment, and daycare size (quartiles of children registered).

Table 3
Associations between DCP application mode and child wheeze.^a

	Ever wheeze (n = 536)			Recurrent wheeze (n = 435)			Wheeze ever treated with ICS (n = 441)		
	Ever wheeze, n (%)	OR (95% CI)	p	Recurrent wheeze, n (%)	OR (95% CI)	p	Wheeze ever treated with ICS, n (%)	OR (95% CI)	p
Spray	n = 172			n = 71			n = 77		
Low use ^b of DCP	83 (28.7)	1		35 (14.5)	1		34 (14.2)	1	
High use ^c of DCP, low use of sprays	27 (34.6)	1.31 (0.85–2.01)	0.22	15 (22.7)	1.95 (1.03–3.67)	0.04	14 (21.5)	1.68 (0.95–2.98)	0.07
High use of DCP, high use of sprays	62 (36.7)	1.45 (0.97–2.17)	0.07	21 (16.4)	1.11 (0.61–2.02)	0.74	29 (21.3)	1.74 (1.01–3.00)	0.05
Wipe									
Low use of DCP	83 (28.7)	1		35 (14.5)	1		34 (14.2)	1	
High use of DCP, low use of wipes	61 (37.4)	1.47 (1.01–2.15)	0.04	24 (19.1)	1.41 (0.79–2.52)	0.25	31 (23.3)	1.93 (1.15–3.24)	0.01
High use of DCP, high use of wipes	28 (33.3)	1.25 (0.73–2.14)	0.41	12 (17.7)	1.25 (0.63–2.48)	0.53	12 (17.7)	1.35 (0.75–2.43)	0.31
Liquid									
Low use of DCP	83 (28.7)	1		35 (14.5)	1		34 (14.2)	1	
High use of DCP, low use of liquids	22 (34.9)	1.28 (0.82–2.00)	0.27	8 (16.3)	1.14 (0.56–2.31)	0.73	12 (22.6)	1.75 (0.92–3.33)	0.09
High use of DCP, high use of liquids	67 (36.4)	1.46 (0.99–2.16)	0.06	28 (19.3)	1.46 (0.83–2.58)	0.19	31 (21.0)	1.70 (1.02–2.85)	0.04

^a Models adjusted for child age (months), parental smoking status, parental educational attainment, and daycare size (quartiles of children registered).

^b Low use is defined as an exposure score ≤ the daycare median.

^c High use is defined as an exposure score > the daycare median.

visited March 2020 or later were not different in age compared to those from daycares visited before. No association was found between the daycare area-level deprivation index and DCP use score.

3.3. Associations between DCP exposures and child wheeze

Above-median DCP exposure scores were associated with ever wheeze (OR = 1.40, 95 % CI: 0.98–2.00, $p = 0.07$) and more strongly associated with wheeze ever treated with ICS (OR = 1.72, 95 % CI: 1.07–2.75) (Table 2). The observed effect estimate was lower, with 95 % CI straddling zero, for the association between binary categories of DCP score and recurrent wheeze. Regarding specific DCP application modes, all odds ratios for relationships with wheezing outcomes were above one (Table 3). For wheeze ever treated with ICS, the pattern of association suggested increased risks for exposure profiles of high use of DCP whatever the form (liquids, sprays, wipes). However, no strong association emerged for the category of high use of DCP, high use of wipes. A similar pattern was observed for ever wheeze. For recurrent wheeze, the association pattern was less consistent. When considering an IQR increase of exposure score, results remained consistent (ever wheeze: OR = 1.22, 95 % CI: 0.97–1.52, $p = 0.09$; recurrent wheeze: 1.23 (0.86–1.75), $p = 0.26$; wheeze ever treated with ICS: 1.51 (1.11–2.05), $p = 0.01$; Table 2).

Sensitivity analyses regarding the outcomes (a stringent definition of recurrent wheeze, and wheeze ever treated with ICS and/or hospitalization) remained consistent with the main results (Table S5). Other sensitivity analyses also remained largely consistent with results previously described, despite wider confidence intervals due to the restricting of the population (Table S6). When stratifying by sex, point estimates of models with binary DCP exposure scores were higher among female children for ever wheeze and for wheeze ever treated with ICS (1.61 and 2.41 compared to 1.26 and 1.44, respectively), and higher among male children for recurrent wheeze (1.56 compared to 1.10) (Table S7). However, the confidence intervals largely overlapped and no significant interaction was evidenced. Stratification by age yielded stronger effect estimates for wheeze ever treated with ICS among children <24 months old (OR = 2.12, 95 % CI: 1.12–4.00) compared with those 24 months or older (OR = 1.29, 95 % CI: 0.60–2.79), although estimates for all wheezing outcomes in both strata were above one and there was no significant interaction (Table S7).

Analyses including only those daycares without visible mold yielded results consistent with main analyses (Table S8). Stratified analyses, with those for children from daycares with exhaust-only mechanical ventilation systems carried out separately from those with balanced systems, resulted in associations between above-median exposure score and ever wheeze as well as wheeze ever treated with ICS only for those daycares with exhaust-only systems, with p -interaction of 0.27 and 0.07, respectively.

4. Discussion

CRESPI children attending daycares with exposure scores above the daycare median score, indicating a high use of DCP, were more likely to have ever wheeze and wheeze ever treated with ICS. This and the consistently above-one odds ratios for relationships between specific DCP application modes and wheezing outcomes, as well as the robustness of the results to a number of sensitivity analyses, suggest an association between high daycare DCP use and child wheeze.

The present study is the first to investigate daycare DCP use and child respiratory health; studies focusing on the home environment informed the hypothesis of association (Casas et al., 2023; Parks et al., 2020). This makes our findings novel, while our results are at the same time in line with the existing literature from these other settings. That products in specific application modes, especially sprays, did not clearly emerge to be associated with wheezing outcomes is unexpected, as a number of other studies have documented domestic spray use in association with

child respiratory health (Herr et al., 2012; Casas et al., 2013b; Franklin, 2008). A recent study also showed that weekly use of disinfecting wipes is associated with current asthma in a large cohort of French adults, although no studies have investigated exposure to wipes in cohorts of children (Pacheco Da Silva et al., 2022). In CRESPI, there was much concurrent use of products within individual participating daycares, especially of spray and liquid application modes, limiting possibilities to independently study exposure to specific product application modes.

Wheeze is a potential sign of the type of variable airway obstruction that characterizes asthma, although wheeze that occurs early in life may not persist or develop into asthma (Bobolea et al., 2019). Indeed, wheeze can be caused by lower respiratory tract infections (LRTI) in early life, including bronchiolitis (Dumas et al., 2019). A distinguishing feature of potential asthma is a positive response to bronchodilators and inhaled corticosteroids, contrary to bronchiolitis (Ducharme et al., 2014). We observed a lower effect estimate for the association between DCP use and recurrent wheeze, perhaps due to the difficulty of assessing multiple episodes of wheeze by parental questionnaire and of subsequently defining the outcome, which remains nonspecific (Brand et al., 2008). In France, as recommended by the High Authority for Health (HAS), ICS are prescribed as soon as preschool wheeze is classified as persistent (i.e. diurnal symptoms 1–2 days per week and/or nocturnal symptoms 1–2 nights per month and/or impact on activities, and/or at least 2 exacerbations per year). Early-onset asthma treatment follows similar recommendations (*J Pédiatrie Puériculture.*, 2009). Our finding of a stronger association between DCP exposure and wheeze ever treated with ICS may thus be suggestive of an association with persistent wheezing symptoms, possibly leading to asthma, though follow-up data will be needed to address this question. Stratified analyses also revealed a marked association between DCP score and wheeze ever treated with ICS only for children younger than 24 months old, suggesting that early exposure windows might affect risk. To date, one study has focused on DCP exposure in relation to asthma in young children, while many others have focused on wheezing symptoms (Casas et al., 2023; Parks et al., 2020).

Parks et al. previously investigated interaction by sex involving the association between DCP exposure in the domestic environment and early childhood wheezing and asthma. Due to sex differences in wheezing and asthma prevalence and evidence of effect modification regarding environmental risks for adult and childhood asthma, it is important to test for interaction by sex, even in the absence of strong hypotheses with mechanistic explanations (Leynaert et al., 2023). Parks et al. found that the odds of developing wheeze and asthma given high DCP exposure at home were higher in female children, although interaction was not found to be significant (Parks et al., 2020). Given results in CRESPI, in which odds of wheeze ever treated with ICS were higher among female children than among male children (although also with non-significant interaction), and no differences or a reverse trend were observed for ever and recurrent wheeze, more research is needed regarding potential sex differences beyond hypothesis-generating interpretations.

A strength of the present analyses within the CRESPI cohort is the comparability with the literature in terms of wheezing prevalence. The prevalence of ever wheeze, at 32.1 % in the CRESPI cohort, is in line with the literature, citing about 35 % prevalence in infants of 18 months (Herr et al., 2012), although in CRESPI it was higher (41.6 %) before March 2020 compared with March 2020 or later (29.9 %). The CRESPI cohort was slightly older than 18 months, composed of children on average just under two years old, which could explain the somewhat higher prevalence of ever wheeze in “normal” circumstances, i.e., before the onset of the Covid-19 pandemic in Europe. In the children from daycares visited March 2020 or later, however, there was a markedly lower wheezing prevalence. This corresponds with a general observation of decreases in other respiratory illnesses among children in the first two years of the pandemic due to interventions such as social distancing and lockdowns (Ulrich et al., 2021; Trenholme et al., 2020; Ye and

Wang, 2022). Although comparison between questionnaire-based wheezing outcomes and data from children's health booklets was limited to a small subsample of children and may not be considered as a true validation study, it suggested high specificity for questionnaire-based definitions, and "wheeze ever treated with ICS" was the outcome for which the best specificity/sensitivity balance was found. While three outcomes were considered in analyses, we did not correct for multiple testing, since these outcomes were not independent and the research question remained the same.

Furthermore, the manner of exposure data collection, with a barcode-based smartphone app, is another strength of CRESPI. Often, questionnaires are used to assess exposure to DCP in epidemiological studies, introducing the potential for recall bias and the possibility of both non-differential and differential exposure misclassification. Utilization of a barcode-based app to measure exposure to DCP has been hypothesized to overcome several limitations of questionnaire-based exposure assessment, such as poor recall of products used and little knowledge of DCP chemical composition. Therefore, barcode-based methods are thought to result in more accurate exposure data collected (Lemire et al., 2022, 2021), although a formal validation of this assessment method is not possible due to lack of a gold standard. With CRESPI's study design, products used in daycares were scanned or manually input, and frequencies of use were reported by personnel via the app-integrated questionnaire. Given that daycare personnel, and not parents, reported DCP frequency of use, differential misclassification of exposure by child respiratory health status was presumably limited. Since parents were not aware of the specifics of daycare DCP use, differential misclassification of the outcome by exposure status was probably limited. In addition, that 79.2 % of daycares reported doing the main cleaning tasks during the daytime, including in the presence of children for some, indicates that for most children, data on DCP product use likely represents child exposure to associated chemicals. However, the presence of reporting bias, by both parents and daycare staff, cannot be excluded, and exact irritant concentrations contained in the products are not known.

Another strength of this study is that the main results were also consistent after examining several building characteristics, such as visible mold and type of mechanical ventilation system. Exhaust-only mechanical ventilation systems are based on passive air supply inlets in the window frames combined with mechanical exhaust outlets, while balanced ventilation systems mechanically provide fresh air from the outside (i.e. filtered) in addition to mechanical exhaust outlets (Ramalho et al., 2013). Associations between exposure score and child wheeze remained only for daycares with exhaust-only mechanical ventilation systems, suggesting a potential role of mechanical ventilation in modifying exposure to DCP chemicals, and more specifically a beneficial role of balanced mechanical ventilation systems, though the interaction was close to significance only for wheeze ever treated with ICS.

Despite the use of GEE models to take into account potentially influential differences between daycares, it is possible that some residual confounding remains. To address this, we first conducted a sensitivity analysis in which we restricted the population to those children from daycares with 15 children included in the CRESPI cohort. In this way, we minimized the possibility that results would be highly influenced by a small number of daycares with many recruited children but atypical DCP use profiles. Results similar to those in the overall analyses indicated that this was likely not the case. To consider the possibility of residual confounding, we calculated the E-value, defined as the minimum strength of association that an unmeasured confounder would need to have with both the exposure and outcome to fully explain away a specific exposure-outcome association, conditional on the measured covariates (VanderWeele and Ding, 2017). For the exposure of above- versus below-median DCP use score, the E-value for the association with wheeze ever treated with ICS is 2.83. The observed odds ratio could therefore be explained away by an unmeasured confounder associated with both daycare DCP use score and child wheeze ever treated with ICS

by 2.83-fold each, above and beyond the considered confounders, but weaker confounding could not do so.

While a strength of the CRESPI study is the inclusion of a relatively large number of daycares as well as children, it must be noted that there are a number of factors which imply that the results from the CRESPI cohort may not be generalizable to all populations of children in daycare settings, whether in France or elsewhere. The participation rate of families was somewhat low, at 9.5 % (Le Moual et al., 2023), but remains similar to the participation rate in recent, well-known population-based cohorts such as Constances in France (~7 %) (Goldberg et al., 2017). A slightly higher participation rate (21 %) was achieved in the French Sepages mother-child cohort where families were invited during a medical examination (Lyon-Caen et al., 2019). While all epidemiological studies face the issue of low participation, the question of selection bias is a central concern when discussing results. In the present study, while daycares, chosen at random, were contacted progressively until sufficient numbers were reached, daycares that agreed to participate may have differed from daycares that did not. Indeed, daycares included in CRESPI were found to be more frequently situated in less socioeconomically advantaged areas compared with daycares which refused to participate. However, daycares in less socioeconomically advantaged areas had lower participation rates of families. In addition, parents completing the questionnaires were on average highly educated, most with at least five years of further study after high school. Taken together, this indicates that families participating in CRESPI may still be of a higher socioeconomic position than the general population. However, it is unlikely that a selection bias strongly impacted our findings. This is due to the nature of exposure considered in terms of daycare DCP use instead of as individual family household use, and because we did not find any association between the daycare area-level deprivation index and DCP use score.

A central limitation of the data collection for CRESPI was its timing relative to Covid-19. Unfortunately, just as the study was getting started, the Covid-19 pandemic took a turn for the worse, and lockdown measures were implemented in France (L'Obs, 2023). This put CRESPI on pause, and daycare visits were tentatively restarted in the summer of 2020, before picking up again in November of the same year (Le Moual et al., 2023). Recruitment of participants may also have been impacted, as Covid-19 took a toll on the mental loads of people the world over (Delaney et al., 2023). This perhaps made voluntary participation in an epidemiological cohort study a low priority for parents of young children. In any case, a lack of power due to lower than hoped-for numbers of participants is something to be considered in the interpretation of results from CRESPI inclusion data.

Due to the delicate balance between the prevention of respiratory infections on one hand and the mitigation of exposures to indoor air pollutants on the other, strategies for cleaning and disinfecting in non-medical group settings such as daycares must be developed and advocated. One approach for decreasing related risks is that of targeted hygiene, a term developed by Rook and Bloomfield as a clarification of the so-called hygiene hypothesis (Rook and Bloomfield, 2021; Bloomfield et al., 2016) and perhaps better thought of today within the context of One Health (Kelly et al., 2022). That is to say, a certain level of cleanliness involving lowering the concentrations of allergens and pathogens people are exposed to indoors should be compatible with cultivating a biodiverse environment which promotes the exchange of beneficial commensal microbes. Such a strategy would limit the use of chemical agents, shown to be airway irritants or sensitizers (Casas et al., 2023). Moreover, DCP use may not only indicate exposure to chemicals, but also exposure to a disinfected environment, inducing a modification of the environmental microbiome. In line with this, a precautionary approach to DCP use could minimize microbial environment disruption and be respiratory-health promoting in all populations, including in children.

CRediT authorship contribution statement

Franziska Bright: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Emilie Pacheco Da Silva:** Writing – review & editing, Validation, Data curation. **Flore Amat:** Writing – review & editing, Validation, Methodology, Conceptualization. **Pierre Bonnet:** Writing – review & editing, Validation, Project administration, Data curation. **Anastasia Eworo Nchama:** Writing – review & editing, Validation, Project administration, Data curation. **Etienne Sévin:** Writing – review & editing, Validation, Resources, Methodology. **Valérie Siroux:** Writing – review & editing, Validation, Methodology. **Corinne Mandin:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Nicole Le Moual:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Orianne Dumas:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2024.178016>.

Data availability

The authors do not have permission to share data.

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