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Use of household cleaning products, exhaled nitric oxide and lung function in children

To the Editor:

The application of domestic cleaning agents increases the risk of asthma and respiratory symptoms in adults [1], in particular when products are applied in spray form [2]. Despite the associations observed in adults, the potential effects of passive exposure on children's respiratory health have not been extensively explored. Analyses of data from birth cohorts have suggested that frequent use of cleaning agents and their use in spray form increased the risk of wheezing and lower respiratory tract infections (LRTIs) during the first year of life [3, 4] and the risk of persistent wheezing at school age [5, 6]. By contrast, a cross-sectional study reported protective effects of using bleach at home on the prevalence of asthma and allergic sensitisation at school age [7]. Our study investigates the effects of the use of 10 common cleaning products on exhaled nitric oxide fraction (F_{ENO}) and on lung function (forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1)) during childhood in a population-based birth cohort in Menorca, Spain [8].

Recruitment was performed during pregnancy and 482 children were enrolled at birth. Written informed consent was obtained from all participants and the study was approved by a committee on ethical practice. Questionnaires on wheezing, asthma, treatment and allergies (rhinitis, eczema or hay fever) were administered by the mother repeatedly from birth until the age of 10 years. At the age of 10–13 years, F_{ENO} (NIOX MINO; Aerocrine AB, Solna, Sweden) and forced spirometry (EasyOne; ndd Medical Technologies, Inc., Andover, MA, USA) testing was carried out. In addition, an interviewer-led questionnaire on the frequency of use of 10 different cleaning products (bleach, ammonia, polishes or waxes, acids, solvents, furniture sprays, glass cleaning sprays, degreasing sprays, air freshening sprays, and air freshening plug-in devices) was carried out. A total of 295 individuals completed the 10-year follow-up visit and the cleaning products questionnaire and performed the F_{ENO} and/or the lung function test.

For statistical analyses, we computed a combined spray variable incorporating the four sprays (furniture, glass cleaning, degreasing and air freshening sprays) and a semiquantitative total score for cleaning product use. The means of the reported days of use per week (never=0, <1 day per week=0.5, 1–3 days per week=2 and 4–7 days per week=5.5) for each product were summed providing a score ranging from 0 (no exposure) to 55 (exposed to all 10 products used 4–7 days per week). Multivariable linear regression models were developed to predict log-transformed F_{ENO} concentration and non-transformed levels of FVC and FEV_1. Models were adjusted for sex, age, maternal education, parental smoking indoors, asthma medication, season of respiratory test measurement, and for height and weight for lung function measurements only. The coefficients obtained from the log-transformed F_{ENO} models were back-transformed

TABLE 1 Weekly use of cleaning products and adjusted[#] associations with exhaled nitric oxide fraction (F_{ENO}), forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1)

Cleaning product[¶]	n (%)	F_{ENO} ppb GM ratio (95% CI)	FVC mL β (95% CI)	FEV_1 mL β (95% CI)
Bleach	197 (67)	1.05 (0.86 to 1.29)	3 (-94 to 99)	44 (-33 to 120)
Ammonia	46 (16)	0.86 (0.66 to 1.12)	3 (-127 to 133)	-28 (-131 to 76)
Polishes or waxes (for floor or furniture)	69 (24)	0.86 (0.68 to 1.08)	-100 (-210 to 9)	-30 (-118 to 57)
Acids, including decalcifiers and liquid scale removers	44 (15)	1.17 (0.89 to 1.55)	-77 (-208 to 54)	-78 (-183 to 26)
Solvents, including stain removers	52 (18)	1.10 (0.86 to 1.42)	-115 (-236 to 5)	-47 (-143 to 50)
Spray[+]	209 (73)	1.44 (1.15 to 1.79)	22 (-84 to 128)	-33 (-117 to 51)
Furniture sprays	104 (36)	1.26 (1.03 to 1.54)	27 (-71 to 125)	-49 (-128 to 29)
Glass cleaning sprays (for windows or mirrors)	138 (48)	1.16 (0.95 to 1.41)	-1 (-95 to 93)	-27 (-101 to 48)
Degreasing sprays, including oven cleaning sprays	81 (28.3)	1.10 (0.88 to 1.37)	-35 (-141 to 70)	-22 (-106 to 62)
Air freshening sprays	57 (19.6)	1.21 (0.95 to 1.53)	-56 (-170 to 58)	-101 (-191 to -10)
Plug-in or other electric air freshening devices	75 (25.4)	1.01 (0.82 to 1.25)	2 (-101 to 105)	-40 (-121 to 42)
Score of days per week of product use[§]	8 (5.5–12)	1.08 (0.95 to 1.23)	-37 (-99 to 26)	-27 (-77 to 23)

GM: geometric mean. [#]: adjusted for sex, age, asthma medication, season of respiratory measurement, maternal education and parental smoking. FVC and FEV_1 models were additionally adjusted for height and weight. [¶]: used at least 1 day per week. [+]: includes furniture, glass cleaning, degreasing and air freshening sprays. [§]: the second column shows the median (interquartile range), the third to the fifth columns show the change in F_{ENO}, FVC and FEV_1 per interquartile range increase of the score (interquartile range=6.5 days of product use per week).

to obtain geometric mean ratios. Potential effect modification of the associations by children's lifetime wheezing, asthma or reported allergies, were evaluated by the p-value for multiplicative interaction.

The geometric mean F_{ENO} was 13.7 ppb and the mean lung function values were 2.9 L and 2.4 L for FVC and FEV_1, respectively. The prevalence of persistent or late onset wheezing was 14%, and any history of asthma or allergies from 4 to 10 years of age were reported as 9% and 36%, respectively. Bleach was the most commonly used product, while sprays were used in almost three-quarters of the homes (table 1). F_{ENO} levels were significantly higher in children exposed to sprays and furniture sprays. The use of air freshening sprays was significantly associated with lower FEV_1. No statistically significant associations were observed between the FVC and any of the cleaning products.

After stratifying the analyses for asthma or allergies, the associations between the use of cleaning products, F_{ENO} and lung function were not consistently different for the two groups of children (data not shown). Cleaning product-related health outcome changes were either higher or lower (p-value for interaction <0.1) in children with asthma or allergies.

Our study suggests that bystander exposure to domestic cleaning sprays may have adverse effects on school-age children's airway inflammation by increasing exhaled nitric oxide. In addition, exposure to air freshening sprays may decrease lung function at school age. Domestic cleaning involves exposure to a large variety of chemicals including both irritant and sensitising agents that can have adverse effect on respiratory health [9]. The use of sprays for domestic cleaning may lead to a higher degree of inhalatory exposure compared with liquid products [2, 10].

Our results are consistent with those reported in infants and children of the younger INMA (INfancia y Medio Ambiente (Environment and Childhood) Project) cohorts, the PARIS (Pollution and Asthma Risk: an Infant Study) and ALSPAC (Avon Longitudinal Study of Parents and Children) cohorts, and with those observed in a Belgian cross-sectional study [3–7]. However, the main findings reported in these studies are mostly based on the associations with reported symptoms or diseases. Our study adds statistically significant associations with objective measurements of airway inflammation and lung function. In line with our findings, the ALSPAC studies [5, 6] showed positive associations between prenatal exposure to a composite score of cleaning products and persistent wheezing at 3 and 7 years of age, and lower spirometric volumes at aged 8.5 years. The INMA and PARIS studies showed an increased risk of wheezing and LRTI in infants exposed to sprays [3, 4], which is consistent with our findings in F_{ENO} at school age. Furthermore, the previous INMA study observed adverse respiratory health effects in infants exposed to air fresheners. Finally, the Belgian cross-sectional study [7] observed a protective effect of using bleach for home cleaning on reporting of asthma and allergic sensitisation in school-aged children. We did not find significant associations between the use of bleach and the respiratory outcomes monitored in this study.

Our cross-sectional study is nested in a longitudinal birth cohort with a long follow-up that includes prospectively collected data, starting at pregnancy and continuing for >10 years. This prospective design provides our cross-sectional analysis with more detailed information on environmental exposures and health outcomes. In addition, our study benefits from the objective measurement of the outcomes. However, we must consider a few limitations when interpreting our results. First, the sample size was relatively small and may have limited the power of our study. Nevertheless, several associations in our study reached statistical significance. Secondly, 35% of the recruited population were excluded because information on the household use of cleaning products and/or on respiratory tests was not available. Nevertheless, the children included were not different from those excluded regarding most characteristics (sex, atopy, asthma, parental asthma and parental smoking at home). However, as anticipated, mothers of participants were more likely to have higher education. Finally, exposure to cleaning products was assessed through parental report. Unfortunately, measurements of indoor volatile organic compounds or home inspections were not performed. Thus, some parents may have over-reported the use of cleaning products or changed their cleaning behaviour according to the asthmatic or atopic status of the parents or the child. Nevertheless, sensitivity analyses suggested that asthma, wheezing, allergy or parental asthma did not modify the observed associations and associations with the objectively measured respiratory health outcomes were apparent in children without asthma or allergic disorders.

In conclusion, the domestic use of household sprays may increase children's airway inflammation and may have adverse effects on lung function. The use of cleaning products in private homes is common and many of these products are applied in a spray formulation. Therefore, our findings may have significant implications for public health. Further investigation is required to obtain a better assessment of exposure and validation of the reported exposure, as well as to identify the underlying pathophysiological mechanisms.

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Use of household cleaning agents including sprays may have adverse effects on respiratory health in school-age children http://ow.ly/nSmWd

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Concurrent coxibs and anti-platelet therapy unmasks aspirin-exacerbated respiratory disease

To the Editor:

Aspirin-exacerbated respiratory disease (AERD) is a clinical tetrad of chronic hypertrophic eosinophilic sinusitis, nasal polyps, asthma and sensitivity to any medication that inhibits cyclooxygenase (COX)-1, namely aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) [1].

The final metabolites of the degradation of arachidonic acid *via* COX-1 pathway are thromboxanes, prostacyclin and prostaglandins (PG); the most crucial ones are PGE_2 and PGD_2. According to the classical ''cyclooxygenase'' hypothesis, inhibition of COX-1, but not COX-2, triggers various mechanisms leading to asthmatic and/or nasal symptoms in AERD patients. The central mechanism was regarded as the deprivation of PGE_2 as a consequence of COX-1 inhibition, which would lead to an even more increased local and systemic generation of cysteinyl leukotrienes (LT). The overproduction of cysteinyl LT, due to upregulation of LTC_4 synthase and/or cysteinyl LT receptors in the airways, the hallmark of the disease, occurs at baseline as well, although at a much lower degree than after aspirin/NSAIDs intake [2].

After the introduction of the selective COX-2 inhibitors, casually referred to as coxibs, several well-designed studies reported the excellent safety profile of these new NSAIDs in patients with AERD [3, 4]. Nevertheless, shortly afterwards, as the use of coxibs extended, so did the number of case reports warning the clinicians that some AERD patients may not tolerate coxibs [5, 6]. In fact, all the position papers and updates on AERD evaluation and management recommend giving the first full dose of these drugs in the physician's office [7].

A recent study by Daham *et al.* [8] proposes a theory that might explain the underlying mechanism. These authors demonstrate that biosynthesis of PGD_2 (bronchoconstrictor and pro-inflammatory mediator) in patients with asthma (of which one-third had AERD), is increased at baseline, catalysed by constitutive COX-1 only, and is not inhibited by a short 3-day treatment with celecoxib. Meanwhile, whole body formation of PGE_2 (bronchodilator and anti-inflammatory) is predominantly COX-2 dependent and decreases progressively, with a reduction of $>50\%$ as compared to baseline, during coxib treatment.

Although none of the AERD patients in this study experienced bronchoconstriction throughout the coxib treatment, COX-2 inhibition definitely had a much lesser impact on the decrease in bronchoconstrictory PGD_2 than on protective PGE_2, thus creating an imbalance in the airway homeostasis, which seems to be generally well tolerated by most AERD patients, except perhaps for the small subset of them who do react to selective COX-2 inhibitors in real life. This minority supposedly includes those AERD patients suffering from a more severe form of the disease [1], and/or associating other pathogenic features, such as a reduced expression of the PGE_2 receptor E-prostanoid-2 on bronchial mucosal leukocytes [9], but the mechanisms underlying coxibs intolerance are not yet completely understood. Of course in real life nonselective COX inhibitors inhibit both COX-1 and -2 in a dose- and potency-dependent fashion, and other mechanisms, such as mast-cell degranulation, are involved, thus inducing reactions in all AERD patients [1, 2].

We herein report on an unusual case of AERD that supports and illustrates this hypothesis. The patient is a 75-year-old male with personal history of hypertension, dyslipidaemia and a stroke in 2001, for which he has been receiving treatment with acetylsalicylic acid (ASA) 100 mg per day. In 2006 he started to complain of perennial nasal congestion and occasional hyposmia, and has been followed up ever since by an ear, nose