Abstract

The prevalence of the asthmatic symptoms among children increases globally over the time. Reduced exposure to pathogens in early childhood and increased exposure to anthropogenic irritants result in increased risk of wheezing in children, and all of this may be related to the usage of household chemicals. Objective of this analysis thus was to study the potential effects of overall exposure to home chemicals in the early life on the phenotypes of wheezing from birth until five years of age. 3,411 mother-infant pairs from the Czech part of the European Longitudinal Study of Pregnancy and Childhood (ELSPAC-CZ) participated in the study. The exposure was estimated by the composite household chemical score from 18 chemical-based products. Social, medical and environmental factors were taken into account as covariates in multivariable multinomial logistic regression using phenotypes of wheezing as a study outcome. We were able to determine the association between several wheezing childhood phenotypes and the frequent usage of household chemicals in the fully adjusted model. Statistically significant odds ratios (OR) for increasing exposures per 1 SD of exposure score were obtained for the intermediate onset transient (OR 1.27, 95% CI 1.10-1.47), intermediated onset persistent (OR 1.23, 95% CI 1.03-1.46), and early onset persistent phenotypes (OR 1.36, 95% CI 1.04-1.77) in comparison to never wheezing children. Moreover, the persistent phenotypes were significantly associated with school age asthma. Our study has shown the negative role of the increased household chemicals usage on the respiratory outcomes in children up to five years of age. Overall evaluation of the household chemical exposure may be useful tool for any large epidemiological studies.

Keywords:

wheezing, household chemicals, asthma, ELSPAC, cohort, children, indoor

Abbreviations:

ELSPAC-CZ - The Czech part of the European Longitudinal Study of Pregnancy and Childhood

ALSPAC – Avon Longitudinal Study of Pregnancy and Childhood

OR – Odds Ratio

PIAMA - Prevention and Incidence of Asthma and Mite Allergy

EFQ - Exposure Frequency Questionnaire

CHCE - Composite Household Chemical score

ETS – Environmental Tobacco Smoke

BMI – Body Mass Index

CI - Confidence Interval

VOCs - Volatile Organic Chemicals

Conflict of Interest

The authors have declared that no competing interests exist.

Introduction

There is a clear ongoing rising trend of the prevalence of asthma and asthma-like symptoms among children over the last three decades (Franklin and Kusel, 2014; Sherriff et al., 2005) ranking asthma among the most common non-communicable diseases in children (GINA, 2017). Asthma is usually considered to result from individuals´ genetic susceptibility and being triggered by environmental exposure. The observed increase in the prevalence of asthma is suggesting that environmental rather than genetic drivers may play the key role in such increase (Franklin and Kusel, 2014), but both need to be studied in connection with different wheezing phenotypes to elucidate the origins of asthma (Savenije et al., 2011; Sherriff et al., 2001). Lasso-Pirot et al. (2015) stated that prevalence of asthma

is more likely to be a combination of the diverse environmental and genetic factors, rather than single exposure.

Several studies have shown that the usage of the household chemicals influences bronchial responsiveness (Becher et al., 1996; Casas et al., 2013; Liu et al., 2016). This phenomenon has been already confirmed in the highly exposed cleaning workers, with increased diagnosis of asthma-like respiratory symptoms (Jaakkola and Jaakkola, 2006; Rosenman, 2006).

Infants spend most of their days indoor in the early childhood. It is thus possible the indoor environment may influence the maturation of the immune and respiratory systems, possibly disturbed and reflected in the development of the chronic diseases such as asthma and other allergic manifestations. The sensitization to indoor-inhaled aero-allergens is believed to be more important than outdoor allergens in relation to asthma (GINA, 2017). To study the potential negative respiratory effects based on the hygiene hypothesis, many confounders must be taken into account together with a long prospective follow-up of the studied outcomes. This has not been evaluated in many studies (Casas et al., 2013). Such research is of importance for characterisation of the indoor anthropogenic environment contamination caused by the elevations of the used household chemicals (Moran et al., 2012).

Wheezing in children is a very heterogeneous condition, therefore not all of wheezing problems are necessarily leading to the clinical presentation of childhood asthma additionally, some asthma cases may be of non-allergic origin (GINA, 2017). It is important to evaluate whether some exposures may trigger reversible irritations or whether they affect the development of chronic respiratory diseases such as asthma. Wheezing phenotypes in childhood are commonly used to evaluate lung function in later life (Duijts et al., 2016; Ernando et al., 1995; Hodgekiss et al., 2016; Matricardi et al., 2008). Thus, studying wheezing phenotypes associations with different exposures may also help with study of asthma.

Household chemicals are a part of the exposome, which should be evaluated towards its potentially negative effects on human health, mainly at critical life stages (Gold et al., 2017). Although

several specific indoor chemical components (such as fomaldehyde, aromatics, benzene, ethybenzene, phtalate esters, benzyl amonium chloride) were found to stimulate the adverse respiratory symptoms (Braun et al., 2013; Mendell, 2007; Nazaroff and Weschler, 2004; Rosenman, 2006; Rumchev et al., 2004), not much is known about the effects of many other substances used in the chemical products. Moreover, when sub-chronic effects leading to asthmatic symptoms cannot be ruled out. Roseman (2006) has summarized that many of the case reports concluded that the health outcomes are related to the working in the exposed area rather than being shortly exposed to the product during application. This may be important when considering the infants, although usually not in the direct contact with household chemicals, but spending lots of the time indoor after application of such products. For several reasons parents of young children could clean toilets and floors almost daily. According to the American Association of Poison Control Centers, personal care products are first and household cleaning products second most frequently involved substance categories in paediatric (<5 years) exposures (Gummin et al., 2017). Not much is known about the role of exposure to household chemicals in development of wheezing, although the increased risk of wheezing during the first year of life associated with indoor exposure to cleaning sprays was reported in the Paris study (Herr et al., 2012).

Using data from the Czech part of the European Longitudinal Study of Pregnancy and Childhood (ELSPAC-CZ), the aim of the present study is to investigate, if the increased usage of the overall household chemicals in the newborns might influence the different wheezing phenotypes of preschool children while accounting for many potential covariates, including the genetic predisposition (the inherited risk), trying to unmask the true relation. We also aim to study which specific phenotypes of wheezing are related to the asthma at school age.

Materials and Methods

Population characteristics

The ELSPAC-CZ is one of seven prospective birth cohort studies initiated by the World Health Organization (WHO) in six European countries. In the Czech Republic, all eligible mothers from Brno and Znojmo in the South Moravian region, who were expected to have a child within period of 16 months were selected as the target study population. More details of the ELSPAC-CZ study and study population can be found in Piler et al. (2016).

Mothers were asked to complete the questionnaires at 6, 18, 36 and 60 months after delivery. Women included in this analytical sample had to have delivered a live baby, responded to the exposure frequency questionnaire (EFQ) at the age of six months, completed the questionnaire on maternal characteristics and answered the questions regarding the wheezing in all studied years. Of a total number of 5,151 mothers willing to participate at the beginning of the study, 3,411 (66.2%) mother-infant pairs were included in this analytical sample population having data from all time points required in this analysis. Population characteristics are summarized in the Table 2 in the Results section.

Wheezing and asthma

In the construction of the wheezing phenotypes we have followed the similar classification as presented in the prospective Tucson Children's Respiratory Study (Taussig et al., 2003) and applied in the other cohort studies such as PIAMA and ALSPAC (Savenije et al., 2011) with respect to the timing of the questionnaires available in the ELSPAC-CZ study. The question construct was the same as in the ALSPAC; asking whether the child had experienced wheezing with whistling on his/her chest during each of the study periods. This question is consistent with that used in the International Study of Asthma and Allergies in Childhood, which has been found to be reliable in large population studies (Jenkins et al., 1996). For the simplicity, we use only "wheezing" in the further text. Six mutually exclusive wheezing phenotypes were constructed; where *never wheezed* stands for no episode of wheezing in the study period; *early onset* for episodes present already at 6 months; *intermediate onset* for the first episodes at 18 months or 36 months; *late* for first episodes at 5 years of age. *Transient*

phenotypes are those without wheezing present at 5 years of age contrary to persistent ones. Paediatricians reports were used to evaluate the presence or absence of the asthma at age of seven years.

Exposure to household chemicals

EFQ filled by mothers at six months of child´s age was a list of 31 various products and materials. Mothers were asked:‘‘During the last several months how often have you used the following?’’ Available responses were: not at all; less than once a week; about once a week; most days; and every day. From the initial list of 31 products and materials included in the questionnaire, 18 chemical-based products relevant for the household chemical exposure were selected (Table 3). Other questions consisted of products and activities like dental amalgams, soldering, plastics and fabrics were not considered as a potential chemical exposure sources for household.

According to the methodology previously used in the ALSPAC study (Henderson et al., 2008) and recently by Liu et al. (2016); a composite household chemical score (CHCE) has been calculated with contribution of each product on the basis of its frequency with scores between 0 for “not at all” and 4 for “every day”. CHCE score could thus ranges between 0-72 with the higher score indicating increased usage of chemical-based products at home. The final CHCE scores were then transformed into z-scores. Similar approaches estimating the exposure to overall household chemicals or specific product categories has been used previously to study the health impacts of this activity (Alderton et al., 2006; Casas et al., 2013; Sherriff et al., 2005; Svanes, 2018; Zock et al., 2007)

Covariates

Selection of covariates used in the analysis was based on literature review and variables previously reported to affect the study outcome were used as covariates in current analysis.

Several variables with yes/no answers were treated as dichotomous in the analysis; these included history of maternal and paternal asthma and allergy, parity (primiparous/multiparous),

caesarean section and child sex. Four variables were categorised; body mass index (five categories according to WHO classification) (WHO, 2016), gestational age (five categories according to the American Congress of Obstetricians and Gynecologists classification) (ACOG, 2013), breastfeeding (none/up to six months/more than six months) and smoking status (smoker during pregnancy/former smoker (quitting smoking before pregnancy)/ non-smoker. Age was treated as a continuous variable.

Maternal marital status was dichotomised into mothers not living with partner and mothers with partner. Maternal education was grouped into three categories according to the highest achieved education level (elementary education/secondary education/university education). Tendency to open windows was dichotomised into often open and often closed windows. Equalised income was based on the so called "OECD-modified scale". This scale, first proposed by Hagenaars et al. (1994), assigns a value of 1 to the household head, 0.5 to each additional adult member and 0.3 to each child. The reported household income is divided by household size estimated by this calculation and the final equalised income is obtained. Crowding was calculated as a ratio of number of people living in the household to the number of rooms (excluding kitchen), and later dichotomised with ratio >1 considered as crowding (Henderson et al., 2001). The environmental tobacco smoke (ETS) variable was based on the question "How many hours per day is the baby in a room where there are people smoking?" Final exposure to ETS was dichotomised as none or any. In the questionnaire, specific questions were asked about severity of dampness and mould in the household. Presence of dampness/mould in the household was then classified as no reported problem/only one of the problems/both problems present. Presence of the pets was recorded with the specific description of various animals. Similar to Paris study (Herr et al., 2012), only furry animals were selected as the relevant exposure in relation to the wheezing and the exposure to furry animals was dichotomised as yes/no.

An atopic rash score of the children was established as a proxy for the risk of atopy at six and 42 months, when mothers were asked if children had a rash in the joints and creases of their body and

whether there was an itchy, dry, oozing or crusted rash on the face, forearm or shins. Rash score introduced by Sheriff et al. (2001) was calculated to represent the atopic risk factor and ranged between 0 (no reported rash) and 2 (at both time points).

Statistical analysis

All statistical analyses were performed using IBM SPSS software (version 24.0.0.1). All p-values were derived from 2-sided statistical tests, and p-values of less than 0.05 were considered statistically significant. Multinominal logistic regression was used to determine the odds ratios. The "never wheeze" phenotype was used as a reference category to all other phenotypes. Missing values were imputed using Markov Chain Monte Carlo full-data imputation (Soley-Bori, 2013) with 20 imputation with 100 iterations, with limitation boundaries for three continuous variables (age (14 to 48), family size (1 to 6), z-score of family equalised income (-2 to 17)). Number of missing values is summarized in the descriptive Table 1. Pearson chi-square goodness of fit was used to determine how well the model fits the data, and likelihood ratio test statistics was used to determine whether the additional variables significantly improve the model compared to the simpler model.

Results

Population characteristics

Number of children belonging to the different phenotypes, are summarized in the Table 1. Most of the children never wheezed within the observed period, but 34% experienced wheezing at some point, with the intermediate onset persistent phenotype being the most abundant (10.3%).

[Please place Table 1 near here]

Mothers were mostly married, between 20-30 years of age; 112 (3.3%) reported wheezing history, 193 (5.7%) smoked during the pregnancy and 110 (3.2%) delivered preterm, and 274 (8.0%)

gave birth by caesarean section. 2,942 Mothers were from Brno and 469 from Znojmo. Sex of the newborn children was almost equally distributed, most of the children were breastfed at least 6 months and up to 10% were exposed to ETS within the first half year.

Mothers excluded from the analysis, were on average one year younger, had lower education, less likely to be married and had lower mean z-score for income (0.14). Other relevant parameters were not statistically significant.

[Please place Table 2 near here]

Household chemicals and wheezing phenotypes

Most frequently reported household chemical products were sprays, such as window cleaners, deodorants and aerosols (including hair sprays) (Table 3). In our study sample CHCE score ranged from 0 to 32. There was one mother with the score 53, who was excluded from further analysis as outlier.

[Please place Table 3 near here]

In the unadjusted multinominal logistic regression almost all phenotypes of wheezing were significantly related to household chemical exposure. In the final model, persistent and intermediate onset transient phenotypes remained significantly different from never-wheezing phenotype, more transient phenotypes became non-significant although still following the same trend. The z-score of the household chemicals span from the -2.05 up to 4.01. The significant odds ratios per unit (standard deviation) increase in z-score for fully adjusted models were obtained for the intermediate onset transient (OR 1.27, 95%CI 1.10-1.47), intermediate onset persistent (OR 1.23, 95%CI 1.03-1.46), and early onset persistent (OR 1.36, 95%CI 1.04-1.77) phenotypes.

[Please place Table 4 near here]

Wheezing phenotypes were then compared with the doctor-diagnosed asthma in the school age. All persistent phenotypes were strong predictors of the asthma with odds ratio ranging from 5.26 to 7.58.

[Please place Table 5 near here]

Discussion

Results of our large longitudinal study suggest statistically significant link between overall usage of the various household chemicals in the early life and different phenotypes of wheezing in preschool children. In addition, it has been shown that the persistent phenotypes of the onset of wheezing were strong predictors of school age asthma.

While the other studies (Casas et al., 2013; Savenije et al., 2011; Sherriff et al., 2005) focused on the exposure in pregnancy, our study has concentrated on the effect of the household chemicals usage within the vulnerable period of the first six months after birth, when the child is presumably spending majority of the time with mother. Therefore, most of the reported usage of the household chemicals in that period might be also related to the newborns exposure to this chemical mixture. Our results support some earlier findings. In the Australian and Swedish studies, significantly higher amount of volatile organic chemicals (VOCs) were found in the homes of the asthmatic children and women compared to the controls (Choi et al., 2010; Rumchev et al., 2004). Such cleaning behaviour may be reflected in the reduction of the exposure to environmental antigens in children with asthma (Henderson et al., 2008). This is in line with the lower risk of asthma at 7 years of age associated with higher exposure to indoor pet- and pest-related allergens in infancy reported by O'Connor (2017). The importance of studying the early-life exposure has also been demonstrated in the pooled analysis of the ETS from eight European cohorts, where ETS exposure in pregnancy and within the first year of life were found to be independent risk factors for childhood wheeze and asthma (Neuman et al., 2012).

We also examined whether the several groups of the chemicals (aerosol-based chemicals, volatile chemicals, bleach) independently have stronger effects on the outcome by repeating the

analysis, but there was no statistical improvement of the results (data not shown). The same was observed when we tried to group the household chemicals by the principle component analysis, which was recently investigated for the 14 household chemicals by Liu et al (2016). Unfortunately, many studies considered only spraying products (Farrow et al., 2003; Herr et al., 2012; Zock et al., 2007) as a relevant products effecting the respiratory system outcomes. This makes the comparison with our study difficult. Generalization of exposure in epidemiological studies may be also justified by similar approach used in studies observing the influence of the particulate matter in the air on the respiratory health, where particulate matter is also a composite of many various chemicals (Sherriff et al., 2005).

Both transient and persistent phenotypes of wheezing were significantly associated with the chemical household exposure of the newborns. There was a higher significance of the CHCE exposure in the persistent and intermediate transient phenotypes, indicating that studied chemical products may act like the irritant of the immature respiratory system leading to both reversible and irreversible bronchial responsiveness. In the transient phenotypes, atopy of children had no significant influence on the outcome contrary to the persistent ones. Association of the chemicals and the transient phenotypes was demonstrated only for the intermediate onset phenotype. We suggest that the CHCE exposure in the early childhood may be one of the trigger factors resulting in the persistent wheezing as well as reversible intermediate onset of the wheezing. It has, however, lower influence on the early onset transient phenotype, where other exposures such as breastfeeding have a large protective effect, and late onset phenotypes, when the immune and respiratory systems are more developed and/or other environmental factors may play an important role (such as attendance of the childcare, outdoor environment or medication) (Tanaka et al., 2007).

We also looked at asthma in similar multinominal regression, but the results were statistically not significant, most likely due to low number of events resulting in low analytical power (data not shown). Household chemical exposure seems to influence the childhood wheeze, but not the manifestation of the asthma itself. Therefore, our results suggest a need for an advice on reducing the

excessive usage of chemical products in the households, at least in the early childhood to avoid wheezing complications in pre-school children. It is worth to mention that a study by Nikmilder et al. (2007) controversially published the opposite association in the households regularly cleaned with chlorine bleach having reduced risk of developing asthma in the children between 10-13 years.

We should consider several methodological issues when interpreting our findings. The limitations of the study are in the self-reported nature of the questionnaire related to the wheezing episodes in children, and in the non-chemical specific evaluation of the household chemical exposure. Although the limitations of the study include the estimation of the household chemical exposure by questionnaire only, we also believe that our results showed that such overall evaluation may be useful tool for any large epidemiologic studies, including the evaluation of the historical cohorts. Additionally, for practical reasons, it may be difficult to measure household chemical exposure in large population-based studies in any other way. Moreover, the chemical-specific studies usually represent only fraction of the compounds emitted from the consumer products. It is worth to mentioned that personal care products may be added in order to include possible exposure to several endocrine disrupting chemicals like phatlates (Guo and Kannan, 2013). The usefulness of the self-reported exposure to household chemicals has been shown in many studies in relation to lung function (Casas et al., 2013; Henderson et al., 2008; Liu et al., 2016; Sherriff et al., 2005; Svanes, 2018; Zock et al., 2007). The major strength of this study is, on the other hand, in its prospective design and in the adjustment for many important covariates, thus reducing the possibility of confounding, and revealing the associations between exposure and studied health outcome. Another advantage of our study is that the school age asthma has been based on medical reports, rather than self-reported.

The follow-up study would benefit greatly from studying the longitudinal effect of the household chemical exposure in relation to the participant's health, and from studying other risk factors especially focused on the indoor exposure of the young children with immature immune and respiratory systems. The Central European region is currently understudied and its closer observation,

especially in the period of its socioeconomic transition in the early nineties, may be helpful to discuss the findings from other countries.

This study is, to our knowledge, the first prospective assessment of the effects of household chemical exposure on respiratory outcomes in the region of Central Europe during period of social, economic and demographic transition, and one of the few studies looking on the role of household chemical exposure within the vulnerable immunological development window in the newborns. In summary, our study has shown the negative influence of the increased household chemicals usage on the respiratory outcomes in children up to five years of age. Household chemical exposure was the most relevant for the persistent and intermediate onset transient wheezing phenotypes. There was no clear effect of a specific products or groups of products, resuming the concept of the multiple exposure to various irritants. This suggests that specific agents should be further studied to reveal pathophysiology of wheezing in children. It also suggests studying the overall contribution of as many products used at home as possible is necessary and its inclusion as a confounder in other studies may be relevant to include in household chemosphere.

Our findings show that mothers should be instructed by paediatricians to avoid excessive use of the household chemicals to prevent or at least reduce infant's respiratory tract irritation.

Acknowledgement

The authors of this study wish to thank the participating families as well as the gynaecologists, paediatricians, school heads and class teachers who took part. Our thanks also go to Dr. Lubomír Kukla, Ph.D., ELSPAC national coordinator 1990–2012, and the entire ELSPAC team. This study was funded by the Ministry of Education, Youth and Sports of the Czech Republic and European Structural and Investment Funds (CETOCOEN PLUS project: CZ.02.1.01/0.0/0.0/15_003/0000469 and the RECETOX research infrastructure: LM2015051 and CZ.02.1.01/0.0/0.0/16_013/0001761).

References

ACOG, 2013. Definition of Term Pregnancy. ACOG Committee Opinion No. 579. Obs. Gynecol 122, 1139–1140.

Alderton, L.E., Spector, L.G., Blair, C.K., Roesler, M., Olshan, A.F., Robison, L.L., Ross, J.A., 2006. Child and maternal household chemical exposure and the risk of acute leukemia in children with Down's syndrome: A report from the children's oncology group. Am. J. Epidemiol. 164, 212–221. https://doi.org/10.1093/aje/kwj203

Becher, R., Hongslo, J.K., Jantunen, M.J., Dybing, E., 1996. Environmental chemicals relevant for respiratory hypersensitivity: the indoor environment. Toxicol. Lett. 86, 155–62.

Braun, J.M., Sathyanarayana, S., Hauser, R., 2013. Phthalate exposure and children's health. Curr. Opin. Pediatr. 25, 247–254. https://doi.org/10.1097/MOP.0b013e32835e1eb6

Casas, L., Zock, J.-P., Torrent, M., García-Esteban, R., Gracia-Lavedan, E., Hyvärinen, A., Sunyer, J., 2013. Use of household cleaning products, exhaled nitric oxide and lung function in children. Eur. Respir. J. 42.

Choi, H., Schmidbauer, N., Sundell, J., Hasselgren, M., Spengler, J., Bornehag, C.G., 2010. Common household chemicals and the allergy risks in pre-school age children. PLoS One 5. https://doi.org/10.1371/journal.pone.0013423

Duijts, L., Granell, R., Sterne, J.A.C., Henderson, A.J., 2016. Childhood wheezing phenotypes influence asthma, lung function and exhaled nitric oxide fraction in adolescence. Eur. Respir. J. 47.

Ernando, F., Artinez, D.M., Nne, A., Right, L.W., Ynn, L., Aussig, M.T., Atharine, C., Olberg, J.H., Arilyn, M., Alonen, H., Ayne, W., Organ, J.M., Roup, G., Ealth, H., Edical, M., Ssociates, A., 1995. Asthma and wheezing in the first six years of life 332.

Farrow, A., Taylor, H., Northstone, K., Golding, J., 2003. Symptoms of Mothers and Infants Related to

Total Volatile Organic Compounds in Household Products. Arch. Environ. Heal. An Int. J. 58, 633–641. https://doi.org/10.3200/AEOH.58.10.633-641

Franklin, P., Kusel, M., 2014. Environmental Contributions to Childhood Asthma. J. Enviromental Immunol. Toxicol. 1, 53–57. https://doi.org/10.7178/jeit.5

GINA, 2017. Global Strategy For Asthma Management and Prevention, Global Initiative for Asthma. https://doi.org/10.1183/09031936.00138707

Gold, D.R., Adamkiewicz, G., Arshad, S.H., Celedón, J.C., Chapman, M.D., Chew, G.L., Cook, D.N., Custovic, A., Gehring, U., Gern, J.E., Johnson, C.C., Kennedy, S., Koutrakis, P., Leaderer, B., Mitchell, H., Litonjua, A.A., Mueller, G.A., O'Connor, G.T., Ownby, D., Phipatanakul, W., Persky, V., Perzanowski, M.S., Ramsey, C.D., Salo, P.M., Schwaninger, J.M., Sordillo, J.E., Spira, A., Suglia, S.F., Togias, A., Zeldin, D.C., Matsui, E.C., 2017. NIAID, NIEHS, NHLBI, and MCAN Workshop Report: The indoor environment and childhood asthma-implications for home environmental intervention in asthma prevention and management. J. Allergy Clin. Immunol. 116, 1058–1063. https://doi.org/10.1016/j.jaci.2017.04.024

Gummin, D.D., Mowry, J.B., Spyker, D.A., Brooks, D.E., Fraser, M.O., Banner, W., 2017. 2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report. Clin. Toxicol. 55, 1072–1252. https://doi.org/10.1080/15563650.2017.1388087

Guo, Y., Kannan, K., 2013. A Survey of Phthalates and Parabens in Personal Care Products from the United States and Its Implications for Human Exposure. Environ. Sci. Technol. 47, 14442–14449. https://doi.org/10.1021/es4042034

Hagenaars, A.J.M., Vos, K. de., Zaidi, M.A., Statistical Office of the European Communities., 1994. Poverty statistics in the late 1980s : research based on micro-data. Office for Official Publications of the European Communities.

Henderson, A.J., Sherriff, A., Northstone, K., Kukla, L., Hruba, D., 2001. Pre- and postnatal parental smoking and wheeze in infancy: cross cultural differences. Avon Study of Parents and Children (ALSPAC) Study Team, European Longitudinal Study of Pregnancy and Childhood (ELSPAC) Co-ordinating Centre. Eur. Respir. J. Off. J. Eur. Soc. Clin. Respir. Physiol. 18, 323–329.

Henderson, J., Sherriff, A., Farrow, A., Ayres, J.G., 2008. Household chemicals, persistent wheezing and lung function: Effect modification by atopy? Eur. Respir. J. 31, 547–554. https://doi.org/10.1183/09031936.00086807

Herr, M., Just, J., Nikasinovic, L., Foucault, C., Marec, A.-M., Giordanella, J.-P., Momas, J.I., 2012. Influence of host and environmental factors on wheezing severity in infants: findings from the PARIS birth cohort. Clin. Exp. Allergy 42, 275–283. https://doi.org/10.1111/j.1365-2222.2011.03933.x

Hodgekiss, C., Arshad, S.H., Roberts, G., Jenkins, E., Kurukulaaratchy, R., 2016. Characterisation of lung function at 18 by early life wheeze phenotype. Eur. Respir. J. 48.

Jaakkola, J.J., Jaakkola, M.S., 2006. Professional cleaning and asthma. Curr. Opin. Allergy Clin. Immunol. 6, 85–90. https://doi.org/10.1097/01.all.0000216849.64828.55

Jenkins, M.A., Clarke, J.R., Carlin, J.B., Robertson, C.F., Hopper, J.L., Dalton, M.F., Holst, D.P., Choi, K., Giles, G.G., 1996. Validation of Questionnaire and Bronchial Hyperresponsiveness against Respiratory Physician Assessment in the Diagnosis of Asthma. Int. J. Epidemiol. 25, 609–616. https://doi.org/10.1093/ije/25.3.609

Lasso-Pirot, A., Delgado-Villalta, S., Spanier, A.J., 2015. Early childhood wheezers: identifying asthma in later life. J. Asthma Allergy 8, 63–73. https://doi.org/10.2147/JAA.S70066

Liu, X., Lao, X.Q., Chiu-Yi Wong, C., Tan, L., Zhang, Z., Wong, T.W., Tse, L., Lau, A.P.S., Yu, I.T.S., 2016. Frequent use of household cleaning products is associated with rhinitis in Chinese children. J.

Allergy Clin. Immunol. 0, 2841–2865. https://doi.org/10.1016/j.jaci.2016.03.038

Matricardi, P.M., Illi, S., Gruber, C., Keil, T., Nickel, R., Wahn, U., Lau, S., 2008. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. Eur. Respir. J. 32, 585–592. https://doi.org/10.1183/09031936.00066307

Mendell, M.J., 2007. Indoor residential chemical emissions as risk factors for respiratory and allergic effects in children: A review. Indoor Air 17, 259–277. https://doi.org/10.1111/j.1600-0668.2007.00478.x

Moran, R.E., Bennett, D.H., Tancredi, D.J., Wu, X.M., Ritz, B., Hertz-Picciotto, I., 2012. Frequency and longitudinal trends of household care product use. Atmos. Environ. 55, 417–424. https://doi.org/10.1016/j.atmosenv.2012.03.021

Nazaroff, W.W., Weschler, C.J., 2004. Cleaning products and air fresheners: Exposure to primary and secondary air pollutants. Atmos. Environ. 38, 2841–2865. https://doi.org/10.1016/j.atmosenv.2004.02.040

Neuman, Å., Hohmann, C., Orsini, N., Pershagen, G., Eller, E., Kjaer, H.F., Gehring, U., Granell, R., Henderson, J., Heinrich, J., Lau, S., Nieuwenhuijsen, M., Sunyer, J., Tischer, C., Torrent, M., Wahn, U., Wijga, A.H., Wickman, M., Keil, T., Bergström, A., ENRIECO Consortium, 2012. Maternal Smoking in Pregnancy and Asthma in Preschool Children. Am. J. Respir. Crit. Care Med. 186, 1037–1043. https://doi.org/10.1164/rccm.201203-0501OC

Nickmilder, M., Carbonnelle, S., Bernard, A., 2007. House cleaning with chlorine bleach and the risks of allergic and respiratory diseases in children. Pediatr. Allergy Immunol. 18, 27–35. https://doi.org/10.1111/j.1399-3038.2006.00487.x

O'Connor, G.T., Lynch, S. V., Bloomberg, G.R., Kattan, M., Wood, R.A., Gergen, P.J., Jaffee, K.F., Calatroni, A., Bacharier, L.B., Beigelman, A., Sandel, M.T., Johnson, C.C., Faruqi, A., Santee, C.,

Fujimura, K.E., Fadrosh, D., Boushey, H., Visness, C.M., Gern, J.E., 2017. Early-life home environment and risk of asthma among inner-city children. J. Allergy Clin. Immunol. 0. https://doi.org/10.1016/j.jaci.2017.06.040

Piler, P., Kandrnal, V., Kukla, L., Andrýsková, L., Švancara, J., Jarkovský, J., Dušek, L., Pikhart, H., Bobák, M., Klánová, J., 2016. Cohort profile: European Longitudinal Study of Pregnancy and Childhood (ELSPAC) in the Czech Republic. Int. J. Epidemiol. https://doi.org/10.1093/ije/dyw091

Rosenman, K.D., 2006. Cleaning Products-Related Asthma. Clin. Pulm. Med. 13, 221–228. https://doi.org/10.1097/01.cpm.0000227253.84652.77

Rumchev, K., Spickett, J., Bulsara, M., Phillips, M., Stick, S., 2004. Association of domestic exposure to volatile organic compounds with asthma in young children. Thorax 59, 746–751. https://doi.org/10.1136/thx.2003.013680

Savenije, O.E., Granell, R., Caudri, D., Koppelman, G.H., Smit, H.A., Wijga, A., de Jongste, J.C., Brunekreef, B., Sterne, J.A., Postma, D.S., Henderson, J., Kerkhof, M., 2011. Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. J. Allergy Clin. Immunol. 127, 1505–1512.e14. https://doi.org/10.1016/j.jaci.2011.02.002

Sherriff, a, Farrow, a, Golding, J., Henderson, J., 2005. Frequent use of chemical household products is associated with persistent wheezing in pre-school age children. Thorax 60, 45–49. https://doi.org/10.1136/thx.2004.021154

Sherriff, a, Peters, T.J., Henderson, J., Strachan, D., 2001. Risk factor associations with wheezing patterns in children followed longitudinally from birth to 3(1/2) years. Int. J. Epidemiol. 30, 1473–1484. https://doi.org/10.1093/IJE/30.6.1473

Soley-Bori, M., 2013. Dealing with missing data: Key assumptions and methods for applied analysis. technical report No.4. Boston.

Svanes, 2018. Cleaning at home and at work in relation to lung function decline and airway obstruction Ø. Am J Respir Crit Care Med. 9, 1157–1163. https://doi.org/https://doi.org/10.1164/rccm.201706-1311OC

Tanaka, K., Miyake, Y., Kiyohara, C., 2007. Environmental factors and allergic disorders. Allergol. Int. 56, 363–96. https://doi.org/10.2332/allergolint.R-07-143

Taussig, L.M., Wright, A.L., Holberg, C.J., Halonen, M., Morgan, W.J., Martinez, F.D., 2003. Tucson children's respiratory study: 1980 to present. J. Allergy Clin. Immunol. 111, 661–675. https://doi.org/10.1067/mai.2003.162

WHO, 2016. Body mass index - BMI [WWW Document]. URL http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi (accessed 1.7.16).

Zock, J.P., Plana, E., Jarvis, D., Antó, J.M., Kromhout, H., Kennedy, S.M., Künzli, N., Villani, S., Olivieri, M., Torén, K., Radon, K., Sunyer, J., Dahlman-Hoglund, A., Norbäck, D., Kogevinas, M., 2007. The use of household cleaning sprays and adult asthma: An international longitudinal study. Am. J. Respir. Crit. Care Med. 176, 735–741. https://doi.org/10.1164/rccm.200612-1793OC

Tables

Table 1. Structure of the wheezing phenotypes in ELSPAC children

	N	Marginal Percentage
Never wheezed	2,251	66.0%
Early onset transient	209	6.1%
Intermediated onset transient	350	10.3%
Early onset persistent	124	3.6%

Intermediate onset persistent	260	7.6%
Late onset wheeze	217	6.4%
Total	3,411	100.0%

Table 2. Maternal and child characteristics and other covariates and their association with CHCE score.

	Mother-child pairs		
	Count	N %	Mean (Standard deviation)
BMI category prior to pregnancy			
18.5-24.9	2,096	61.4%	11.12 (5.13)
<18.5	228	6.7%	10.79 (5.05)
24.9-29.9	284	8.3%	10.71 (5.04)
30+	168	4.9%	10.55 (5.53)
Missing	635	18.6%	11.41 (5.51)
Maternal allergy			
No	2,009	58.9%	10.87 (5.13)
Yes	740	21.7%	11.37 (5.10)
Missing	662	19.4%	12.63 (6.69)
Paternal allergy			
No	1,999	58.9%	11.01 (5.04)
Yes	588	17.2%	10.96 (5.37)
Missing	824	24.2%	9.41 (5.86)
Maternal asthma			
No	2,578	75.6%	11.03 (5.10)
Yes	75	2.2%	11.69 (5.60)
Missing	758	22.2%	10.31 (5.74)
Paternal asthma			
No	2,417	70.9%	11.04 (5.12)

Yes	119	3.5%	10.07 (4.98)
Missing	875	25.7%	10.59 (5.60)
Maternal highest achieved education			
Basic	147	4.3%	10.22 (5.28)
Secondary	2,029	59.5%	11.19 (5.13)
University	585	17.2%	10.60 (5.13)
Missing	650	19.1%	11.42 (5.50)
Smoking in pregnancy			
Non-smoker	1,670	49.0%	10.74 (5.07)
Former smoker	888	26.0%	11.35 (5.27)
Smoker	193	5.7%	11.43 (4.88)
Missing	660	19.3%	11.55 (5.54)
Maritial status			
Married	3,084	90.4%	11.12 (5.19)
Single	278	8.2%	10.71 (5.36)
Missing	49	1.4%	11.47 (5.58)
City			
Brno	2,942	86.3%	11.2 (5.18)
Znojmo	469	13.7%	10.43 (5.39)
Maternal age at delivery			
<20	296	8.7%	10.90 (5.37)
20-24.9	1,324	38.8%	11.50 (5.26)
25-29.9	1,183	34.7%	11.05 (5.18)
30-34.9	424	12.4%	10.35 (5.01)
35+	175	5.1%	10.46 (5.01)

Missing	9	0.3%	9.89 (5.99)
Gestational week			
<37 Preterm	110	3.2%	12.07 (5.52)
37-38 Early term	790	23.2%	11.01 (5.27)
39-40 Full term	1,644	48.2%	11.14 (5.20)
41-42 Late term	432	12.7%	10.76 (5.01)
>42 Post term	364	10.7%	10.91 (5.23)
Missing	71	2.1%	12.20 (5.38)
Cesarian section			
Non-cesarian	3,070	90.0%	11.06 (5.24)
Cesarian	274	8.0%	11.28 (4.87)
Missing	67	2.0%	11.76 (5.17)
Parity			
Primipara	1,049	30.8%	10.88 (5.30)
Multipara	1,727	50.6%	11.1 (5.05)
Missing	635	18.6%	11.41 (5.51)
Sex			
Male	1,716	51.3%	11.11 (5.11)
Female	1,632	48.7%	11.04 (5.33)
Tendency to open windows			
Often open windows	1,524	44.7%	11.11 (5.20)
Often close windows	1,217	35.7%	10.92 (5.00)
Missing	670	19.6%	10.34 (7.32)
Equalised family income			

Below 1,000 CZK	48	1.4%	11.08 (4.22)
1,000-2,500 CZK	782	22.9%	11.36 (5.37)
2,500-5,000 CZK	1,786	52.4%	11.13 (5.14)
Above 5,000 CZK	184	5.4%	11.84 (5.02)
Missing	611	17.9%	10.41 (5.31)
Length of breastfeeding			
Never	671	19.7%	11.00 (5.25)
Some until 6th month	2,282	66.9%	11.27 (5.21)
More than 6 months	440	12.9%	10.41 (5.19)
Missing	18	0.5%	8.67 (2.89)
Rash score for the newborns			
No rash	1,988	58.3%	10.92 (5.17)
One type of rash	824	24.2%	11.16 (5.15)
Both type of rashes	171	5.0%	11.51 (5.05)
Missing	428	12.5%	11.59 (5.56)
Crowding			
No	685	20.1%	11.76 (5.46)
Yes	2,637	77.3%	10.97 (5.13)
Missing	89	2.6%	9.63 (5.16)
Environmental tobacco smoke			
No	3,071	90.0%	10.96 (5.19)
Yes	339	9.9%	12.28 (5.28)
Missing	1	0.0%	16.00 (-)
Presence of furry animals in home			
No furry animals	2,506	73.5%	11.08 (5.14)

Furry animals	848	24.9%	11.14 (5.34)
Missing	57	1.7%	10.96 (6.49)
Dampness or mould in the household			
No problem	2,908	85.3%	11.11 (5.19)
Dampness or mould	184	5.4%	12.09 (5.48)
Dampness and mould	261	7.7%	10.44 (5.13)
Missing	58	1.7%	10.03 (5.52)

Table 3. Percentages of any use of the studied products by study participants.

Product	Reported use (%)
Window cleaner	88.4
Deodorants	82.4
Aerosols (incl. hair sprays)	73.6
Carpet cleaner	54.4
Disinfectant	52.3
Bleach	51.3
Oven and drain cleaners	49.3
Glues	46.8
Paint strippers	46.7
Paint and varnishes	25.8
Air fresheners	25.7
Degreasers and polishers	22.8
Hair colour	21.8
Dry cleaning	14.5
Insecticides	12.4
Turpentine and spirits	11.6
Gasoil	7.9
Herbicides	2.1

Table 4. Odds ratios (95% CI) per unit increase in CHCE z-score in unadjusted and fully adjusted analysis.

Wheezing phenotypes	Unadjusted		Fully adjusted*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Early onset transient	**1.19 (1.03-1.38)**	**0.015**	1.15 (0.95-1.39)	0.144
Intermediate onset transient	**1.20 (1.07-1.34)**	**0.002**	**1.27 (1.10-1.47)**	**0.001**
Early onset persistent	**1.30 (1.09-1.55)**	**0.003**	**1.36 (1.04-1.77)**	**0.022**
Intermediate onset persistent	1.13 (0.99-1.29)	0.061	**1.23 (1.03-1.46)**	**0.025**
Late onset wheeze	**1.21 (1.05-1.39)**	**0.007**	1.11 (0.92-1.35)	0.276

Significant results are marked in bold.* Adjusted for maternal and paternal asthma and allergy, mother age, prepregnacy body mass index of mothers, marital status, maternal education, region, smoking in pregnancy, parity, gestational age, births performed by caesarean section, sex, problems with the dampness and/or mould at household, exposure to ETS, presence of the furry animals at household, length of breastfeeding, rash score, overcrowding, ventialation, and equalised family income.

Table 5. Odds ratios (95% CI) of doctor-diagnosed asthma at 7 years of child age by wheezing phenotypes

Asthma in 7 years	Early onset transient	Intermediate onset transient	Early onset persistent	Intermediate onset persistent	Late onset
OR	0.26	1.63	**5.26**	**7.52**	**7.58**
(95% CI)	(0.04-1.93)	(0.83-3.21)	**(2.63-10.53)**	**(4.63-12.20)**	**(4.57-12.65)**
p-value	0.189	0.154	**<0.001**	**<0.001**	**<0.001**

Significant results are marked in bold.