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Association between Caregiver Exposure to Toxics during Pregnancy and Childhood-onset Asthma: A Case-control Study

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ABSTRACT

The aim of this study was to evaluate the associations between caregiver-reported use of medications, alcohol, cigarette and/or waterpipe (WP), and exposure to pesticides/detergents during pregnancy with childhood-onset asthma.

The study design consisted of a case-control study, conducted between December 2015 and April 2016, recruited 1503 children, aged between 3-16 years old. A questionnaire assessed the sociodemographic characteristics (age, gender, education level of both parents), the family history of asthma, and other known risk factors of asthma (heating system at home, child history of recurrent otitis, humidity in the house, child went to a daycare, smoking and drinking alcohol during pregnancy, exposure to pesticides and detergents).

The multivariate analysis showed that children living in North and South Lebanon and the children living in areas where pesticides are frequently used had an increased risk of asthma (ORa=1.625, CI 1.034-2.554, p=0.035, ORa=13.65, CI 3.698-50.385; p<0.001 and ORa=3.307, CI 1.848-5.918, p<0.001 respectively). Smoking WP during pregnancy and cigarette during lactation would increase the risk of asthma in children (ORa=6.11; CI 1.244-30.008; p=0.026 and ORa=3.44; CI 1.024-11.554; p=0.046 respectively).

We conclude that asthma may originate from the environmental exposure to toxics such as pesticides and tobacco (cigarettes and WP) or to alcohol and prescribed medications during pregnancy and lactation. Spreading awareness by health professionals about these preventable causes can help educate the parents and children to prevent asthma and its exacerbation.

Keywords: Asthma; Children; Cigarette smoking; Environmental exposure; Lebanon; Pesticides; Pregnancy; Waterpipe smoking

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INTRODUCTION

Many risk factors are linked to asthma in children, including familial history of asthma in one or both of the parents, smoking, exposure to pesticides and use of medications during pregnancy. The effect of parents' smoking, either in early life (pregnancy)[1-3] or active smoking,[4] on children is a well-established trigger to express childhood-onset asthma. There is convincing evidence that maternal smoking during pregnancy and breastfeeding, leading to in utero and perinatal exposures to environmental tobacco smoke, are associated with increased risk of asthma.[3] In Lebanon, similar results were shown in a post-hoc analysis, where passive exposure to mother's smoke from cigarettes and from waterpipe was associated with asthma and allergic diseases in children.[5] On the other hand, the role of alcohol consumption during pregnancy in triggering asthmatic responses in the child at birth has not been well described. One study showed that approximately one third of asthmatic outpatients reported a worsening of asthma symptoms after alcohol consumption.[6] Another study showed that alcoholic drinks, and particularly wines, appear to be important triggers for asthmatic responses, possibly attributable to the sensitivity to the sulfite additives[7] and yeast in wines.[8]

Children of parents working with pesticides may be exposed from occupational sources (storing working equipment in the house, contamination of clothes).[9-12] Residing near pesticide treated areas or in agricultural regions, or having home and yard treated with pesticides also contribute to children exposure.[11-15] Direct indoor application of pesticides contaminates the house and exposes its occupants to volatile ingredients and residues. Salameh et al also found that exposure to pesticides was associated with chronic respiratory symptoms and asthma in children.[16] Domestic use of cleaning products, in particular, those in spray form, has been also suggested as a risk factor for asthma.[17,18]

Moreover, an association has been found between in utero exposures to several xenobiotics and increased risk of asthma. The literature is replete with evidence of a relationship between prescribed medications' intake by the mother during pregnancy and asthma in children.[19-21]

While we know that exposures to toxics are common during pregnancy among Lebanese women,[22] in utero and young childhood exposures to these toxics have not been fully assessed in Lebanon. A previous pilot study revealed that waterpipe, smoking and alcohol intake during pregnancy, recurrent otitis and humidity at home seem to be significantly correlated with asthma in children.[23] Although composition details may differ by culture, tobacco waterpipes most often seen in Lebanon have a fired-clay head, metal body, glass or acrylic water bowl, and leather or plastic hose. The bowl is partially filled with water and the head is filled with moistened tobacco upon which a lit piece of charcoal is placed (tobacco and charcoal are often separated by perforated aluminum foil). The smoker inhales through the hose, thus drawing air over the burning charcoal, heating the tobacco, and producing smoke that travels through the body of the waterpipe, the water, and the hose to the user. The objective of this study is to evaluate the associations between caregiver-reported use of medications, alcohol, cigarette and/or waterpipe, and exposure to pesticides/detergents during pregnancy and childhood-onset asthma, hoping that our results will help set up educational and awareness programs to protect our children.

MATERIALS AND METHODS

Ethical Aspect

The Institutional Review Board of the University Faculty of Pharmacy waived the need for an approval based on the facts that it was an observational study that respected participants' autonomy and confidentiality and induced minimal harm to them.

Study Design

This case-control study was conducted between December 2015 and April 2016. In addition to cases (asthmatic) and controls (healthy), a third group of participants (undiagnosed/ probable asthma) was defined as the presence of respiratory symptoms (wheezing, cough, excess bronchial secretions, respiratory distress), but without a physician diagnosis of asthma.

Participants' Characteristics

Controls were chosen using a sample of healthy Lebanese students, from schools in all districts of Lebanon, including children from different socioeconomic levels. Directors of the schools were contacted to take the permission to enter classrooms to distribute the questionnaires. Children were then given the questionnaire to be filled at home by their parents after a parental written informed consent. Classification into a control (healthy child) requires a double absence of a diagnosis of a respiratory disease by a physician and absence of respiratory symptoms (wheezing,

cough, dyspnea).

As for cases, they were taken mainly (85%) from a specialized center for the treatment of asthma in children, which provides free services to children with respiratory diseases from all areas of the country. Children came to the center either as new patients or for follow-up visits on their asthma symptoms, and not for any other reason. After the administration's approval, the questionnaire was distributed in the Asthma Center to asthmatic children's parents after a written informed consent was obtained. Classification into the diagnosed asthma group was defined as the child having asthma-related symptoms (chronic wheezing, cough, and dyspnea), as well as an affirmative answer to the question "Have your doctor ever told you that your child has asthma?". We note that some asthmatic children encountered in schools and fullfilling the case criteria were also enrolled in the study as cases (15%); this allowed an increase in the sample size and the power of the study.

A third group of participants that had a state of "probable asthma" was suggested for children in schools, having chornic respiratory symptoms but no physician confirmation of asthma diagnosis. They were neither cases nor controls. "Probable asthma" was thus defined as the presence of one of the following symptoms: a recurrent wheezing during the day, the evening, the night, the whole day or at exercise, a recurrent cough during the day, the evening, the night, the whole day or at exercise, a history of more than one dyspnea plus wheezing episode treated by a doctor.

Children with diagnosed asthma and those with probable asthma constituted the mixed group of children with "respiratory problem". Finally, no matching was done for cases and controls regarding any variable.

Questionnaire and Variables

A self-administered questionnaire adapted to local Arabic language (the native language of the country) from the standardized and validated American Thoracic Society chronic respiratory disease questionnaire, was used.[24] The same conditions were applied for questionnaires for all participants, to evaluate the diagnosis of asthma and respiratory symptoms. The standardized international study of asthma and allergies in childhood (ISAAC) questionnaire was translated into Arabic and back translated into English to ensure the accuracy of questions.[25] Questions regarding wheezing and night cough without having a cold were also taken from the ISAAC questionnaire.[25] More details about the used questionnaire can be found in previous studies.[23,26-28]

This questionnaire assessed the socio-demographic characteristics, including age, gender, region, the number of rooms and the number of persons living in the house, the level of education for both parents, the family history of asthma, and other known risk factors of asthma (i.e. the heating system used at home, child history of recurrent otitis, humidity inside the house defined as molds seen on the house's walls, the presence of pets at home, if the child went to a daycare, breastfeeding).

Questions about smoking or alcohol intake during pregnancy and during breastfeeding, the kind of smoking or alcohol along with the quantity were included, in addition to the use of any prescribed medication during pregnancy or lactation, occupational, regional, local, and domestic pesticides exposures and cleaning products use. For pesticide exposure, information was recorded using the following questions: i.e. ''Have you ever used pesticides in your work?'' ''Have you ever used pesticides out of your work (for house or garden treatment)?'' ''Do you live in a region heavily treated by pesticides?'' ''Do you live in the proximity of a heavily treated field by pesticides?'' along with the duration of exposure during work and the number of times the house or the garden get sprayed by pesticides per week or per year. Active smoking was determined by several questions (i.e. number of daily cigarettes, weekly waterpipes smoked, other nictotine/tobacco use), categorizing subjects in non-smokers or current smokers. Passive smoking will be characterized by the number of smokers at home.

Detergents use was determined by questions about who uses these products at home, the type of detergents and if there is any mixture of these products or not (the use of 2 or more detergents simultaneously). Education level was quantified according to the number of years of studying. Information about the heating system used at home, the presence of an air conditioner and a dehumidifier, the presence of humidity or mold at home as seen on walls, the child's history of recurrent otitis, tonsillectomy, cardiac problems, premature birth, and kindergarten were also recorded.

Sample Size Calculation

Using the Gpower 3.1.9.2 software for the calculation of the minimal sample size needed for our study, with a 1-β=0.8, a proportion $p2$=0.05 (5% reflects the percentage of the mothers that smoked

during pregnancy in the healthy children group) according to the pilot study that was done last year[23] and considering a ratio of 4 controls for every case and an odds ratio OR=2, the results showed that we need 296 cases versus 1184 controls.[29]

Statistical Analysis

Data analysis was performed using SPSS version 23 (IBM, USA). Percentages were shown for qualitative variables, while means and standard deviation were given for quantitative variables.

Two sided statistical tests were used to compare between group percentages and Student's t test for quantitative variables of normal distribution and homogeneous variances. Moreover, two multivariable backward logistic regressions were applied taking healthy children versus asthmatics and healthy children versus those with respiratory symptoms (probable asthma) as the dependent variables respectively; the independent variables taken into the multivariable analysis were those that showed a $p<0.2$ in the bivariate analysis. A $p<0.05$ was considered significant.

RESULTS

Socio demographic and socio economic characteristics

Out of 1680 questionnaires distributed in schools, 1503 (89.46%) were collected back from parents of the children aged between 3-16 years old. There were missing values in our results since not all questions were answered by all parents. The sample included 527 children having respiratory problems (35.1%; 95% CI 32.65-37.48), with 300 having diagnosed asthma (20%; 95% CI 17.937-21.983) and 227 having probable asthma (15.1%; 95% CI 13.29-16.92) respectively.

Table 1 summarizes the sociodemographic and socioeconomic factors. The results showed that our sample included 1,503 children aged 3-16 years (51.6% boys and 48.4% girls). 55.9% of these children had 1 or 2 person(s) living with them. Parents' university education was 35.8% for fathers and 55.1% of the mothers.

Bivariate Analysis

The bivariate analysis results for the factors that might be associated with the respiratory problem are summarized in Table 2. A significantly greater proportion of asthmatic children (37%) as compared to healthy ones (4.2%) had more respiratory infections ($p<0001$), a higher number of smokers at home (46% vs 44.7%, $p=0.019$), played in the dust (26% vs 8.1%, $p<0.001$), had respiratory problems or eczema before the age of 2 years ($p<0.001$ for both variables), had recurrent otitis (35.2% vs 16.7%, $p<0.001$) and heart problems (2.7% vs 0.6%, $p=0.01$), had humidity in the house as seen on the walls (26% vs 11%, $p<0.001$), parental history of eczema ($p=0.001$), asthma ($p<0.001$) or rhinitis ($p<0.001$). A higher proportion of children with respiratory disease (14.5%) as compared to the healthy ones (8.5%) had pets at home ($p=0.021$).

Table 3 summarizes the bivariate analysis performed concerning the exposure of pregnant mothers and infancy to active smoking, alcohol, prescribed medication intake and detergent mixing. Taking any medication during pregnancy ($p<0.001$) or breastfeeding ($p=0.001$), alcohol during lactation ($p=0.028$), presence of a person at home working with pesticides ($p<0.001$), the child living in an area with pesticide use ($p<0.001$), pesticide use in the interior of the house ($p<0.001$) were all significantly associated positively with the asthma status.

Multivariate Analysis

At first, a multivariate analysis was performed taking children with diagnosed asthma as the dependent variable as compared to all other children. This analysis showed that the boys had a significantly higher risk of having asthma by 36.4% (ORa=0.646, CI 0.489-0.854, $p=0.002$); increasing the age of one year significantly increased the risk of asthma in 62.5% (ORa=1.625, CI 1.034-2.554, $p=0.035$); children living in North and South Lebanon had an increased risk of asthma in 62.5% and 13.6 times respectively (ORa=1.625, CI 1.034-2.554, $p=0.035$ and ORa=13.65, CI 3.698-50.385; $p<0.001$; respectively). The fact that the child lives in an area that has frequent use of pesticides increased the risk of asthma significantly by more than 3 times (ORa=3.307, CI 1.848-5.918, $p<0.001$ respectively). Smoking waterpipe by the mother during pregnancy increased the risk of asthma in children 6 times (ORa=6.11; CI 1.244-30.008; $p=0.026$), while cigarette smoking by the mother during lactation increased that risk by more than 3 times (ORa=3.44; CI 1.024-11.554; $p=0.046$) (Table 4).

A second multivariate analysis performed on children with a respiratory problem (probable asthma or diagnosed asthma) as dependent variable and compared to totally healthy children showed that boys

have a significantly higher risk of respiratory disease 23.1% as compared to girls (ORa=0.769, CI 0.613-0.965, *p*=0.023); children living in North and South Lebanon have a significant risk of respiratory disease 61.4% and 6 times respectively (ORa=1.614, CI 1.087-2.396, *p*=0.018 and ORa=6.335, CI 1.778-22.574; *p*=0.004 respectively). Living in an area with a frequent use of pesticides or pesticide in the house significantly increased the risk of respiratory diseases in children 2.5 times and 29.3% respectively (ORa = 2.48; CI 1.459-4.217; *p*=0.001 and ORa=1.293, CI 1.029-1.626, *p*=0.028 respectively). Taking any medicine during pregnancy and the paternal positive smoking status significantly increased the risk of respiratory diseases in children by 69.7% and 26.5% (ORa=1.697, CI 1.206-2.387, *p*=0.002 and ORa=1.265, CI 1.01-1.584; *p*=0.04) respectively (Table 4).

Table 1. Demographic and socioeconomic factors associated with a child's health status (healthy, probable and diagnosed asthma)

Disease status/ Factors	Total number of subjects N=1503 (100%)	Healthy Subjects N=976 (64.9%)	Probable Asthma N=227 (15.1%)	Diagnosed Asthma N=300 (20%)	*p*-value
Age (in years)	9.92 ± 3.34	9.12 ± 3.43	8.83 ± 3.60	8.83 ± 3.60	<0.0001
Age category					<0.0001
3-6 years	331 (22%)	163 (16.8%)	68 (30.2%)	100 (33.8%)	
7-10 years	337 (22.4%)	208 (21.5%)	56 (24.9%)	73 (24.7%)	
11-13 years	640 (42.6%)	459 (47.4%)	80 (35.6%)	101 (34.1%)	
> 14 years	181 (12%)	138 (14.3%)	21 (9.3%)	22 (7.4%)	
Gender					<0.0001
Male	775 (51.6%)	476 (48.8%)	113 (49.8%)	186 (62.4%)	
Female	726 (48.3%)	500 (51.2%)	114 (50.2%)	112 (37.6%)	
District					<0.0001
Beirut	348 (23.3%)	241 (24.7%)	46 (20.3%)	61 (20.4%)	
Mount Lebanon	637 (42.4%)	416 (42.6%)	100 (44.1%)	121 (40.5%)	
North	189 (12.6%)	98 (10%)	33 (14.5%)	58 (19.4%)	
South	25 (1.7%)	4 (0.4%)	0 (0%)	21 (7%)	
Bekaa	303 (20.2%)	217 (22.2%)	48 (21.1%)	38 (12.7%)	
Education father					0.027
Low *	133 (8.8%)	70 (7.2%)	27 (12.1%)	36 (12%)	
Intermediate **	820 (54.6%)	545 (56.3%)	112 (50%)	163 (54.5%)	
High ***	538 (35.8%)	353 (36.5%)	85 (37.9%)	100 (33.4%)	
Education mother					0.012
Low *	89 (5.9%)	49 (5%)	10 (4.4%)	30 (10.1%)	
Intermediate **	577 (38.4%)	383 (39.4%)	81 (35.8%)	113 (38%)	
High ***	828 (55.1%)	539 (55.5%)	135 (59.7%)	154 (51.9%)	
Number of persons per room					0.844
[0-1]	542 (36.3%)	354 (36.5%)	80 (35.6%)	108 (36.4%)	
[1-2]	849 (56.9%)	550 (56.7%)	133 (59.1%)	166 (55.9%)	
More than 2	101 (6.8%)	66 (6.8%)	12 (5.3%)	23 (7.7%)	

* Low level of education: Education for 8 years or less

** Intermediate level of education: Education for more than 8 years but no university degree

*** High level of education: university degree

Table 2. Bivariate analysis for the factors associated with the health status (healthy, probable and diagnosed asthma)

Disease status/ Factors	Total number of subjects N=1503 (100%)	Healthy Subjects N=976 (64.9%)	Probable Asthma N=227 (15.1%)	Diagnosed Asthma N=300 (20%)	*p*-value
Respiratory infections					<0.0001
No	1324 (88.1%)	935 (95.8%)	200 (88.1%)	189 (63%)	
Yes	179 (11.9%)	41 (4.2%)	27 (11.9%)	111 (37%)	
Number of smokers at home					0.019
0	828 (55.1%)	540 (55.3%)	126 (55.5%)	162 (54%)	
1 or more	675 (44.9%)	436 (44.7%)	101 (44.5%)	138 (46%)	
Pets in the house					0.021
No	1358 (90.4%)	893 (91.5%)	194 (85.5%)	271 (90.3%)	
Yes	145 (9.6%)	83 (8.5%)	33 (14.5%)	29 (9.7%)	
Play in dust					<0.0001
No	1318 (87.7%)	897 (91.9%)	199 (87.7%)	222 (74%)	
Yes	185 (12.3%)	79 (8.1%)	28 (12.3%)	78 (26%)	
Play outside					0.032
No	786 (52.3%)	530 (54.3%)	119 (52.4%)	137 (45.7%)	
Yes	717 (47.7%)	446 (45.7%)	108 (47.6%)	163 (54.3%)	
Play on carpet					<0.0001
No	425 (28.3%)	314 (32.2%)	45 (19.8%)	66 (22%)	
Yes	1078 (71.7%)	662 (67.8%)	182 (80.2%)	234 (78%)	
Pulmonary problems forbidding daily activities					<0.0001
No	1351 (89.9%)	962 (98.6%)	197 (86.8%)	192 (64.2%)	
Yes	151 (10.1%)	14 (1.4%)	30 (13.2%)	107 (35.8%)	
Humidifier at home					<0.0001
No	1190 (79.2%)	781 (80%)	158 (69.6%)	251 (83.7%)	
Yes	313 (20.8%)	195 (20%)	69 (30.4%)	49 (16.3%)	
Respiratory problems before 2 years of age					<0.0001
No	1334 (88.8%)	947 (97%)	212 (93.4%)	175 (58.3%)	
Yes	169 (11.2%)	29 (3%)	15 (6.6%)	125 (41.7%)	
Eczema before the age of 2 years ago					<0.0001
No	1404 (93.4%)	933 (95.6%)	210 (92.5%)	261 (87%)	
Yes	99 (6.6%)	43 (4.4%)	17 (7.5%)	39 (13%)	
Recurrent otitis					<0.001
No	1186 (79%)	813 (83.3%)	180 (79.3%)	193 (64.8%)	
Yes	315 (21%)	163 (16.7%)	47 (20%)	105 (35.2%)	
Heart problems					0.01
No	1487 (98.9%)	970 (99.4%)	225 (99.1%)	292 (97.3%)	
Yes	16 (1.1%)	6 (0.6%)	2 (0.9%)	8 (2.7%)	

Premature birth					0.005
No	1400 (93.1%)	922 (94.5%)	211 (93%)	267 (89%)	
Yes	103 (6.9%)	54 (5.5%)	16 (7%)	33 (11%)	
Humidity at home seen on walls					<0.0001
No	1273 (84.7%)	869 (89%)	182 (80.2%)	222 (73%)	
Yes	230 (15.3%)	107 (11%)	45 (19.8%)	78 (26%)	
Child sent to the kindergarten					0.066
No	863 (57.4%)	581 (59.5%)	118 (52%)	164 (57.4%)	
Yes	640 (42.6%)	395 (40.5%)	109 (48%)	136 (45.3%)	
Smoking father					0.099
No	828 (55.5%)	561 (58%)	113 (50.4%)	154 (51.5%)	
Yes	661 (44.3%)	406 (41.9%)	111 (49.6%)	144 (48.2%)	
Parents respiratory problems					<0.0001
No	1327 (88.3%)	892 (91.4%)	208 (91.6%)	227 (75.9%)	
Father	92 (6.1%)	43 (4.4%)	12 (5.3%)	37 (12.4%)	
Mother	67 (4.5%)	33 (3.4%)	7 (3.1%)	27 (9%)	
Parents with rhinitis problems					<0.0001
No	1290 (85.9%)	887 (90.9%)	185 (81.5%)	218 (72.9%)	
Father	94 (6.3%)	49 (5%)	17 (7.5%)	28 (9.4%)	
Mother	87 (5.8%)	24 (2.5%)	18 (7.9%)	45 (15.1%)	
Both	31 (2.1%)	16 (1.6%)	7 (3.1%)	8 (2.7%)	
Parents history of eczema					0.001
No	1268 (84.4%)	852 (87.3%)	179 (78.9%)	237 (79.3%)	
Father	113 (7.5%)	61 (6.3%)	27 (11.9%)	25 (8.4%)	
Mother	84 (5.6%)	42 (4.3%)	16 (7%)	26 (8.7%)	
Both	37 (2.5%)	21 (2.2%)	5 (2.2%)	1 (3.7%)	
Parental asthma history					<0.0001
No	1270 (84.6%)	859 (88%)	201 (88.5%)	210 (70.2%)	
Father	124 (8.3%)	69 (7.1%)	15 (6.6%)	40 (13.4%)	
Mother	70 (4.7%)	28 (2.9%)	7 (3.1%)	35 (11.7%)	
Both	38 (2.5%)	20 (2%)	4 (1.8%)	14 (4.7%)	
Maid at home					0.051
No	1095 (72.9%)	722 (74%)	171 (75.3%)	202 (67.3%)	
Yes	408 (27.1%)	254 (26%)	56 (24.7%)	98 (32.7%)	
Reflux					<0.0001
No	1379 (91.7%)	940 (96.3%)	197 (86.8%)	242 (80.7%)	
Yes	124 (8.3%)	36 (3.7%)	30 (13.2%)	58 (19.3%)	

Table 3. Association between exposure to toxics during pregnancy and infancy and the health status (healthy, probable and diagnosed asthma)

Disease status/ Factors	Total number of subjects N=1503 (100%)	Healthy Subjects N=976 (64.9%)	Probable Asthma N=227 (15.1%)	Diagnosed Asthma N=300 (20%)	*p*-value
Any drug used by the mother during pregnancy					<0.0001
No	1317 (87.7%)	890 (91.2%)	186 (82.7%)	241 (80.3%)	
Yes	184 (12.3%)	86 (8.8%)	39 (17.3%)	59 (19.7%)	
Any drug used by the mother during breastfeeding					0.001
No	1461 (97.2%)	957 (98.1%)	222 (97.8%)	282 (94%)	
Yes	42 (2.8%)	19 (1.9%)	5 (2.2%)	18 (6%)	
Active smoking mother during pregnancy					0.122
No	1433 (95.3%)	938 (96.1%)	215 (94.7%)	280 (93.3%)	
Yes	70 (4.7%)	38 (3.9%)	12 (5.3%)	20 (6.7%)	
Kind of smoking during pregnancy					0.172
Non smoker	1433 (95.3%)	938 (96.1%)	215 (94.7%)	280 (93.3%)	
Cigarette	47 (3.1%)	26 (2.7%)	7 (3.1%)	14 (4.7%)	
Waterpipe	19 (1.3%)	10 (1%)	3 (1.3%)	6 (2%)	
Active smoking mother during breastfeeding					0.289
No	1436 (95.5%)	938 (96.1%)	216 (95.2%)	282 (94%)	
Yes	67 (4.5%)	38 (3.9%)	11 (4.8%)	18 (6%)	
Kind of smoking during breastfeeding					0.212
Non smoker	1436 (95.5%)	938 (96.1%)	216 (95.2%)	282 (94%)	
Cigarette	45 (3%)	25 (2.6%)	5 (2.2%)	15 (5%)	
Waterpipe	19 (1.3%)	11 (1.1%)	5 (2.2%)	3 (1%)	
Alcohol during pregnancy					0.515
No	1469 (97.7%)	957 (98.1%)	221 (97.4%)	291 (97%)	
Yes	34 (2.3%)	19 (1.9%)	6 (2.6%)	9 (3%)	
Alcohol drinking during breastfeeding					0.028
No	1476 (98.2%)	962 (98.6%)	218 (96%)	296 (98.7%)	
Yes	27 (1.8%)	14 (1.4%)	9 (4%)	4 (1.3%)	
Person at home using pesticides					<0.0001
No	1187 (79%)	770 (78.9%)	154 (67.8%)	263 (87.7%)	
Yes	316 (21%)	206 (21.1%)	73 (32.2%)	37 (12.3%)	
Child living in a region with pesticide use					<0.0001
No	1428 (95%)	947 (97%)	215 (94.7%)	266 (88.7%)	
Yes	75 (5%)	29 (3%)	12 (5.3%)	34 (11.3%)	
Child living near a prairie/field treated with pesticides					0.065
No	1247 (83%)	826 (84.6%)	182 (80.2%)	239 (79.7%)	
Yes	256 (17%)	150 (15.4%)	45 (19.8%)	61 (20.3%)	
Pesticides use at home					<0.0001
No	854 (56.8%)	586 (60%)	105 (46.3%)	163 (54.3%)	
Yes	649 (43.2%)	390 (40%)	122 (53.7%)	137 (45.7%)	
Active smoking father					0.099
No	828 (55.5)	561 (58%)	113 (50.4%)	154 (51.5%)	
Yes	661 (44.3%)	406 (41.9%)	111 (49.6%)	144 (48.2%)	
Father smoking kind					0.054
Non smoker	836 (55.6%)	566 (58%)	114 (50.2%)	156 (52%)	
Cigarette	439 (29.2%)	285 (29.2%)	68 (30%)	86 (28.7%)	
Waterpipe	199 (13.2%)	110 (11.3%)	38 (16.7%)	51 (17%)	
Cigarette&waterpipe	27 (1.8%)	14 (1.4%)	6 (2.6%)	7 (2.3%)	
Detergent mixing					0.004
No	1277 (85%)	849 (87%)	190 (83.7%)	238 (79.3%)	
Yes	226 (15%)	127 (13%)	37 (16.3%)	62 (20.7%)	

Table 4. Multivariable analyses of factors associated with probable and diagnosed asthma

Regression 1: Diagnosed asthma versus healthy children at the dependent variable				
Factors	***p*-value**	**ORa**	**Confidence Interval**	
Gender	0.002	0.646	0.489	0.854
Age	0.035	1.625	1.034	2.554
District*				
Mount Lebanon	0.723	1.067	0.747	1.523
North	0.035	1.625	1.034	2.554
South	<0.0001	13.65	3.698	50.385
Bekaa	0.215	0.743	0.466	1.188
Person using pesticides who lives with the child at home	0.001	0.5	0.337	0.744
Child living in a region sprayed with pesticides	<0.0001	3.307	1.848	5.918
Any drug during pregnancy	0.058	1.462	0.988	2.164
Smoking kind during pregnancy**				
Cigarettes	0.785	0.841	0.243	2.911
Waterpipe	0.026	6.11	1.244	30.008
Smoking kind during breastfeeding**				
Cigarettes	0.046	3.44	1.024	11.554
Waterpipe	0.086	0.154	0.018	1.303

* District as compared to Beirut taken as a reference

** Smoking during pregnancy or breastfeeding as compared to non-smoking mothers

Regression 2: Respiratory disease versus healthy children at the dependent variable				
Factors	***p*-value**	**ORa*****	**Confidence Interval**	
Gender*	0.023	0.769	0.613	0.965
Age	<0.0001	0.892	0.86	0.924
District **				
Mount Lebanon	0.326	1.159	0.864	1.556
North	0.018	1.614	1.087	2.396
South	0.004	6.335	1.778	22.574
Bekaa	0.851	1.035	0.722	1.485
Child living in a region sprayed with pesticides	0.014	2.709	1.219	6.020
Pesticides use at home	0.016	1.668	1.100	2.527
Any drug use during pregnancy	0.002	2.242	1.355	3.711
Smoking father (cigarette versus non-smoker)	0.012	1.618	1.114	2.351
Alcohol during breastfeeding	0.007	9.961	1.894	52.384

* Male gender as a reference

** District as compared to Beirut taken as a reference

*** ORa= Adjusted Odds Ratio

DISCUSSION

This is a case-control study carried out on schoolchildren in all districts of the country to assess potential risk factors for asthma, respiratory diseases, and allergy, specifically evaluating the effect of exposure to toxic substances during pregnancy and infancy. This type of study has been done before showing similar results,[16,25] however, the originality of the current study was the findings that WP smoking during pregnancy and cigarette smoking during lactation were both significantly associated with the asthma diagnosis in children.

A child living in an area where pesticides are used was significantly associated with both asthma diagnosis and respiratory diseases. A child living with a person that works with pesticides and/or living in a home where pesticides are used was significantly associated with asthma diagnosis and respiratory diseases respectively. Finally, age and gender were both significantly correlated with asthma diagnosis and respiratory diseases while the use of any prescribed medication during pregnancy and the father smoking cigarettes were both positively correlated with respiratory diseases.

We found that age was significantly associated with asthma or allergy but in significant correlation with probable asthma, in line with the observation made by Porsbjerg et al.[30] Living in South Lebanon was significantly associated with a higher risk of asthma and respiratory diseases as compared to all other districts, probably as a consequence of the bombardments during the war in 2006. This finding is opposite to the observation of Salameh et al who found that living in the capital would predispose the child to more respiratory diseases.[16] However, we cannot exclude the fact that healthy families are more likely to leave conflicted zones than families with diseased members and thus the causal relationship may be inverse. Diagnosis of asthma was more frequently done in males compared to females, similar to the results of Waked and Salameh[31] and as shown previously in the literature that male sex is predominant in asthma population in the first decade.[1,32]

Smoking

Our study did show a correlation between waterpipe smoking during pregnancy, cigarette smoking during breastfeeding and asthma on one hand and cigarette smoking in the father and respiratory diseases in children on another hand. This is the first study conducted in Lebanon that shows a positive correlation between waterpipe smoking during pregnancy and asthma in infancy. This could be explained by the fact that a low number of mothers consumed cigarettes during pregnancy maybe due to its known toxicity, while waterpipe's false conception[22] of safety in the Lebanese population induced a higher consumption, the effect of which was easily detected in our study. However, our results showed prominent effects for waterpipe but no significant results for cigarette smoking: These alarming results are to be confirmed by further larger scale studies. Our results were strengthened by other studies done by Neuman et al[33] and Simons et al,[34] showing an increased risk for preschool wheeze and asthma among children exposed to cigarette smoke by their mothers during pregnancy and breastfeeding as well.

Alcohol

Alcohol consumption during lactation, but not during pregnancy, was significantly correlated with respiratory diseases in children. Our results were not in concordance with the results found by Magnus et al[35] that the low levels of alcohol exposure during pregnancy or lactation observed in the cohort study they conducted were not associated with increased risk of asthma.[35] Few studies assess the exposure to alcohol during pregnancy and breastfeeding and the risk of asthma in children, thus more specific studies would be needed for this purpose.

Pesticides, Detergents, Medication Intake

Occupational exposure to pesticides has been associated with respiratory symptoms and chronic respiratory diseases such as asthma.[36] The general population is also exposed to pesticides by domestic use or accidental exposure. Non-occupational chronic respiratory indoor exposure can result in high annual cumulative doses and thus may aggravate or enhance asthmatic symptoms.[37] Child exposure to pesticides (either at home, or in an area surrounding his house, or by living with a person who works with pesticides) was significantly associated with both asthma and respiratory diseases in our study, similarly to the results of Salameh et al that showed that chronic exposure to pesticides in children was associated with chronic respiratory symptoms and diseases, especially asthma.[16]

On the other hand, domestic use of cleaning products, in particular, those in spray form, has been also suggested as a risk factor for asthma.[17,18] Our results did not show any correlation between asthma and detergent use at home by the mother or the maid in the multivariate analysis in opposite to what Vizcaya et al suggested that cleaning workers with asthma or asthma symptoms are characterized by non-reversible airway obstruction and non-eosinophilic inflammation.[38] We hypothesize that mothers clean their home probably when the child is outside the house to avoid exposure; in this way, children may not be exposed to detergents for a long period of time during their life.

Furthermore, the results of this study did show a significant correlation between the use of prescribed medications during pregnancy with respiratory diseases and tended to significance with diagnosed asthma. This goes in line with many studies showing a positive relationship between prescribed medications intake by the mother during pregnancy and asthma in children.[18-20] Further researches might be needed to show the classes of medications that might be implicated in this disease.

Limitations

Our study has several limitations and strength points. The total sample size is acceptable, withdrawn from all districts in Lebanon and might be representative of the whole population. However, a selection bias is still possible because of the ten percent refusal rate. The questionnaire used in our methodology, including ISAAC one, is similar to that used in other case-control studies, which is necessary for international comparisons. This is a case-control study with retrospective reports, and consequently a low level of evidence, due to the possibility of recall bias; parents might have given us wrong information probably because they do not remember what really happened during the pregnancy period or during the childhood period. The use of a questionnaire in parents may not always be accurate: problems in question understanding, recall deficiency and over or under evaluating symptoms as well as a possible underestimation to toxics exposure may still be possible, which can lead to a possible information bias. The study design can only identify associations and whilst agree that evidence from other studies does implicate maternal smoking during pregnancy and pesticides in asthma causation, the authors cannot infer causation since the cotinine levels were not measured in all children. In addition, smoking mothers may be more prone to take other risky behaviors, or that might have low access to healthier lifestyle (alcohol, medications, pregnancy health controls, diet, etc. The frequency of pesticides use in fields nearby living places could not be measured; the answers obtained are subjective by the parents. We did not differentiate between maternal and paternal pesticides use in pregnancy. We did not take into account the season of birth, as this could have an influence on exposure in pregnancy and thus differ between children. Furthermore, we did not assess if the pre- or the postnatal exposure or both had an influence on asthmatic symptoms. Asthmatics were included from all Lebanon, but healthy controls only recruited in schools; this might cause a bias in the results, as there might be less smoking/pesticides in controls. The amounts of alcohol and smoking during pregnancy and breastfeeding are subjective and could not be measured due to the retrospective nature of this study.

Asthma and related diseases seem to be linked to several risk factors in our population of school children across the country. The origin of asthma may be due to the environmental exposure to pesticides, tobacco (cigarettes and waterpipe), alcohol or prescribed medications during pregnancy and lactation. Spreading awareness by health professionals about these preventable causes can help educate the parents and children to prevent asthma and its exacerbation. Additional larger scale studies are necessary to confirm our results, particularly for waterpipe and alcohol exposures.

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