OBJECTIVE: To investigate parental smoking patterns and their association with wheezing in children.

METHODS: We performed a case-control study that included 105 children between 6 and 23 months of age who were divided into two groups: cases (children with 3 previous episodes of wheezing) and controls (healthy children without wheezing). The children’s exposure to cigarette smoking was estimated using a questionnaire completed by the mothers and by the children’s urinary cotinine levels.

RESULTS: Based on both the questionnaire results and cotinine levels, exposure to cigarette smoking was higher in the households of cases in which the incidence of maternal smoking was significantly higher than that of paternal smoking. Children in this group were more affected by maternal smoking and by the total number of cigarettes smoked inside the house. Additionally, the questionnaire results indicated that the risk of wheezing was dose dependent. The presence of allergic components, such as atopic dermatitis and siblings with allergic rhinitis and asthma, greatly increased the odds ratio when wheezing was associated with cotinine levels.

CONCLUSION: Children exposed to tobacco smoke have an increased risk of developing wheezing syndrome. This risk increases in association with the number of cigarettes smoked inside the house and the presence of other allergic components in the family.

KEYWORDS: Air Pollution; Indoor/Adverse Effects; Bronchial Hyperactivity/Chemically Induced; Cotinine/Analysis; Child; Tobacco Smoke Pollution/Adverse Effects.

INTRODUCTION

Children of smokers have an increased morbidity rate related to respiratory diseases (1). An increased death rate associated with sudden death and respiratory diseases during the neonatal period has been associated with parental cigarette smoking (2).

A number of studies have shown an association between exposure to second-hand smoke (SHS) and pulmonary function in children, especially when the mother is a smoker, although an additional effect has been observed with paternal smoking (3). The occurrence of pulmonary changes during critical phases of intrauterine development, at birth and during the first 2 and 3 years of life may predispose children to developing early asthma. One of the main risk factors in children is fetal or postnatal exposure to cigarette smoke; other factors, such as genetic predisposition, use of mechanical ventilation and viral infections of the lower respiratory tract, also play a role (4).

Most studies aimed at determining the levels of SHS exposure in children have been based on individual self-reporting and questionnaires about smoking habits. Self-reported information on smoking patterns and amounts of tobacco smoking is prone to bias and other limitations, as parents may not be willing to accurately describe their smoking habits (5).

To obtain a better estimate of SHS levels, cotinine, a major metabolite of nicotine, has been used as a biological marker of smoke absorption to strengthen the evidence of exposure to tobacco smoke (5). Bakoula et al. considered urinary cotinine levels higher than 10 ng/mg-cr (mg of creatinine) as the cut-off level for significant nicotine absorption in children, and they found that children exposed to tobacco smoke had a 3.5-times higher risk of presenting respiratory-related morbidities compared with children with lower levels (6). Similar findings were obtained when cotinine levels were used as a biological marker to investigate the effect of tobacco smoking in pregnant active smokers and pregnant passive smokers (7).
A number of studies showing an association between exposure to SHS and an increased incidence of respiratory diseases have been undertaken (8-10). Additional studies are necessary to strengthen this association. Given the broad evidence of the harm that SHS causes to the respiratory tract in children (8,9), an association between wheezing in children and exposure to SHS deserves additional investigation.

SHS constitutes the single most important source of passive smoke exposure in childhood (11). A better understanding of smoking habits and patterns among populations is imperative for developing health education programs for parents and the general population with the aim of reducing passive smoking in children.

In this study, a potential association between exposure to domestic tobacco smoke and the occurrence of wheezing in children in a population in the city of São Paulo, Brazil was investigated.

### MATERIALS AND METHODS

#### Study design and population

This case-control study monitored and examined 105 children between 6 and 23 months of age.

The cases included 59 consecutive outpatient children with wheezing syndrome who were being treated at the Pneumology and Immunopathology Unit of the Instituto da Criança do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (ICR-HCFMUSP) and the Department of Pediatrics of the Hospital Israelita Albert Einstein, located in São Paulo, Brazil. The final number of children included in this group was 57; 2 children were excluded because of interference in the urine.

Wheezing syndrome was defined as having had at least 3 previous wheezing episodes (continuous, high-pitched sound from the chest with coughing and difficulty breathing) (12) between 6 and 24 months of age that required bronchodilator medication (albuterol, fenoterol or terbutaline) (13).

Exclusion criteria for this study were severe chronic diseases involving renal, hepatic or cardiac functions or hydroelectrolytic or major metabolic dysfunctions. The patients were investigated under the pneumology and immunopathology unit guidelines, and those diagnosed with cystic fibrosis, tuberculosis, pulmonary bronchial dysplasia or anatomic defects in their respiratory tract were excluded. None of the cases had a history of prematurity.

The control group consisted of 46 consecutive outpatient children without chronic or acute respiratory disease, wheezing or prescribed bronchodilator drugs, according to the mothers. These children were healthy and were being observed at the Universidade de São Paulo (USP) Primary Care Facility “Centro de Saúde Geraldo de Paula Souza” for routine exams and consultations. Table 1 presents the demographics and characteristics of the children in the 2 groups and their families.

The cases and controls were sampled simultaneously during the study.

The following information about the family and the household habits of each child was collected: the child’s age, gender, weight and height; the child’s weight at birth; the month he or she was included in the study; the age at the first wheezing episode and the number of episodes in the last 6 months; the use of pyrethroid insecticides in the house; the presence of tuberculosis, BCG vaccine, and the Mantoux test; the duration of breast feeding; the patient’s history of atopic dermatitis or the presence of siblings with a history of allergic rhinitis or asthma; the number of people living in the household; and the parents’ education level.

#### Measurements of passive smoking

The exposure to cigarette smoking was estimated using two methods: A self-reported questionnaire answered by the mother and determination of urinary cotinine levels in the children.

The questionnaire inquired about the following information: The existence of smoking in the house; whether the mother, father or any other household member smoked; the number of cigarettes smoked daily inside the house by each smoker and the amount of time the smoker stayed in the house daily; whether the mother smoked during pregnancy; and the average amount of time the baby spent outside the house daily (in daycare or elsewhere).

The major goal of the study (to determine whether children’s exposure to cigarette smoking inside the house could be associated with the presence of wheezing syndrome) was revealed after the questionnaire was completed.

Isolated urine samples were collected during outpatient visits, and the creatinine concentration was measured using the modified Jaffe method (14). The remainder of each sample was kept at -20°C to measure free cotinine levels using mass spectrometer gas chromatography performed in

### Table 1 - Information on the families of children in both groups and their living conditions. No significant difference was found between the groups for any of the variables.

| Number of children | Cases 59 | Controls 46 | p-value* |
|--------------------|----------|-------------|----------|
| Age in months      | 15.1 ± 6.0 | 14.2 ± 5.1  | 0.422    |
| Weight (kg)        | 10.2 ± 2.0 | 10.2 ± 1.7  | 0.918    |
| Height (cm)        | 76.9 ± 7.4 | 77.3 ± 6.6  | 0.527    |
| Mother’s age (years)| 29.3 ± 6.0 | 27.1 ± 6.1  | 0.072    |
| Father’s age (years)| 32.4 ± 8.0 | 29.9 ± 5.6  | 0.073    |
| Number of people per room in the house | 1.79 ± 1.55 | 1.58 ± 2.23 | 0.569    |
| Duration of breast feeding (in months) | 3.8 ± 4.9 | 4.7 ± 3.4 | 0.264    |

SD: standard deviation.

*Student’s t-test.
duplicate (15). Creatinine levels were used to adjust the cotinine levels for urine concentration. The levels of urinary cotinine were expressed in ng/mg of creatinine (ng/mg-cr).

### Statistical analysis
Descriptive measures were compared between the groups using Student’s t-test. To test the associations among the variables analyzed in each group, we used the Pearson independence test. In cases in which the frequencies were lower than 5, the Fisher test was used. A number of multiple logistic regression models were established to control for other variables known to be related to wheezing syndrome. These variables included patient atopic dermatitis (16), family allergic rhinitis and asthma (17) and gender (18).

Informed consent was obtained from the parents before the children were enrolled. This study was approved by the committee on ethics in research of the Department of Pediatrics of the Faculdade de Medicina da USP and the Commissions on Ethical Norms and Regulation of ICR-HCFMUSP and Hospital Israelita Albert Einstein.

### RESULTS
Table 2 compares the children with wheezing syndrome (cases) and controls in terms of their exposure to domestic cigarette smoking by their mother, father or other household members (defined as smoking at home). The presence of cigarette smoking was significantly higher in the homes of cases than in those of the control group, and maternal smoking was also significantly higher in the cases’ homes. In homes in which the father was the only household smoker, the association with wheezing syndrome was lower but still significant ($p=0.015$). When investigating whether an association existed among the number of cigarettes smoked daily, the occurrence inside or outside the house, by the mother, father, or other household member, and the presence of wheezing, we found significant values for all cases (Table 3). The number of cigarettes smoked indoors by the mothers was higher than the number smoked by the fathers. The mean urinary cotinine concentration was significantly higher ($p=0.014$) in the cases (7.34 ng/mg-cr) than in the control group (4.30 ng/mg-cr). Similar numbers were obtained by the Fisher test when cotinine levels were adjusted to creatinine levels that were $\geq 10$ ng/mg-cr in both groups ($p=0.023$, data not shown).

The risk of developing wheezing syndrome according to the total number of cigarettes smoked inside the house is presented in Table 4. Logistic regression was used to control for patient history of atopic dermatitis, siblings’ history of allergic rhinitis and asthma and gender. The values of these

### DISCUSSION
According to the questionnaire results and cotinine levels, exposure to cigarette smoking was higher in the households of cases, and the children in the case group came from houses in which the incidence of maternal smoking was significantly higher than that of paternal smoking. Children in the case group were more affected by maternal smoking and by the total number of cigarettes smoked inside the house compared with the children in the control group. According to the questionnaires, the risk of wheezing was dose dependent.

According to the questionnaires, more smokers were present in the homes of wheezing babies (86.4% vs. 39.1%, $p=0.0001$), and these babies were more likely to experience both maternal ($p=0.00016$) and paternal smoking ($p=0.015$). The number of cigarettes smoked inside these children’s homes was also higher.

The risk of developing wheezing syndrome was dose dependent and increased with the number of cigarettes smoked indoors. Regarding the total number of cigarettes, the chances of wheezing increased when the number smoked was higher 7 (OR = 41.95) compared with fewer than 7 daily cigarettes. The association between wheezing and maternal smoking remained strong, while no association was found between wheezing and paternal smoking, regardless of the number of cigarettes smoked. The association we found between wheezing and household tobacco smoking was stronger than the association found between SHS exposure and the incidence of asthma and disturbances of the lower respiratory tract (16).

Although the fathers consumed more cigarettes than the mothers did, the mothers smoked more cigarettes inside the house than the fathers did. When the mother was not a smoker, the fathers usually did not smoke indoors or smoked less. In a study performed by Blackburn et al. (3), the number of cigarettes the fathers smoked inside the house varied according to whether the mother was also a smoker, in which case the fathers consumed more tobacco indoors. The consumption of cigarettes by mothers in a

### Table 2 - Comparison between cases and controls for exposure to overall household tobacco smoking, maternal smoking and paternal smoking.

|                        | Cases n (%) | Controls n (%) | $p$-value*  |
|------------------------|-------------|----------------|-------------|
| Smoking at home        |             |                |             |
| Yes                    | 51 (86.4)   | 18 (39.1)      | $<0.0001$   |
| No                     | 8 (13.6)    | 28 (60.9)      |             |
| Maternal smoking       |             |                |             |
| Yes                    | 33 (55.9)   | 9 (19.6)       | 0.00016     |
| No                     | 26 (44.1)   | 37 (80.4)      |             |
| Paternal smoking       |             |                |             |
| Yes                    | 31 (52.5)   | 13 (28.9)      | 0.015       |
| No                     | 28 (47.5)   | 32 (71.1)      |             |

* - Pearson’s independence test.
mother-only smoking household did not differ from the consumption of cigarettes in households in which both parents smoked. These findings reveal that although the number of cigarettes the fathers smoked inside the house might be high, the number of cigarettes the mothers smoked indoors continued to be higher.

A reasonable assumption is that the mothers of small children spend more time at home while the fathers are away at work. A significant difference was found between the time mothers and fathers spent at home (p<0.001), which may explain why smoking mothers smoked more cigarettes inside. The children were more affected by maternal smoking. The overall number of cigarettes smoked inside the house, which included maternal smoking and all household members’ smoking, had an effect on the children.

A number of studies have found that cotinine levels in children are dose dependent and increase according to the number of smoking parents (5), the number of smokers in the home, the number of daily cigarettes smoked in the home by both parents (11) and the number of daily cigarettes smoked by all household members inside the house (19,20). In an additional study, urinary cotinine levels could increase by as much as 5 times depending on the number of smoking parents (1 or 2 smokers) (21).

Although there was a trend towards an association between higher concentrations of urinary cotinine and more cigarettes smoked in the house, it was not statistically significant (data not shown). Higher concentrations of urinary cotinine are not necessarily associated with greater damage to the lungs. As noted by Margolis et al., (8) the harm caused by passive smoking is most likely caused by the direct local effects of smoke on the lungs and not by the absorption of nicotine, which is the information that cotinine levels provide. Measures of exposure (the questionnaire) and absorption (urinary cotinine levels) may differ in their association level with the variable being tested.

In the case of asthma, passive smoking is a risk factor that increases the severity and frequency of attacks and the hospitalization rate of asthmatic patients (22). The relationship between the risk of wheezing and exposure to cigarette smoke is not an isolated phenomenon; other factors also play a role. Exposure to cigarette smoke cannot be considered as a causal factor. When the variables affecting this relationship are controlled, a strong association continues to be found between exposure to cigarette smoking and wheezing.

Martinez et al. (17) reported that maternal smoking was a risk factor for transient early wheezing. The children of mothers who smoked during pregnancy had significantly lower pulmonary function compared with the children of mothers who did not smoke. In an additional study, wheezing starting in the first year of life was significantly more common among the children of smoking mothers than those of non-smokers (9). More recently, Lannero et al., using parental questionnaires in a cohort of 4,089 newborn infants followed for 2 years, confirmed that in utero smoking was a risk factor for recurrent wheezing at 2 years of age (23). Carlsten et al., using parental questionnaires and cord cotinine levels, found similar SHS risks for children who had the biomarker and reported third trimester smoking by any family member (24).

Table 3 - The association between wheezing syndrome in children (N = 59) and the total number of cigarettes smoked daily and inside the house by the mother, the father and all household members compared with the control group (N = 46).

| Variable                          | Odds ratio | Confidence interval - 95% | p-value* |
|----------------------------------|------------|---------------------------|----------|
|                                  |            | Lower limit               | Upper limit |      |
| Mother - number of cigarettes smoked daily | 6.0571    | 6.0571                    | 35.2842 | 0.0451 |
| Father - number of cigarettes smoked daily | 4.1411    | 4.1411                    | 23.2474 | 0.1065 |
| Number of cigarettes smoked daily by all household members inside the house | 12.3669 | 12.3669 | 125.1073 | 0.0332 |
| Gender: male                     | 6.8027    | 6.8027                    | 30.7567 | 0.0127 |
| N* of cigarettes smoked inside the house | 6.9838    | 6.9838                    | 28.1998 | 0.0063 |
| 0                                | 32.1524   | 32.1524                   | 176.6086 | 0.0001 |

*Student’s t-test.

Table 4 - The risk of developing wheezing syndrome according to the total number of cigarettes smoked inside the house, the child’s gender and the presence of atopic dermatitis and siblings with allergic rhinitis and asthma.

| Variable                          | Odds ratio | Confidence interval - 95% | p-value |
|----------------------------------|------------|---------------------------|---------|
|                                  |            | Lower limit               | Upper limit |     |
| Atopic dermatitis                | 6.0571    | 6.0571                    | 35.2842 | 0.0451 |
| Allergic rhinitis                | 4.1411    | 4.1411                    | 23.2474 | 0.1065 |
| Siblings with asthma             | 12.3669   | 12.3669                   | 125.1073 | 0.0332 |
| Gender: male                     | 6.8027    | 6.8027                    | 30.7567 | 0.0127 |
| N* of cigarettes smoked inside the house | 6.9838    | 6.9838                    | 28.1998 | 0.0063 |
| 0                                | 32.1524   | 32.1524                   | 176.6086 | 0.0001 |
Table 5 - The risk of developing wheezing syndrome according to urinary cotinine levels adjusted for creatinine levels ≥10 ng/mg-cr, the child’s gender and the presence of atopic dermatitis and siblings with allergic rhinitis and asthma.

| Variable                                | Odds ratio | Lower limit | Upper limit | p-value |
|-----------------------------------------|------------|-------------|-------------|---------|
| Atopic dermatitis                       | 10.3133    | 1.9983      | 53.2239     | 0.0053  |
| Allergic rhinitis                       | 7.4892     | 1.7540      | 31.9789     | 0.0066  |
| Siblings with asthma                    | 3.5290     | 0.6162      | 20.2101     | 0.1564  |
| Gender: male                            | 7.0892     | 1.9495      | 25.7814     | 0.0029  |
| Urinary concentration of cotinine ≥10 ng/mg-cr | 8.1610 | 1.0841      | 61.4365     | 0.0045  |

In our study, atopic dermatitis was significantly more common among wheezing babies (p = 0.004) compared with controls, as was having siblings with asthma (p = 0.0006). The presence of allergic components, such as atopic dermatitis and rhinitis, greatly increased the odds ratio in cases in which wheezing syndrome was associated with urinary cotinine levels. An association between wheezing syndrome and atopic dermatitis has been shown in other cases (25).

Cotinine urinary levels were significantly higher (p = 0.014) in the study group (7.34 ng/mg-cr) than in the control group (4.30 ng/mg-cr). Notably, 11 of 57 wheezing babies presented cotinine levels higher than 10 ng/mg-cr, while 2 normal children presented higher levels of cotinine (p = 0.023). In a study that correlated home indoor SHS levels with passive smokers’ cotinine urinary levels in Seoul, Korea, the cotinine levels differed significantly (p<0.001) among the following variables: no smoking inside the house, smoking on the veranda or outdoors and smoking indoors (26). In an additional study, Wakefield et al. (27) reported that the urinary excretion of nicotine in the children of smoking mothers correlated with the number of cigarettes the mother smoked and her smoking habits and that non-smoking parents were associated with lower levels of nicotine in children. In another study, children from households in which both parents smoked had urinary cotinine levels approximately 17 times higher than those of children from smoking-free homes (28). The association between the increased risk of wheezing syndrome and cotinine levels reported in our study (OR = 8.16) was higher than that reported by other authors investigating a potential association between SHS exposure and asthma in children of different ages (29). Although asthma and wheezing are related, the latter is strongly associated with early pulmonary function, while asthma may develop later (30).

The questionnaire used in this study was an evaluation tool that allowed the children’s cigarette smoke exposure to be quantified. The questionnaire and urinary cotinine measurement had limitations. The number of cigarettes that a parent reports smoking daily may not reflect the child’s actual rate of nicotine absorption. The relationship between parental smoking and children’s nicotine absorption may be affected by a number of factors, including the distance between the child and the smoker, the smoker’s smoking style (how he/she inhales the smoke), the size and type of the room and the air circulation in the environment. The data collected by the questionnaire revealed a stronger association between cigarette smoke exposure and wheezing in the children than between wheezing and urinary cotinine levels.

The measurement of cotinine levels as a method to determine cigarette exposure has limitations. The use of free cotinine is preferable because it correlates better with plasma cotinine than total cotinine does (31). Cotinine has a half-life of approximately 20 hours; thus, urinary levels reflect the absorption that took place in the days prior to the test (32). In this case, a lower-than-usual SHS level in the house might have been reflected in the urinary cotinine levels. The findings obtained from the urinary cotinine levels agreed with those obtained from the questionnaire, except that the questionnaire results indicated that the risk of wheezing was dose dependent and increased with the number of cigarettes smoked inside the house, an effect that was not detected by the urinary cotinine levels.

Children between 6 and 23 months of age were included in this study because children in this age group spend the majority of their time in closed environments at home and are more exposed to household pollutants such as tobacco smoke, one of the main components of environmental air pollution. The children in this age group frequently spend

Table 6 - Urinary cotinine concentration in children adjusted for creatinine levels according to the cigarette smoking habits of the mother and the father, as reported in the questionnaire.

| N of children | Urinary cotinine (ng/mg-cr) | p-value* |
|---------------|----------------------------|----------|
|               | mean ± SD                  |          |
| Smoking at home |                           |          |
| Yes           | 67                        | 6.70 ± 6.97 | 0.14 |
| No            | 36                        | 4.65 ± 6.18 |      |
| Maternal smoking |                         |          |
| Yes           | 40                        | 8.36 ± 8.27 | 0.01 |
| No            | 63                        | 4.47 ± 5.08 |      |
| Paternal smoking |                        |          |
| Yes           | 43                        | 6.72 ± 8.87 | 0.37 |
| No            | 59                        | 5.38 ± 4.70 |      |

* - Student’s t-test.
more time with their mothers than with their fathers, which allowed us to calculate the risk factors caused by the smoking habits of each parent.

As in other studies (18), males predominated in this study group, possibly because boys have diminished airway function (length-adjusted maximal expiratory flow at functional residual capacity) compared with girls (33).

Establishing smoking-free campaigns, legislation and programs requires a profound understanding of the target population’s smoking patterns and the effects that these patterns may have on other people, including the smokers’ friends and families. This study is an attempt to better understand the smoking patterns of a sample of families living in one of the biggest cities in the world (São Paulo) and how this pattern may affect the occurrence of wheezing in children.

Based on questionnaires investigating parental smoking habits and children’s urinary cotinine levels, this study concluded that children exposed to tobacco smoke inside the house have an increased risk of developing wheezing syndrome. This risk is even higher when associated with other factors, principally the number of cigarettes smoked inside the home in a dose-dependent effect and the presence of other allergic components in the family.

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■ AUTHOR CONTRIBUTIONS

Schwartsman C and Farhat SC contributed to the project, data collection, analysis and discussion. Schwartsman S contributed to the project, analysis and discussion. Salduba PH contributed to the project and discussion.

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