

ORIGINAL ARTICLE

Characteristics of Early Transient, Persistent, and Late Onset Wheezers at 9 to 11 Years of Age

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Study objective. To investigate the early determinants and characteristics of different phenotypes of wheeze in children on the basis of questionnaire data, lung function, and prick tests. **Design.** Cross-sectional survey. **Setting.** Rome and Fiumicino municipalities in Lazio region, Italy, within the ISAAC phase II project. **Subjects.** Sample of 2107 9–11 year old schoolchildren (response rate 83.5%). **Results.** We divided children into four mutually exclusive groups according to onset of wheeze: 154 early transient (birth to age 2), 51 persistent (birth to age 2 and current), 66 late onset (current only), and 1,446 control subjects (no early or current wheeze). Logistic regression models have shown that a family history of asthma and allergies is strongly associated with persistent and late onset wheezing; exposure to parental smoking—both during pregnancy and during the child's first year of life—is related to persistent wheezing; all children with wheezing show a significantly greater risk to have current respiratory symptoms other than wheeze compared with control subjects; current allergic rhinoconjunctivitis symptoms and atopy are related with both persistent and late onset wheeze. Multiple linear regression models show that forced expiratory rates at 25% to 75% of vital capacity (FEF_{25–75}) and the ratio between forced expiratory volume in 1 second and forced vital capacity (FEV₁/FVC) are significantly lower both in early transient (−305 mL/s, −1.7%) and persistent (−298 mL/s, −3.2%) wheezers; FEV₁/FVC is significantly reduced in late onset wheezers too (−2.0%). **Conclusions.** The strength of the association of family history and exposure to parental smoking varies with the three wheezing phenotypes. Moreover, early, persistent and late onset wheezers have different clinical characteristics in terms of their respiratory health and atopic status.

Keywords childhood asthma, persistent wheezing, objective measures, lung function, atopy

INTRODUCTION

The interpretation of data regarding risk factors for the development of asthma is complicated by the existence of multiple phenotypes of wheezing during childhood. Martinez and colleagues, studying the natural history of wheezing in the first 6 years of life, were the first to describe three phenotypes of wheezing that they called “early transient, persistent, and late onset wheezing” on the basis of time of onset and persistence of symptoms (1). The authors found that most of the children who had started to wheeze in early life had stopped by school age and did not have increased risk of asthma and allergies by the age of 6 years (1). On the contrary, persistent and late onset wheezers were more likely than children who never wheezed to be atopic at the age of 6; persistent wheezers also had a more compromised respiratory health and diminished lung function values at school age (1). Martinez's results were recently confirmed by a longitudinal study on children receiving follow-up to 10 years of age (2). Early life atopy, recurrent chest infections, in addition to genetic predisposition, were found to be the most important predictors of persistence of wheezing during childhood (3).

In epidemiological studies aimed at investigating the association between history of wheezing and possible risk factors, the importance of considering different wheezing conditions has been well illustrated both in cross-sectional and in longitudinal evaluations on children (4–6). However, until now, only one study has provided a phenotypical classification of childhood wheezing up to age 10 based not only on questionnaire data but also on objective measures of atopy and lung function (2, 3). We aimed to evaluate the association of the three wheeze phenotypes with family history of respiratory disorders and exposure to parental smoking in a cross-sectional study on 9- to 11-year-old schoolchildren. Another purpose was to characterize the different clinical patterns of childhood wheeze through their relation with other respiratory symptoms, lung function, and atopic status.

METHODS

The children under study were enrolled in the Italian section of the second phase of the International Study of Asthma and Allergies in Childhood (ISAAC phase two). In the early 1990s, ISAAC phase one applied a standardized questionnaire to measure the worldwide prevalence of childhood asthma, allergic rhinoconjunctivitis, and atopic eczema (7). On the basis of phase one results (8), ISAAC phase two, started in 1998 in a small number of centers, was specifically designed to investigate the relative importance of different

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etiological hypotheses using clinical tests in addition to questionnaires (9). In Italy, ISAAC phase two was performed on a sample of children selected by stratified sampling (a stratum for each city district) of all primary schools, both public and private, within Rome and Fiumicino municipalities (10). Within each school ($n = 40$), we enrolled all children attending the fifth grade during the 2000–2001 school year ($n = 2, 107$).

Questionnaires

We adopted the ISAAC *core* questionnaire to ascertain lifetime and past year prevalence of asthma, hay fever and eczema and added questions about child's respiratory health and some factors known to be related with asthma and allergies, in particular those that occurred during pregnancy and postnatal period. The additional questions had already been validated during the SIDRIA national study (Italian Studies on Respiratory Diseases in Childhood and the Environment) (11), the Italian section of ISAAC phase one. One or both children's parents or another person responsible for the child's care completed the questionnaire. Children were divided into four mutually exclusive groups on the basis of asthma or wheezing onset and presence of wheezing in the past year (current wheezing), derived from questionnaires: (1) those with asthma or wheezing onset in the first 2 years of life and no current wheezing (early transient wheezers); (2) those with asthma or wheezing onset in the first 2 years of life who still wheezed at the age of 10 (persistent wheezers); (3) those with asthma or wheezing onset from 3 years of age and over who still wheezed at the age of 10 (late onset wheezers); (4) those with no wheezing nor asthma in the first 2 years of life and no current wheezing (control group). Informations about parental medical and smoking history were collected by the questionnaires too. For example, the answer to the question, "Has the child's mother/father ever had chronic bronchitis or emphysema?" related to parental chronic obstructive pulmonary disease (COPD); mother's multiple episodes of lower respiratory tract illnesses in her first 3 years of life was based on the question, "Did the child's mother have more than one episode of asthmatic bronchitis, bronchiolitis, or bronchopneumonia during her first 3 years of life?"

Clinical Tests

The child's parents provided written consent before prick and lung function tests were performed on their child at school. Prick tests were executed according to the ISAAC II protocol to provide an objective measure of atopy (9). We adopted ISAAC II *core* allergen extracts: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat fur, mixed grass pollen, mixed tree pollen, *Alternaria tenuis*, using histamine (10 mg/mL) and a saline solution as positive and negative control subjects, respectively. We also used *Olea* and *Parietaria* species. All extracts and control solutions were obtained from ALK Laboratories (Horsholm, Denmark). After 15 minutes the wheals were outlined and markings transferred with tape to millimeter-squared paper. Wheal size was calculated, with over 3 mm² considered a positive result. Subjects with at least one positive result were considered atopic. Children's height and weight were measured and spirometric tests were performed according to American Thoracic Soci-

ety guidelines (12), using a portable spirometer (Biomedin, Padua, Italy). The spirometric values for the best blow of at least three attempts were analyzed. We recorded forced vital capacity (FVC) (mL), forced expiratory volume in one second, FEV₁ (mL), and forced expiratory rates at 25% to 75% of vital capacity (FEF_{25–75}) (mL/s). The FEV₁/FVC ratio (%) was also calculated.

Statistical Analyses

We evaluated the association of wheezing phenotypes with parental smoking during pregnancy and during the child's first year of life and maternal and paternal history of respiratory and allergic diseases. Current clinical characteristics such as respiratory symptoms other than wheezing (nocturnal dry cough apart from colds, cough, and/or phlegm apart from cold), rhinitis symptoms with itchy-watery eyes, itchy rash, and child's gender and prick tests' results were also considered. Associations of the three wheezing phenotypes with each of the above-mentioned variables were estimated through a multinomial logistic regression analysis (command *mlogit* of STATA), which uses a unique reference group (control group) for the three mutually exclusive outcomes. Results are presented as odds ratios (ORs) and 95% confidence intervals (95%CI). Gender was considered *a priori* as a possible confounder of the association between each exposure variable and wheezing phenotypes. To test the hypothesis that gender is an effect modifier, we analyzed the association between the variables included in the analysis and wheezing separately in boys and girls. To reduce misclassification, the analysis of parental history of asthma and allergies was restricted to questionnaires in which the information on this topic referred to biological parents ($n = 1, 674$ for the mother; $n = 1, 683$ for the father). Missing data considered in the analysis were lower than 5%. To evaluate lung function impairment within each pattern of wheeze at the age of 10, we performed a multiple linear regression of the specific lung function parameters for the three outcomes, controlling for gender, age, height (cm), height-squared (cm²), and body mass index (BMI, kg/m²). The linear regression model for the FEV₁/FVC ratio was adjusted only for gender, age, and BMI. Results are the differences in means (95%CI) in each wheeze phenotype compared to the control group.

All statistical analyses were performed using the statistical package STATA version 7.0 (STATA Corporation, College Station, TX, USA).

RESULTS

A total of 1,760 children had a questionnaire properly filled in by parents (83.5% of the target). The children's mean age was 10.1 years (standard deviation, SD = 0.5). Complete data of child's asthma and wheezing were not available for 43 children, leaving a total of 1,717 children (891 boys and 826 girls) for the present analysis. Of the 1,717 children studied, 154 (9.0%) were classified as early transient wheezers, 51 (3.0%) as persistent wheezers, and 66 (3.8%) as late onset wheezers, whereas 1,446 (84.2%) formed the control group. A total of 1,278 children underwent skin prick tests and lung function tests.

Table 1 illustrates the association of wheezing with gender, parental history of disease and parental smoking. The

TABLE 1.—Association of gender, parental disease history,* and parental smoking* with early transient, persistent, and late onset wheezing* in children. Rome, 2000–2001.

Variables	Control group (n = 1,446) %	Early transient wheezing (n = 154)		Persistent wheezing (n = 51)		Late onset wheezing (n = 66)	
		%	OR (95% CI) [†]	%	OR (95% CI) [†]	%	OR (95% CI) [†]
Gender							
Female	49.2	44.8	0.84 (0.60; 1.17)	45.1	0.85 (0.48; 1.48)	33.3	0.51 (0.31; 0.87)
Paternal disease history [‡]							
Asthma	6.2	11.8	2.04 (1.19; 3.49)	17.6	3.25 (1.53; 6.89)	18.5	3.48 (1.79; 6.78)
Hay fever	16.2	21.0	1.39 (0.91; 2.10)	31.4	2.38 (1.29; 4.37)	27.7	2.01 (1.14; 3.53)
Eczema	4.6	7.9	1.77 (0.93; 3.36)	11.8	2.76 (1.13; 6.70)	7.7	1.70 (0.66; 4.38)
Chronic obstructive pulmonary disease (COPD)	4.9	4.6	0.93 (0.42; 2.01)	5.9	1.21 (0.37; 3.97)	4.6	0.92 (0.28; 3.02)
Maternal disease history [‡]							
Asthma	5.3	8.7	1.69 (0.92; 3.13)	21.6	4.91 (2.42; 9.95)	13.8	2.90 (1.38; 6.10)
Hay fever	17.8	22.7	1.36 (0.90; 2.04)	33.3	2.31 (1.27; 4.21)	29.2	1.93 (1.11; 3.36)
Eczema	9.2	11.3	1.25 (0.73; 2.13)	13.7	1.55 (0.68; 3.52)	9.2	0.97 (0.41; 2.29)
COPD [§]	2.8	0.7	0.24 (0.03; 1.73)	11.8	4.67 (1.88; 11.59)	3.1	1.11 (0.26; 4.72)
Lower respiratory tract illness in the first 3 yrs of life [#]	3.5	6.5	1.94 (0.96; 3.90)	9.8	3.0 (1.15; 7.90)	— ^{&}	— ^{&}
At least one parent's disease history [‡]							
Asthma	11.2	19.1	1.89 (1.22; 2.92)	39.2	5.17 (2.87; 9.29)	30.8	3.62 (2.08; 6.30)
Hay fever	31.0	36.8	1.30 (0.92; 1.85)	58.8	3.20 (1.81; 5.65)	50.8	2.34 (1.42; 3.86)
Eczema	12.8	17.8	1.46 (0.94; 2.28)	25.5	2.32 (1.21; 4.44)	15.4	1.21 (0.60; 2.42)
COPD [§]	7.1	5.3	0.73 (0.35; 1.53)	17.6	2.82 (1.33; 5.96)	7.7	1.10 (0.43; 2.80)
At least one parent's smoking							
During pregnancy	38.2	37.7	0.98 (0.70; 1.39)	60.8	2.53 (1.42; 4.48)	45.4	1.39 (0.84; 2.28)
During child's first years of life	42.8	42.2	0.98 (0.70; 1.37)	62.7	2.258 (1.26; 4.01)	50.0	1.34 (0.81; 2.20)

*Based on questionnaire completed by parents.

[†]All ORs were adjusted for gender.[‡]Prevalences and logistic analysis were restricted to questionnaires, in which the information on "parental disease history" was referred to biological parents (father: control group n = 1,415, early transient wheezers n = 152, persistent wheezers n = 51, late onset wheezers n = 65; mother: control group n = 1,408, early transient wheezers n = 150, persistent wheezers n = 51, late onset wheezers n = 65).[§]Chronic bronchitis or emphysema.[#]More than one episode of asthmatic bronchitis or bronchiolitis or broncho-pneumonia during mother's first 3 years of life.

frequency of all wheezing phenotypes tends to be lower in girls than in boys, but a significantly protective odds ratio (OR = 0.51) was found only for late onset wheeze. Weak and not significant associations were found between both paternal and maternal asthma, hay fever, eczema and COPD, and early transient wheeze; the only exception was paternal asthma with OR = 2.04 that reached statistical significance. Conversely, paternal asthma, hay fever, and eczema as well as maternal asthma, hay fever, COPD, and lower respiratory tract illness in the first years of life were strongly related to persistent wheezing. Paternal and maternal asthma and hay fever were associated with late onset wheeze too. Considering a composite variable—at least one parent's disease history—the greatest ORs were found between parental asthma and persistent (OR = 5.17) and late-onset wheeze (OR = 3.62). No effect modification by gender was seen when the association between parental history and wheeze was evaluated in boys and in girls (data not shown). At least one parent's smoking—both during pregnancy and during child's first year of life—was related only to persistent wheezing (OR = 2.53 and OR = 2.25, respectively).

Table 2 shows the clinical features of the three groups of children with wheeze. All children with wheezing display a significantly greater risk to have current respiratory symptoms other than wheeze (nocturnal dry cough apart from colds, cough, and/or phlegm apart from cold) compared with children who never wheezed, although the associations were strongest for persistent wheezers. Persistent and late onset wheezers were significantly more likely than control subjects to have current allergic rhinoconjunctivitis symptoms (OR = 10.05 and OR = 4.93, respectively) and to be atopic at the time of the survey (OR = 5.68 and OR = 7.93, respec-

tively). Late onset wheezing was significantly associated with a positive reaction to each allergen extract we tested, with strongest ORs for *Dermatophagoides* species and cat fur. No association was found between early transient wheezing and atopy. Persistent wheezers were also significantly more likely than the control group to have current eczema symptoms (OR = 3.65).

The results of the spirometric tests are reported in Table 3. FVC and FEV₁ did not differ between all wheezers and the control subjects, whereas FEF_{25–75} and FEV₁/FVC were significantly reduced both in the early transient wheeze group (–305 mL/s lower than the control group and –1.7% lower than the control group, respectively) and the persistent wheeze group (–298 mL/s lower than the control group and –3.2% lower than the control group, respectively). A statistically significant reduction of FEV₁/FVC was also evident in children with late onset wheezing (–2.0%).

DISCUSSION

We found that family history of respiratory disorders and early exposure to parental smoking are strongly associated with persistent wheezing; family history was related to late onset wheeze too. Lung function and prick tests revealed that children who have experienced early transient, persistent, and late onset wheezing present distinct respiratory and allergic features at 9 to 11 years of age.

Wheezing in the first 2 years of life seems to have a rather benign prognosis. In fact, in our population more than 70% of all children who were reported to have had early wheezing were no longer wheezers by the age of 9 to 11 years. The group of early transient wheezers does not have a strong component related to family history; the concomitance of other

TABLE 2.—Association of current clinical symptoms* and skin prick tests† results with early transient, persistent, and late onset wheezing* in children. Rome, 2000–2001.

Variables	Control group (n = 1,446) %	Early transient wheezing (n = 154)		Persistent wheezing (n = 51)		Late onset wheezing (n = 66)	
		%	OR (95% CI)†	%	OR (95% CI)†	%	OR (95% CI)†
Current respiratory conditions							
Nocturnal dry cough (apart from colds)	14.4	21.4	1.62 (1.07; 2.46)	64.7	10.99 (6.01; 20.10)	45.4	5.11 (3.05; 8.58)
Cough and/or phlegm apart from colds	6.6	16.9	2.74 (1.71; 4.39)	43.1	10.39 (5.72; 18.87)	27.3	4.81 (2.69; 8.62)
Current rhinitis symptoms‡ with itchy-watery eyes	7.2	9.7	1.44 (0.81; 2.55)	39.2	10.05 (5.37; 18.81)	28.8	4.93 (2.77; 8.76)
Current itchy rash§	8.8	9.1	1.06 (0.59; 1.89)	25.5	3.65 (1.89; 7.05)	13.6	1.75 (0.84; 3.64)
Positive skin prick test¶							
Any allergen	28.6	23.6	0.74 (0.47; 1.14)	69.0	5.68 (2.90; 11.15)	76.9	7.93 (4.09; 15.40)
<i>Dermatophagoides</i> species	16.8	15.4	0.87 (0.52; 1.46)	50.0	5.06 (2.69; 9.54)	59.6	6.96 (3.89; 12.47)
Mixed grass pollen	12.9	13.0	0.99 (0.57; 1.72)	21.4	1.83 (0.86; 3.92)	34.6	3.43 (1.88; 6.26)
<i>Olea</i>	10.7	10.6	0.96 (0.52; 1.76)	26.2	2.95 (1.44; 6.04)	26.9	2.91 (1.53; 5.55)
<i>Alternaria tenuis</i>	7.7	4.1	0.49 (0.19; 1.22)	16.7	2.38 (1.02; 5.56)	17.3	2.32 (1.09; 4.96)
cat fur	6.1	8.1	1.36 (0.68; 2.73)	28.6	6.14 (3.00; 12.55)	28.8	6.29 (3.27; 12.10)

*Based on questionnaire completed by parents.

†All ORs were adjusted for gender.

‡Frequent sneezing or a runny or blocked nose apart from common cold or the flu in the past year.

§Itchy rash, on the skin of one or more parts of the body, which appeared and disappeared for at least 6 months, affecting any of the following places in the past year: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the necks, ears, or eyes.

¶Prevalences and logistic analysis were performed only on subjects who underwent skin prick tests (control group n = 1,061, early transient wheezers n = 123, persistent wheezers n = 42, late onset wheezers n = 52).

factors such as early infections may play a more important role. In agreement with cohort studies' results (1, 2, 6), our cross-sectional survey shows that early transient wheeze in 10-year-old children is not related to atopy. However, this group continues to experience respiratory symptoms other than wheeze and has reduced lung function at 9 to 11 years of age, an indication contrary to a recent report on younger children by Lau et al. (13). Our results suggest that the respiratory follow-up of early transient wheezers is of clinical importance.

Skin positivity and rhinitis symptoms in the past year, both expressions of child's atopic status, are associated with persistent wheeze, consistently with data from longitudinal evaluations (1, 3, 6). Martinez et al. hypothesized that persistent wheezers are congenitally predisposed to produce large quantities of immunoglobulin E (IgE) in response to a variety of antigens and that different allergens at different ages may provoke this enhanced IgE reactivity (1). Other important results about persistent wheezing are the strong relation to parental history of allergies or respiratory disease and to parental smoking during pregnancy and postnatal period, as also reported by other authors (3, 4, 6, 14). Maternal history of asthma or COPD is more strongly associated than paternal; Litonjua et al. found similar results and postulated that there may be mechanisms for conferring this early-life risk through the maternal line (i.e., genetic inheritance, transplacental

transfer of antigens, maternal antibodies) (15). As already indicated in cohort studies on children (3, 6), atopy, parental smoking, and parental history of asthma and allergies appear to be the most important characteristics of persistent wheeze. It is probable that these factors do not act independently. Sheriff et al. have argued that atopy may exacerbate wheezing in children with pre-existing airway impairment due to genetics or early life factors such as tobacco smoke exposure and infections (6). Kurukulaaratchy and colleagues have recently suggested that both onset and persistence of wheezing may be influenced by an interaction between inheritance and environmental factors such as parental smoking (16).

Atopy is closely connected with late onset wheeze. Since serum IgE levels increase steadily during childhood (17–19), it is likely that wheezing at 10 years of age tends to be predominantly due to an allergic component. A family history of asthma and hay fever is another important feature of late onset wheeze, confirming what other authors have suggested about the role of family history in "programming" this pattern of wheeze (1, 2, 6).

We adopted pulmonary function testing to provide an objective estimate of lung function impairment in the three groups of wheezers. Early transient wheezers have a statistically significant reduction in lung function at 10 years of age, according to their FEV₁/FVC and FEF_{25–75} values.

TABLE 3.—Association of lung function parameters with early transient, persistent, and late onset wheezing* in children. Rome, 2000–2001.

Parameters	Control group (n = 1,080) mean ± SD	Early transient wheezing (n = 126) Difference (95%CI)†	Persistent wheezing (n = 45) Difference (95%CI)†	Late onset wheezing (n = 55) Difference (95%CI)†
FVC (mL)	2,327 ± 400	–3 (–64; 58)	22 (–78; 12)	7 (–85; 99)
FEV ₁ (mL)	2,127 ± 349	–43 (–99; 13)	–63 (–154; 28)	–43 (–13; 41)
FEF _{25–75} (mL/s)‡	2,716 ± 662	–305 (–429; –180)	–298 (–500; –96)	–155 (–341; 30)
FEV ₁ /FVC (%)§	91.3 ± 6.6	–1.7 (–3.0; –0.4)	–3.2 (–5.3; –1.1)	–2.0 (–4.0; –0.1)

*Based on questionnaire completed by parents.

†Differences (95%CI) in means between the wheeze phenotypes and the control group. Multiple linear regression models included terms of gender, age, height (cm), quadratic height (cm²), BMI (kg/m²).‡Subjects who underwent measures of FEF_{25–75} parameter were 1,051 in the control group, 122 early transient wheezers, 44 persistent wheezers, 53 late onset wheezers.§Multiple linear regression model included terms of gender, age, BMI (kg/m²).

Martinez et al. in their cohort study suggested that early transient wheezers probably have congenitally smaller airways that in some cases are outgrown and in some persist during childhood, possibly explaining the compromised respiratory health we observed (1). Persistent wheezers show an important reduction in lung function at the time of the survey, as indicated by the FEV₁/FVC ratio. This result may be a possible explanation of the strong association we found between persistent wheezers and respiratory symptoms other than wheeze in the past year. Late onset wheezers show some degree of decrement in lung function at the age of 10 and a significantly greater risk for having current respiratory symptoms other than wheezing with respect to control group.

Early detection of clinical features and risk factors of childhood wheezing is important not only to improve childhood management of wheezing disorders but also for better understanding and possibly preventing the burden of this disease later in life. There are several indications that wheezing illness during childhood might predispose to chronic obstructive airways disease in adulthood (20–22). Moreover, Strachan et al. found a progressively greater ventilatory function deficit among those adults whose wheezing started earlier in childhood (23). This finding was more recently confirmed by Sears and colleagues (24).

Among the limitations of the present study, it should be noted that the retrospective design might have resulted in a reduced or biased recall of both symptoms and risk factors, especially since the questionnaire were filled in by parents. Regarding the risk factors investigated, selective recall may have induced parents of children with current wheezing (persistent and late onset wheezers) to over- or underreport conditions known to be associated with the disease. For example, a mother with a history of asthma may have overreported the symptoms of her own child. However, the use of objective markers, partially overcomes the effects of recall bias.

In conclusion, our findings indicate that childhood wheezing is a heterogeneous condition with distinct patterns associated with different pathogenesis and risk factors. We demonstrated that objective measures of atopy and lung function at 10 years of age are important to monitor the retrospectively reported clinical course of wheezing illness. The majority of children who wheezed in the first 2 years of life no longer wheeze in later childhood. This group shows compromised respiratory health at 9 to 11 years of age, perhaps reflecting a congenital structural deficit in airways. Parental history of asthma, smoking, and child's atopy seem to be the most important characteristics in persistent wheeze during childhood.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the schools' staff, children, and parents who participated in this study. They also note the valid contributions of P. Lorusso, F. Marsili, V. Zanda, A. Sbrilla, C. Fusco, S. Palange, P. Barni, and A. Tarquini in collecting and codifying questionnaire data, and they thank Dr. M. Becker for her valuable help in editing the paper.

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