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Nocturnal Dry Cough in the First 7 Years of Life is Associated With Asthma at School Age

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Summary. Background: Childhood wheeze is an important, well-known risk factor for asthma, yet little is known about the contribution of nocturnal dry cough. We investigated the association of nocturnal dry cough at ages 1–7 years with doctor-diagnosed asthma at 8 years of age, both in the presence and absence of wheeze. Methods: Data of 3,252 children from the PIAMA birth cohort were studied. Parents reported the presence of nocturnal dry cough, wheeze, and doctor-diagnosed asthma in the past 12 months yearly, from birth up to the age of 8 years. Results: Nocturnal dry cough without wheeze was significantly associated with doctor-diagnosed asthma at age 8, except for age 1 (range of Relative Risks (RR) at ages 2–7: 1.8 (age 5) – 7.1 (age 7), all *P*-values <0.048). As expected, wheeze without nocturnal dry cough was strongly associated with doctor-diagnosed asthma at age 8 (range of RR: 2.0 (age 1) – 22.2 (age 7), all *P*-values <0.003). Of interest, nocturnal dry cough with wheeze showed the strongest association with doctor-diagnosed asthma at age 8 (range of RR: 3.7 (age 1) – 26.0 (age 7), all *P*-values <0.001). The relative excess risk of asthma at age 8 due to interaction of nocturnal dry cough with wheeze at age 1 year was 1.8 (0.1–3.6, $P<0.01$). Conclusion: Nocturnal dry cough and wheeze in early childhood are both independently associated with asthma at school age. The presence of both nocturnal dry cough and wheeze at age 1 almost doubles the risk of asthma at age 8 compared to wheeze alone. **Pediatr Pulmonol. 2015;50:848–855.** © 2014 Wiley Periodicals, Inc.

Key words: asthma; children; nocturnal dry cough; wheeze; birth cohort.

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INTRODUCTION

Asthma is a common heterogeneous disease, with symptoms like wheeze, dyspnea, and cough. The first symptoms of asthma are usually present at preschool age,[1,2] yet diagnosing asthma is difficult at that time of life. Nevertheless it is important, since early treatment may reduce symptoms and improve the quality of life of these children.

Wheeze, dyspnea, and cough are common symptoms in the early presentation of asthma, where wheeze seems to have the strongest association with asthma.[3,4] The Tucson Children's Respiratory Study proposed an asthma prediction index where wheeze combined with several other risk factors accounted for an increased risk of asthma.[5] We have performed a study on preschool children with wheeze, nocturnal dry cough, or their combination.[6] Wheeze again was significantly associated with asthma at age 7 and 8 years, but not nocturnal dry cough. However, the added value of nocturnal dry cough on top of wheeze was not studied.

Chronic or persistent cough as single symptom early in life poorly predicts childhood asthma.[7,8] So far, most studies have not differentiated between nocturnal and daytime cough. This has implications, since nocturnal respiratory symptoms are a common manifestation in asthma.[9] Cross-sectional studies provided ambiguous results about the association between nocturnal cough and asthma,[10–12] whereas longitudinal studies are scarce. One study followed 77 children, 8–9 year-old, with nocturnal cough and showed that 15.6% had developed asthma after 2 years in contrast to 1.1% of the asymptomatic children.[13]

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort contains yearly data on the prevalence of respiratory symptoms and asthma development in children until the age of 8 years. We hypothesized that nocturnal dry cough early in life is an important early determinant of asthma at school age. The aim of our study was therefore to investigate the association between nocturnal dry cough in early childhood, either alone or on top of wheeze, and asthma (symptoms) at 8 years of age. Finally, we assessed which risk factors contribute to the presence of nocturnal dry cough in childhood.

MATERIAL AND METHODS

Study Population

We studied children participating in the PIAMA birth cohort. Details of the study design have been published previously.[14] Four thousand one hundred and forty six pregnant women gave their written informed consent to participate in the study. Questionnaires for parental completion, partly based on the International Study of Asthma and Allergies in Childhood core questionnaires [15] were sent to parents during pregnancy, at the child's age of 3 months and yearly from age 1–8 years. We excluded children without information in the 8-year questionnaire about a doctor's diagnosis of asthma, which resulted in a study population of 3,252 children. Questionnaires from age 1 year to 8 years were available for 3,194, 3,223, 3,226, 3,174, 3,184, 3,189, 3,129, and 3,252 children respectively. The PIAMA study also included an intervention part (n = 855) to investigate whether the use of mite-impermeable mattress encasings could prevent the development of asthma and allergy next to the 'natural history study' (n = 3,291). Only allergic mothers were included in the intervention study, while allergic (n = 472) and non-allergic (n = 2,819) mothers were included in the natural history study. The prevalence of nocturnal dry cough without a cold at age 2 was slightly, but significantly, lower in the group with active mattress covers than in the group with placebo covers (adjusted odds ratio 0.65; 95% confidence interval 0.4–1.0).[16] At other ages, the intervention did not influence the risk of having respiratory symptoms.[17] We evaluated whether the association between nocturnal dry cough at age 2 and doctor-diagnosed asthma at age 8 was different after exclusion of children from the intervention study and this was not the case. We therefore included these children into the study population.

The study was approved by the medical ethics committees of participating university hospitals and was performed according to the declaration of Helsinki.

Definition of Variables

Data on nocturnal dry cough and wheeze were used from age 1–7 years. Questions were:

- Nocturnal dry cough: "In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?"
- Wheeze: "Has your child ever had wheezing or whistling in the chest?" Followed by: "Has your child had wheezing or whistling in the chest in the last 12 months?"

Doctor-diagnosed asthma at age 8 was defined as a "yes" to the following two questions in the 8-year questionnaire: "Has your child ever been diagnosed with asthma by a doctor?", followed by "Has your child had asthma in the last 12 months?".

Determinants of Nocturnal Dry Cough

We studied the following possible determinants of nocturnal dry cough: gender, birth weight (kilograms),

ABBREVIATIONS:
NDC Nocturnal dry cough
PIAMA Prevention and Incidence of Asthma and Mite Allergy

maternal smoking during pregnancy (yes/no), breastfeeding (no breastfeeding, < 3 months or $\geq$ 3 months), educational level of mother (low, intermediate, high), maternal and paternal self-reported history of atopy, intervention type mattress covers (none, placebo, active), environmental tobacco smoke at ages 1–7, cats or dogs present in the house at ages 1–7, the presence of other children in the household at age 1, day-care attendance and Particulate Matter ($PM_{2.5}$) exposure (per 3.2 $\mu g/m^3$) at the child's birth address modelled by means of land-use regression.[18,19]

Statistical Analysis

We estimated the risk of having doctor-diagnosed asthma at 8 years for four groups of children at 1–7 years:

1. Children without nocturnal dry cough and without wheeze (reference group);
2. Children with nocturnal dry cough, without wheeze;
3. Children without nocturnal dry cough, with wheeze;
4. Children with nocturnal dry cough and with wheeze.

We estimated Relative Risks (RR) and corresponding 95% confidence intervals of having asthma at age 8 for groups 2–4 compared to the reference group from age 1 to 7 years.

To study whether the effect of the presence of both nocturnal dry cough and wheeze on the risk of having asthma at age 8 years was larger than the sum of individual effects of these symptoms, we calculated the relative excess risk due to interaction (RERI) as follows: RERI = RR (NDC+/Wheeze+) − RR (NDC+/Wheeze−) − RR (NDC−/Wheeze+) + 1. A RERI > 0 indicates interaction on the additive scale, which is generally considered most appropriate for assessing the public health importance of interaction.[20] The RERI 95% confidence interval (CI) was estimated by parametric bootstrapping of 50,000 samples with a continuity correction,[21] a CI > 0 indicating significant interaction.

To study whether the association of nocturnal dry cough with doctor-diagnosed asthma was confounded by other potential risk factors, we performed multiple logistic regression analysis. We included determinants of nocturnal dry cough as defined earlier. Variables were considered confounders if inclusion into the model changed the coefficient of nocturnal dry cough without wheeze, nocturnal dry cough with wheeze or wheeze without nocturnal dry cough by more than 10%.

We studied whether asthma cases at age 8 had more frequently nocturnal dry cough at ages 1–7, independent from the simultaneous presence of wheeze and taking the correlation between nocturnal dry cough at different ages into account by analyzing the association between doctor-diagnosed asthma at age 8 as independent variable and nocturnal dry cough at ages 1–7 as the outcome variable, adjusted for wheeze by generalized estimating equations (GEE). A six dependent correlation matrix accounted for correlations between repeated observations in the same individual. We assessed whether the association varied by age by assessing the interaction of age with doctor-diagnosed asthma (significance $P < 0.05$). These analyses were adjusted for all possible determinants of nocturnal dry cough as listed above. Finally, we studied risk factors of nocturnal dry cough by including all possible determinants in a GEE model (without inclusion of doctor-diagnosed asthma and wheeze). Statistical analyses were performed with SPSS, version 18.0.3 (SPSS inc, Chicago, IL).

RESULTS

Descriptives

The prevalence of doctor-diagnosed asthma at age 8 in the study population was 3.6%. Characteristics of all children (n = 3252), the children with asthma at age 8 (n = 116), and the children without asthma at age 8 (n = 3136) are shown in Table 1.

The prevalence of nocturnal dry cough in the study population varied between 22.8% at age 5 to 14.8% at ages 2 and 7; the prevalence of wheeze decreased continuously from age 1 (25.3%) to age 7 (5.7%) (Fig. 1).

The prevalence of nocturnal dry cough without wheeze was higher than the prevalence of nocturnal dry cough with wheeze and higher than the prevalence of wheeze without nocturnal dry cough from age 3 onwards (Fig. 2). The prevalence of nocturnal dry cough without wheeze increased to 17.9% in the first 5 years and decreased to 12.0% at age 7.

The Association of Nocturnal Dry Cough With Asthma at 8 years

Nocturnal Dry Cough Without Wheeze

Children having nocturnal dry cough without wheeze had a significantly higher risk of doctor-diagnosed asthma at age 8 than children without both nocturnal dry cough and wheeze at all ages up to 7 years, except for age 1 (Table 2); relative risks varied between 1.8 (age 5) and 7.1 (age 7). The prevalence of doctor-diagnosed asthma at age 8 in children having nocturnal dry cough without wheeze earlier in life varied between 2.3% (age 1) and 7.8% (age 7).

Wheeze Without Nocturnal Dry Cough

Children with wheeze and without nocturnal dry cough at 1–7 years had a significantly higher risk of doctor-diagnosed asthma at age 8 than children without both nocturnal dry cough and wheeze (Table 2); relative risks varied between 2.0 (age 1) and 22.2 (age 7). The risk of

TABLE 1— General Characteristics of the Study Population (n = 3252)

	All children (n = 3252)	Asthma at 8 year (n = 116)	No asthma at 8 year (n = 3136)	*P*-value
Doctor diagnosed asthma at 8 years	116 (3.6)			
Perinatal factors				
Male sex	1670 (51.4)	69 (59.5)	1601 (51.1)	0.07
Birth weight in kilograms	3.5 (0.5)[1]	3.5 (0.6)[1]	3.5 (0.5)[1]	0.16
Maternal smoking during pregnancy	503 (15.7)	18 (15.5)	485 (15.7)	0.97
Breastfeeding				0.30
No breastfeeding	541 (16.8)	24 (20.9)	517 (16.6)	
<3 months	1213 (37.7)	46 (40.0)	1167 (37.6)	
≥3 months	1467 (45.5)	45 (39.1)	1422 (45.8)	
Maternal educational level				0.64
Low	695 (21.5)	29 (25.0)	666 (21.3)	
Intermediate	1361 (42.0)	46 (39.7)	1315 (42.1)	
High	1182 (36.5)	41 (35.3)	1141 (36.5)	
Family history				
Atopy mother	911 (28.0)	45 (38.8)	866 (27.6)	**0.01**
Atopy father	988 (30.4)	43 (37.1)	945 (30.2)	0.11
Intervention type mattress covers				**0.01**
No	2731 (84.0)	85 (73.3)*	2646 (84.4)*	
Placebo	249 (7.7)	14 (12.1)	235 (7.5)	
Active	272 (8.4)	17 (14.7)**	255 (8.1)**	
Environmental exposures				
Tobacco smoke exposure at age 1 year	733 (22.8)	29 (25.2)	704 (22.7)	0.53
Pets present in the household				
Cat at age 1 year	999 (30.8)	32 (27.6)	967 (31.0)	0.44
Dog at age 1 year	471 (14.5)	13 (11.2)	458 (14.7)	0.30
Other children in the household at age 1 year	1652 (51.1)	54 (46.6)	1598 (51.3)	0.32
Air pollution (per 3.2 $\mu g/m^3$)				
$PM_{2.5}$	5.4 (4.6–5.7)[2]	5.5 (5.2–5.7)[2]	5.4 (4.6–5.7)[2]	**0.02**
Day care attendance at age 1 year	812 (25.2)	25 (21.7)	787 (25.3)	0.39

data are presented as number (%), mean (±standard deviation)[1], or median (interquartile range)[2].
*$P = 0.001$.
**$P = 0.01$.

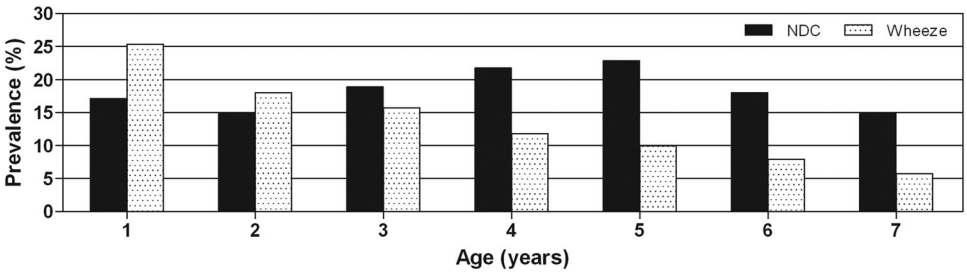

Fig. 1. Prevalence of nocturnal dry cough (NDC) and wheeze in the study population (n = 3252).

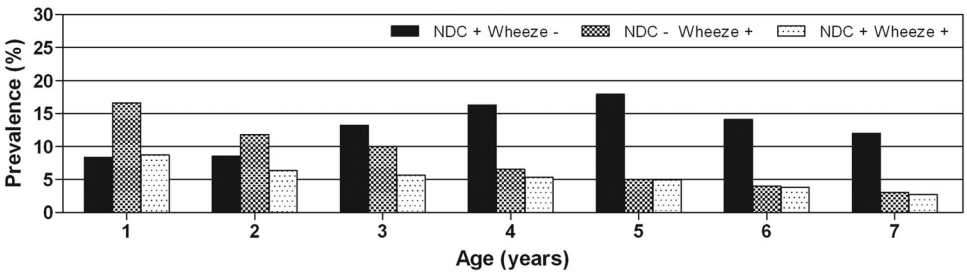

Fig. 2. Prevalence of nocturnal dry cough (NDC) with and without wheeze in the study population (n = 3252).

TABLE 2— Univariate Association of Nocturnal Dry Cough With and Without Wheeze With Doctor-Diagnosed Asthma at 8 Years of Age

	Prevalence of doctor-diagnosed asthma at age 8 within each group	Unadjusted RR (95%CI)[1]	RERI (95%CI)[2]
Age 1			
NDC− Wheeze−	54/2095 (2.6%)	Ref	
NDC+ Wheeze−	6/262 (2.3%)	0.9 (0.4–2.0)	
NDC− Wheeze+	27/522 (5.2%)	2.0 (1.3–3.2)	
NDC+ Wheeze+	26/274 (9.5%)	3.7 (2.3–5.8)	1.8 (0.1–3.6)
Age 2			
NDC− Wheeze−	50/2332 (2.1%)	Ref	
NDC+ Wheeze−	16/269 (5.9%)	2.8 (1.6–4.8)	
NDC− Wheeze+	26/373 (7.0%)	3.3 (2.1–5.2)	
NDC+ Wheeze+	22/199 (11.1%)	5.2 (3.2–8.3)	0.1 (−2.7–2.9)
Age 3			
NDC− Wheeze−	38/2258 (1.7%)	Ref	
NDC+ Wheeze−	17/420 (4.0%)	2.4 (1.4–4.2)	
NDC− Wheeze+	30/316 (9.5%)	5.6 (3.5–9.0)	
NDC+ Wheeze+	24/177 (13.6%)	8.1 (4.9–13.1)	1.0 (−2.8–4.9)
Age 4			
NDC− Wheeze−	30/2255 (1.3%)	Ref	
NDC+ Wheeze−	14/513 (2.7%)	2.1 (1.1–3.8)	
NDC− Wheeze+	28/205 (13.7%)	10.3 (6.3–16.8)	
NDC+ Wheeze+	36/166 (21.7%)	16.3 (10.3–25.8)	5.0 (−1.0–11.9)
Age 5			
NDC− Wheeze−	36/2259 (1.6%)	Ref	
NDC+ Wheeze−	16/558 (2.9%)	1.8 (1.0–3.2)	
NDC− Wheeze+	25/156 (16.0%)	10.1 (6.2–16.3)	
NDC+/Wheeze+	34/152 (22.4%)	14.0 (9.0–21.8)	3.2 (−2.4–9.3)
Age 6			
NDC− Wheeze−	35/2467 (1.4%)	Ref	
NDC+ Wheeze−	21/445 (4.7%)	3.3 (2.0–5.7)	
NDC− Wheeze+	23/127 (18.1%)	12.8 (7.8–20.9)	
NDC+/Wheeze+	31/120 (25.8%)	18.2 (11.6−28.5)	3.1 (−4.0–10.2)
Age 7			
NDC− Wheeze−	28/2545 (1.1%)	Ref	
NDC+ Wheeze−	29/370 (7.8%)	7.1 (4.3–11.8)	
NDC− Wheeze+	23/94 (24.5%)	22.2 (13.3–37.1)	
NDC+/Wheeze+	24/84 (28.6%)	26.0 (15.8–42.8)	−2.4 (−15.6–10.0)

[1]RR, relative risk, CI, confidence interval.
[2]RERI, Relative excess risk of interaction.

asthma in children with wheeze as sole symptom was higher than in children having nocturnal dry cough only. The prevalence of doctor-diagnosed asthma at age 8 in children having wheeze without nocturnal dry cough earlier in life increased with age from 5.2% (age 1) to a maximum of 24.5% (age 7).

Nocturnal Dry Cough With Wheeze

Children with nocturnal dry cough in combination with wheeze at ages 1–7 had a significantly higher risk of having doctor-diagnosed asthma at 8 years than children without nocturnal dry cough and without wheeze (Table 2); relative risks varied between 3.7 (age 1) and 26.0 (age 7). The risk of asthma in children with both nocturnal dry cough and wheeze was higher than in children with either nocturnal dry cough alone or wheeze alone. The prevalence of doctor-diagnosed asthma at age 8 in children with both nocturnal dry cough and wheeze earlier in life increased with age from 9.5% (age 1) to 28.6% (age 7).

Within the subgroup of children with wheeze, children with cough had a significantly higher risk of asthma at age 8 than children without cough at age 1 only (RR:1.8; CI: 1.1–3.1) and age 4 only (RR:1.6; CI: 1.0–2.5). Within the subgroup of children with cough, children with wheeze had a significantly higher risk of asthma at age 8 than children without wheeze at all ages (range of RR's: 1.9 (age 2) to 8.0 (age 4)).

Relative Excess Risk Due to Interaction (RERI)

The RERI between nocturnal dry cough and wheeze was significantly higher than 0 at age 1: the relative risk of having asthma at age 8 for the combined presence of wheeze and NDC in the first year of life was larger than the sum of the relative risks for wheeze or nocturnal dry cough alone (significant interaction on

an additive scale). At ages 2–7 years, the excess risk of nocturnal dry cough and wheeze did not reach significance.

Multiple Regression Analysis

We tested whether the relationship between nocturnal dry cough and asthma at age 8 years was confounded by other variables in a multiple regression model. None of the selected variables changed the coefficient of nocturnal dry cough without wheeze, nocturnal dry cough with wheeze or wheeze without nocturnal dry cough by more than 10% (data not shown).

Longitudinal Analysis of Nocturnal Dry Cough

GEE analysis showed that nocturnal dry cough at ages 1–7 significantly associated with doctor-diagnosed asthma at age 8, independent from the presence of wheeze. This association significantly varied by age: the association between asthma at age 8 and nocturnal dry cough became stronger with increasing age, odds ratios being 1.6 at age 1 and 4.6 at age 7 (Fig. 3). As the strongest associations of nocturnal dry cough with asthma were seen at ages 6 and 7, we repeated the GEE analysis for age 1–5 only. Overall, we found again that nocturnal dry cough at ages 1–5 was significantly associated with later doctor-diagnosed asthma (odds ratio [OR] 1.9; 95% confidence intervaI [CI]: 1.4–2.5). There was no significant interaction with age in this analysis.

Risk Analysis of Nocturnal Dry Cough

We found that male sex (OR: 1.2; CI: 1.0–1.3), maternal atopy (OR: 1.4; CI: 1.2–1.7), paternal atopy (OR: 1.3; CI: 1.2–1.5), and Particulate Matter exposure (OR: 1.1; CI: 1.0–1.2) were independently associated with an increased risk of nocturnal dry cough at age 1–7, whereas an inverse association with nocturnal dry cough was seen for a higher educational level of the mother (OR: 0.8; CI: 0.7–0.9) and a higher birth weight (OR: 0.9; CI: 0.8–1.0).

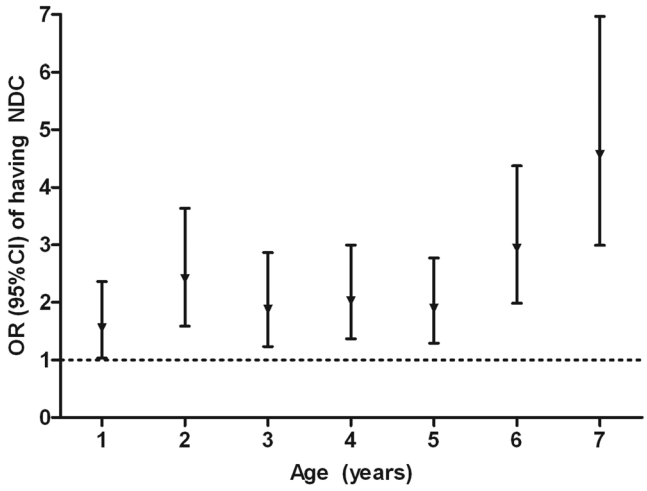

Fig. 3. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) of having nocturnal dry cough (NDC) at ages 1–7 years, in children with a doctor's diagnosis of asthma at age 8. The dotted line represents an odds ratio of 1.

DISCUSSION

This prospective birth cohort study shows that nocturnal dry cough in early childhood is associated with the presence of doctor-diagnosed asthma at age 8, independent of the presence of wheeze. However, the prevalence of asthma at age 8 in children having nocturnal dry cough without wheeze at ages 2–7 was relatively low (<10%). Interestingly, the combined presence of nocturnal dry cough and wheeze at age 1 almost doubled the risk of having asthma at age 8 compared to the risk in children with wheeze alone. The relevance of nocturnal dry cough was supported by our longitudinal analysis showing that an asthma diagnosis at age 8 was independently associated with nocturnal dry cough at ages 1–7.

It is well established that wheezing children at preschool age have more likely asthma later in life.[5,22] This was also the case in our study and wheeze (with or without nocturnal dry cough) had the strongest association with asthma at age 8. Several studies have developed an asthma prediction score,[3–6] including the study of Caudri et al. using data from the PIAMA study.[6] The latter reported that nocturnal dry cough was not associated with asthma. However, Caudri investigated the prediction of asthma in symptomatic children (wheeze and/or nocturnal cough), so the predictive value of nocturnal cough is inherently different than in the present study design. Two further studies did not report whether nocturnal dry cough was selected as a candidate predictor.[3,5] We here show that nocturnal dry cough in childhood is associated with asthma at age 8. Therefore, we suggest to incorporate nocturnal dry cough as a respiratory symptom in future studies about diagnosing or predicting asthma.

Follow-up studies on the association between nocturnal cough and asthma are rare. In line with our results, a recent study suggests that nocturnal dry cough in early life is associated with an asthma diagnosis at 4 years of age.[23] One study showed that 12 out of 77 children with nocturnal cough (15.6%) developed asthma 2 years later.[13] There are more studies reporting on "undefined" cough. The Tucson study showed that recurrent cough as a single symptom at age 6 is associated with an increased risk (12.6%) of asthma at age 11.[24] This risk was lower than in children reporting both cough and wheeze (33.3%) or wheeze alone (21.1%). Within the same cohort, chronic cough at 3–4 years, but not at 1–2 years, was a significant predictor of asthma development at 5–11 years.[25] Brooke et al. on the other hand reported that few children with recurrent cough developed wheeze.[8] Furthermore, in a

review of nine prospective birth cohorts, cough was a poor marker of asthma development.[7] All these studies used chronic or recurrent cough as outcome, whereas our study reports more specifically nocturnal dry cough. Although no formal comparisons have been made regarding the various cough definitions used, the different results suggest to us that 'nocturnal dry cough' is closer related to asthma development than 'cough' alone.

Nocturnal respiratory symptoms in asthmatics implicate more severe disease, i.e., FEV_1 levels are lower in children with than without nocturnal asthma symptoms [26]. In addition, children with nocturnal symptoms score their asthma as more severe. With this in mind, the presentation of nocturnal dry cough as an early feature of asthma seems plausible.

In line with previous reports on traffic-related air pollution,[27–29] we found that the risk of nocturnal dry cough increased with the level of $PM_{2.5}$. Furthermore, several other factors associated with the development of asthma were determinants of nocturnal dry cough. Parental atopy and male sex increased the risk of nocturnal dry cough in children from age 1 to 7. The latter is partially in line with a previous study showing that a cluster of children with nocturnal cough had more frequently allergic parents.[23] However, there was no significant difference in sex. We also showed that a higher birth weight reduced the risk of nocturnal dry cough, which is in line with previous findings within our cohort.[30] Finally, a high maternal education had a protective effect on developing nocturnal dry cough. Since these risk factors for nocturnal dry cough have been previously reported as risk factors for childhood asthma,[6,31–33] these findings corroborate the relevance of taking nocturnal dry cough into account when assessing the risk of asthma in early childhood.

A strong aspect of this study is its prospective design with annual measurements, allowing us to assess the relation between nocturnal dry cough and asthma longitudinally. Additionally, the large size of the study population contributes to its strength, with a follow-up of 80% up to 8 years. A limitation of the study might be that we used reported nocturnal dry cough, since Dales et al. stated that parents usually underreport coughing of their child.[34] However, this most likely resulted in underestimating of the effect.

In conclusion, diagnosing asthma early in life remains a difficult and delicate task. We investigated nocturnal dry cough and wheeze as early symptoms of asthma. Wheeze in early childhood has the strongest association with asthma at age 8. An interesting and new observation is that nocturnal dry cough in early childhood has a significant association with asthma at age 8, independently from wheeze. Moreover, it particularly increases the risk of asthma when it is present in very young wheezing children. Cough is a common symptom in children and a frequent reason for consultation in primary care. Our information contributes to the knowledge about the natural course of asthma and may help clinicians in diagnosing asthma.

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