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Running Title: Transient childhood wheeze and atopy

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Abstract

Background

The relationships between childhood wheeze phenotypes and subsequent allergic conditions other than asthma, including hayfever, eczema, and sensitization have not been widely reported. We aimed to investigate this relationship up to late adolescence.

Methods

Using five childhood wheeze phenotypes defined from 620 children in a high-atopy risk birth cohort (Melbourne Atopy Cohort Study), we investigated their relationships with sensitization, eczema, hay fever, and fractional exhaled nitric oxide (FeNO) at ages 12 and/or 18 years using logistic and linear regression models.

Results

"Early Persistent wheeze" was associated with increased risk of eczema (odds ratio 3·69; 95% CI 1·23,11·12) and sensitization (4·52; 1·50,13·64) at 12 years."Intermediate Onset wheeze" was associated with increased risk of eczema at 12 years (2·57;1·11,5·97), hay fever at 12 (2·87; 1·44,5·74) and 18 years (2·19;1·20,4·02), sensitization at 12 (2·25;1·17,4·34) and 18 years (2·46;1·18,5·12), and raised FeNO at 18 years."Late Onset wheeze" was associated with increased risk of hay fever at 12 (5·18;1·11,24·20) and 18 years (4·20;1·03,17·11) and sensitization at 12 years (3·27;0·81,13·27). In contrast,"Early Transient wheeze" was associated with reduced risk of eczema (0·44 ;0·20,0·96), hay fever (0·57; 0·33,0·99) and sensitization (0·59; 0·35,0·99) at 18 years and a lower FeNO compared with "Never/Infrequent wheezers".

Conclusions

Persistent wheeze phenotypes were associated with allergic outcomes up to 18 years with "Intermediate Onset wheeze" being the most atopic group. In contrast, "Early Transient wheezers" had less risk of allergic outcomes at 18 years. This protective effect may reassure parents of wheezy infants and young children.

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Key-words: Wheeze, Asthma, Atopy, Nitric Oxide, Childhood, Adolescence

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Impact Statement

Children with persistent wheeze are more likely to have other allergic manifestations in later childhood and adolescence. In contrast early transient wheeze was associated with less allergic phenomena, suggesting that early life viral respiratory infection may be important for immune development and prevention of allergic disease. The finding that transient wheeze may be protective for future allergic disease and atopy may be a reassuring message to parents with wheezing infants and young children.

Introduction

Childhood wheeze is responsible for a large global burden of disease, with 11.6% of all six-seven year old children affected.[1] Prevalence is particularly high in early childhood, with one third of children affected before the age of three years. Estimates of the prevalence of any episode of wheeze from birth up to the age of six years may be higher; up to 48% in Arizona, America[2] and 68% in Valencia, Spain[3], although in other countries and regions where wheeze and asthma are less prevalent, this figure may be lower.

Wheeze is a cardinal symptom of asthma, but is heterogeneous in terms of aetiology and prognosis.[4] There is increasing interest in accurate classification of childhood wheeze phenotypes and their prognoses. [2,5-8] While most early childhood wheeze is transient, resolving without subsequently developing into asthma, approximately a third of early life wheezers have persistent disease and asthma in later childhood.[9] Further research seeks to determine which children with early life wheeze will develop asthma and whether early life exposures may influence this development.

Inhaled anti-inflammatory medications are effective in controlling wheeze and there is some inconclusive evidence that they may help preserve lung function [10-13] although a recent systematic review found little evidence for long term disease modifying effects.[14] However, these agents may have serious side effects, [15,16] so it is important to be able to distinguish benign transient wheeze in early childhood from phenotypes that have long term implications.

Our finding, from analysis of previously defined wheeze phenotypes[6], that early transient wheeze is benign with respect to later respiratory health[17] agrees with some[18], but not all previous research.[5,7,8,19,20] Different findings may relate to variation in criteria for classification of early childhood wheeze groups. Our analysis, where wheeze was recorded prospectively 18 times in the first two years of life, is likely to have detected more episodes of mild wheeze than other studies, where wheeze was only recorded at six or 12-month intervals[5].

There were conflicting findings concerning the long-term implications of early transient wheeze and the lack of evidence for associations with other common allergic conditions including eczema, hayfever and sensitization. We aimed to investigate associations between our previously defined childhood wheeze phenotypes ("Never/Infrequent wheeze", "Early Transient wheeze","Persistent wheeze", "Intermediate Onset wheeze" and "Late Onset wheeze", and eczema, hayfever and biomarkers including skin prick testing to common food and aero-allergens and exhaled nitric oxide up to 18 years.

Methods

Participants

The Melbourne Atopy Cohort Study (MACS) is a longitudinal birth cohort. From 1990-1994, we enrolled 620 children, with a family history of allergic disease, whilst in utero, and have followed them to 18 years. Methods, baseline characteristics, follow-up times and data/samples collected have been described elsewhere.[21] Although originally conceived as an RCT trialing the association of infant formulas with allergic disease (registered retrospectively with the Australian and New Zealand Clinical Trials Registry [ACTRN12609000734268]), MACS has been utilized as a prospective birth cohort. The Mercy Maternity Hospital Ethics Committee approved initial study phases. The 18-year follow-up was approved by the University of Melbourne and Royal Children's Hospitals Ethics Committees. All mothers and children (when of consent age) provided written informed consent.

Exposure phenotypes defined using data collected in the first seven years of life

Childhood wheeze phenotypes were defined previously.[6] Briefly, we identified five independent wheeze phenotypes from wheezing patterns from the age of four weeks to seven years (wheeze recorded 23 times). Names of classes were based on temporal patterns. Latent class probabilities for the five identified classes were: "Never/infrequent wheeze" 47 % (n=290); "Early Transient wheeze" 26%(n=160); "Early Persistent wheeze" 5% (N=33); "Intermediate Onset wheeze" 19% (n=115); and

"Late Onset wheeze" 3% (n=33). Never/infrequent wheezers had a low probability of wheeze at all 23 Timepoints (Prob <0.1). Early transient wheezers had an early increase in wheeze probability between 6 months and 2 years (Prob 0.25-0.3) but after 2 years the wheeze probability was low. Early persistent wheezers had a relatively high probability of wheeze at all timepoints. Intermediate onset wheezers had increasing probability of wheeze from 18 months, and late onset wheezers started to wheeze at around 4 years of age.

Outcome data collected at age 12 and 18 years

Skin Prick Testing (SPT)

Trained research personnel conducted tests at ages six, 12 and 24 months, and 12 and 18 years. Up to 12 years, cow's milk, egg white, peanut, house dust-mite, rye grass pollen and cat dander [Bayer, Spokane, WA, USA] were used. At 18 years, additional allergens tested were Alternaria tenuis, Penicillium notatum, Homodendrum cladosporiodes, mixed grass pollen, cashew and shrimp. Details of methods were previously published.[22] Positive SPT was defined as a wheal response with a mean diameter ≥ 3mm.

Fractional exhaled nitric oxide (FENO)

Exhaled NO was collected at 18-years by an off-line method [HypAir™ FENO, Médisoft, P.A.E de Sorinnes, Belgium]. NO deplete air was inhaled and then expired at 50ml/sec. FENO concentration was measured in parts per billion (ppb). Up to five blows were performed for reproducible values (two readings within ten % if values >20ppb, or within 15% if below 20ppb).

Current eczema and hay fever

Eczema by six months was defined as participants' report of a doctor's consultation for eczema, or any rash treated with steroid creams by six months (excluding rashes confined to scalp and nappy area). Current eczema and hay fever at 12 and 18 years were defined from questionnaire responses for occurrence and treatment in past 12 months.

Covariates

Parental smoking, parental asthma, pets at birth, birth order, gender and parental education were defined by responses to the baseline questionnaire (at birth). Parental education was used as a marker of socioeconomic status and defined as one or two parents versus neither parent having studied at a tertiary level. Parental smoking was defined as one or both parents reporting current

147 smoking at baseline. "Heavy parental smoking" was defined as ≥ 10 cigarettes/day for either or
148 both parents.

149 Lower respiratory tract infection (LRTI) was defined by parental reports of doctor visits for LRTI
150 (reported every four weeks during the child's first year). Breastfeeding ≥ three months was any
151 breastfeeding at or beyond three months regardless of other food intake.

152 Statistical analysis
153 Two-sample comparison of proportion tests (z-tests) were used to identify differential follow-up.
154 Associations between wheezing classes defined by LCA[6] with questionnaire definitions of hay fever
155 and eczema, and sensitization at 12 and 18 years were estimated using logistic regression (Stata,
156 release 11.0, Stata Corporation, College Station, TX, USA), with weights equal to the probability of
157 membership of each wheeze phenotype for each child. Models were adjusted for sex, LRTI by one
158 year, breastfeeding ≥ three months, heavy parental smoking, parental asthma, allergen sensitization
159 at one year, eczema by six months, first in birth order, dog in the home at child's birth, and parental
160 education. Associations between wheeze phenotypes and FENO were performed using linear
161 regression of natural log transformed data adjusted for age, height and sex. Confounders included
162 in this model were similar to other models except for early allergen sensitization. The analysis was
163 repeated with current sensitization included, as this is known to be a determinant of FENO.[23]
164 Adjustment for initial formula allocation did not change estimates.

165

166 **Results**

167 Participant characteristics
168 Parents of participants represented a high socio-economic status group with 72% of couples (one or
169 both parents) educated at tertiary level. Most parents (85%) were born in Australia. There were
170 375 (60%) participants who responded to questionnaires at 12 years and 411 (66%) at 18 years with
171 both questionnaire and expired NO data. Those with missing data were more likely to have parents
172 who smoked and were not tertiary educated at baseline.[21]

173 Hay fever and Eczema at ages 12 and 18 years (Table 1)

174 "Early Transient wheezers" had evidence of reduced risk of both current eczema and current hay
175 fever at 18 years when compared with "Never/Infrequent wheezers."(Table 1). There was some
176 weaker evidence of increased risk of eczema at 18 years for persistent wheezers and reduced risk
177 for both intermediate and late onset wheezers "

"Intermediate Onset" and "Late Onset wheeze" phenotypes were associated with an increased risk of current hay fever at both 12 and 18 years, when compared with "Never/Infrequent wheezers". Although "Early Persistent" and "Intermediate Onset wheeze" phenotypes were associated with increased risk of current eczema at 12 years, there was no association for any wheeze phenotype with current eczema at 18 years.

Allergen sensitization at 12 and 18 years by wheeze phenotype (Table 2)
"Early Transient wheezers" had a reduced risk of sensitization when compared to "Never/Infrequent wheezers" at 18 years. The risk of allergen sensitization was increased in "Intermediate Onset wheezers" at both ages: 12 years and 18 years when compared to "Never/Infrequent wheezers" and in "Early Persistent wheezers" at age 12

Fractional exhaled nitric oxide (FENO) at 18 years by wheeze phenotype
The "Early Transient wheeze" phenotype was associated with lower FENO at age 18 when compared with "Never/infrequent wheezers". (Figure 1). The "Intermediate Onset wheeze" phenotype was associated with an increased risk of raised FENO at 18 years when compared with the "Never/Infrequent wheeze" phenotype.

Discussion

Finding a link between transient wheeze in early childhood and reduced risk of later allergic disease is novel. At 18 years of age, "Early Transient wheezers" had reduced risks of hay fever and eczema along with lower FENO levels and lower risk of sensitization, when compared with "Never/Infrequent wheezers." In contrast, both "Intermediate Onset" and "Late Onset" wheeze phenotypes were associated with increased risk of current hay fever at 12 and 18 years. The "Intermediate Onset" wheeze phenotype was also associated with an increased risk of sensitization and higher exhaled nitric oxide.

Our current findings with respect to the childhood wheeze phenotypes who continue to wheeze are similar to the findings of others.[5,19,20] However, our findings with respect to "Early Transient wheeze" are novel and differ from the existing literature. Early transient wheeze characterized by Martinez et al. in the Tucson study, using age cut-offs of three and six years, was associated with reduced lung function and atopy in later life.[19] Similarly, the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) cohorts, that also used latent class analysis to identify wheeze phenotypes, found impaired lung

function in children with early transient wheeze. [5,20] However, it is likely that methods for classifying childhood wheeze phenotypes in these three cohorts differed from ours, specifically in the determination of who was included in the early transient wheeze phenotype.

The Tucson study began with a group of children who visited their physician with a wheezy illness in the first 3 years of life, as opposed to our birth cohort, which enrolled children based on a family history of atopic disease.[2] The ALSPAC and PIAMA cohorts recorded the presence of wheeze only 2-3 times in the first 3 years,[5] compared to our cohort where it was documented up to 19 times. Although wheeze data in ALSPAC and PIAMA were measured prospectively, by asking parents to recall wheezing episodes over 6-12 months, these studies are likely to have predominantly identified children with more severe and frequent wheeze, compared to the group identified in our study where the occurrence of wheeze was ascertained every 4 weeks. Our group of children with "Early Transient wheeze" is more likely to include children with mild and less frequent transient wheezing episodes.

Differences in the associations of wheeze phenotypes with other allergic diseases or biomarkers may give clues to differing aetiologies or pathogeneses. The finding that "Early Transient wheezers" had reduced risks of current eczema, hay fever and sensitisation at 18 years may be explained by the microbial diversity hypothesis and early education of the immune system through exposure to a diverse microbiological environment.[24,25] Children exposed to more infectious agents in early life may benefit through development of a more robust, less allergic immune response. This theory is supported by our previous finding that "Early Transient wheezers" more commonly attended childcare at an early age[6], where they would have been so exposed.

The results concerning allergen sensitization at ages 12 and 18 years also differed between phenotypes. The "Intermediate Onset" phenotype was most consistently associated with an increased risk of sensitization at both 12 and 18 years. "Early Persistent wheeze" was associated only with an increased risk of sensitization at 12 years. Again, these differences may point towards the pathogenesis of wheeze in each phenotype. The "Intermediate Onset wheezers", who show the greatest association, may indeed be an "atopic" phenotype. This hypothesis is supported by the early life associations outlined in our previous work, where this phenotype was uniquely associated with both food and aeroallergen sensitization in early life along with early life eczema.[6]

The findings concerning FENO are strongly related to and reflect the findings on sensitization. Exhaled nitric oxide is a measure of eosinophilic airway inflammation,[26] but there is also evidence that sensitization is an independent predictor of raised FENO.[23,27] The relationship between wheeze phenotypes and FENO was investigated in the PIAMA cohort[28]. At 8 years of age, the authors

found raised FENO in their Intermediate and Persistent wheeze phenotypes, but no association for the Transient wheeze group. Our findings into early adulthood suggest that the "Intermediate Onset wheeze" phenotype is a primarily atopic wheeze phenotype as distinct from the other phenotypes. In addition, "Early Transient wheeze" is not only a benign condition, as suggested by our previous work, but is associated with protection against subsequent allergic disease and sensitization. These relationships between wheeze phenotypes and atopy may change over time, with the protective effect of "Early Transient wheeze" being more pronounced in later life, particularly given that these associations were not identified at age 12 in this cohort.

It is clinically important to determine whether early wheezers are likely to be transient or become persistent. Treatment with asthma medications is beneficial for symptoms and exacerbations, although there is no evidence for preservation of long term (lifetime) lung function from existing short-term trials. However, identification of children with early transient wheeze may lead to reduction in potentially unnecessary treatment with possible side effects. Currently, despite predictive indices and known risk factors for wheeze persistence,[29] prediction of those who will continue to wheeze remains inexact. More work is required using existing longitudinal cohorts for determining and validating predictive models using advanced modelling techniques.

The strengths of this work include the wealth of early life data and long follow-up time to 18 years, when 66% of the original cohort participated, and the use of Latent Class Analysis to define wheezing classes. Children whose parents had not attended university and/or were smokers were under-represented at 18 years. As this study investigated a high-risk cohort, the associations found may differ in children with no family history of allergic disease. However, these findings may still be applicable to a large proportion of the Australian population, as the prevalence of atopic disorders in Australian families is high (65% of all children)[30]. Although there were extensive data, and relatively few dropouts for studies of this type, participant numbers were modest, making some subgroup analyses difficult and reducing the power to detect associations. This is apparent in the relationship between wheeze classes and eczema at 18 years. Although the point estimates for these relationships provided some evidence of increased or decreased risk, the width of the confidence intervals indicated that power may be insufficient to determine these relationships fully.

The differences between childhood wheeze phenotype associations with sensitization, exhaled nitric oxide, eczema and hayfever, highlights the underlying differences in pathophysiology between phenotypes. Findings from this analysis together with our previous observation that transient wheeze in early childhood did not influence subsequent lung function provide evidence that "Early Transient wheeze" is a benign disorder in this high-risk cohort. Early transient wheeze may indicate

the presence of childhood viral infections that are potentially protective against allergic disease through Th1 immune mechanisms. In contrast, children who continue to wheeze are at higher risk of not only asthma and reduced lung function growth as documented previously, but also of sensitization and hay fever up to age 18 years. Efforts should be made to determine host, environment, viral and pharmacological factors which direct early life respiratory viral encounters towards transient rather than persistent wheeze.

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Authors and Contributors

All authors meet the ICMJE requirements of authorship. All authors, except SZ, made substantial contributions to the study conception, implementation, conduct and/or protocols and data collection. CL conceived and developed the analysis with input from SD, AL, and MA, and with substantial input to the statistical analysis by SZ. All authors contributed to the interpretation of the data. The manuscript was initially drafted by CL with critical intellectual input from all authors. All authors approved the final submitted version

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Tables

Table 1. Hay fever and Eczema at ages 12 and 18 years by wheeze phenotype - Odds Ratios (95% Confidence Intervals)

	Wheeze Phenotypes				
	Never/Infre	Early Transient	Early Persistent	Intermediate Onset	Late Onset
Current symptoms/disease at age 12 years (In the past 12 months) (N=375)					
Eczema	1(ref)	1·09 (0·50, 2·34)	3·69 (1·23, 11·12)*	2·57 (1·11, 5·97)*	3·26 (0·59, 18·09)
Hay fever	1(ref)	0·90 (0·50, 1·63)	1·37 (0·51, 3·71)	2·87 (1·44, 5·74)*	5·18 (1·11, 24·20)*
Current symptoms/disease at age 18 years (In the past 12 months) (N=411)					
Eczema	1(ref)	0·44 (0·20, 0·96)*	1·37 (0·38, 5·00)	0·83 (0·37,1·83)	0·34 (0·07,1·65)
Hay Fever	1(ref)	0·57 (0·33, 0·99)*	1·21 (0·44, 3·35)	2·19 (1·20,4·02)*	4·20 (1·03,17·11)*

Adjusted for gender, lower respiratory tract infection by 1 year, breastfeeding for at least 3 months, heavy parental smoking, parental asthma, allergen sensitization at 1 year (3mm), eczema by 6 months, first born, dog in home at birth and parental tertiary education *p<0.05

Table 2 Association of wheeze phenotypes to any allergen sensitization at 12 and 18 years- Odds Ratios (95% Confidence Intervals)

	Wheeze phenotypes				
	Never/Infrequent	Early Transient	Early Persistent	Intermediate Onset	Late Onset
Allergen sensitization					
12 years (200/366)	1(ref)	0·78 (0·46, 1·33)	4·52 (1·50, 13·64)*	2·25 (1·17, 4·34)*	3·27 (0·81, 13·27)*

18 years (269/396)	1(ref)	0·59 (0·35, 0·99)*	2·38 (0·66, 8·57)	2·46 (1·18, 5·12)*	2·10 (0·53, 8·23)

Wheal sizes > 3mm considered positive

Adjusted for gender, lower respiratory tract infection by 1 year, breastfeeding for at least 3months, heavy parental smoking, parental asthma, allergen sensitization at 1 year (3mm), eczema by 6 months, first born, dog in home at birth and parent tertiary education *p<0.05.

Figure legends

Figure 1 Fractional exhaled nitric oxide (adjusted means & 95%CI) by wheeze phenotype at 18 years

Adjusted for age, and height at time of testing, gender, lower respiratory tract infection by 1 year, breastfeeding for at least 3 months, heavy parental smoking, parental asthma, eczema by 6 months, first born, dog in home at birth and parent tertiary education