

## LUNG FUNCTION BY WHEEZE STATUS

### Background

Given the possible relationship between early childhood wheeze and subsequent low lung function[1], it is possible that the observed association between risk of new onset asthma and low baseline lung function is really due to unreported early childhood wheezers (early transient). However, if the children who developed new onset asthma during the follow up are average lung function at study entry in those who developed new onset asthma were markedly higher than those with previous history of wheezing, then it is less likely that the incident cases represented pre-existing wheeze or undiagnosed asthma.

### Method

To assess the relationship between lung function and children with different pattern of wheeze at study entry, we compared the mean lung function at study entry of the CHS participants with different patterns of wheeze (who were excluded from the main analysis) to disease-free children who subsequently developed new onset asthma (*New Asthma*), using analysis of variance (ANOVA) adjusting for race/ethnicity, community of residence, sex and age at study entry. Wheeze groups were defined based on the parental baseline questionnaire according to the temporal pattern of onset and persistence that is known to reflect different wheeze phenotypes which have different associations with true asthma [1]. Wheeze was classified as *early transient* (wheezing during the first three years of life), *late onset* (wheezing first occurring after age 3 but before age 6), *early persistent* (wheezing occurring both during the first three years of life and during 4-6 years of age), and *never wheeze* (never wheezed from birth till last follow up) wheeze groups. Children who developed wheeze between age 6 and study entry were defined as *other wheeze*. Using analysis of variance (ANOVA) procedure (Proc

GLM in SAS), the average lung function of different wheeze groups were compared to the New Asthma group by performing t-tests with Tukey correction for multiple testing.

## Result

According to the ANOVA, the never wheeze group had higher flow rates (percent predicted FEV<sub>1</sub> and FEF<sub>25-75</sub>) and ratios (FEV<sub>1</sub>/FVC and FEF<sub>25-75</sub>/FVC) than any other group except those with late onset wheeze (Table E3 ). Similarly, those children who developed new onset asthma (New Asthma) had substantially larger flow rates in small airways (percent predicted FEF<sub>25-75</sub>) than those with early persistent and early transient wheeze (children who are more likely to be misclassified as never having wheezed by a forgetful parent). However, no difference was observed between children who developed new onset asthma and those who developed wheeze after age 3.

## Discussion

As this is not a birth cohort, the temporal relationship between lung function and asthma diagnosis remains a potential concern. Because low lung function tracks over time and is associated with different patterns of wheeze[1-5], it is possible that the new onset asthma cases in our study were undiagnosed cases of asthma at study entry. Though children with any history of wheeze or asthma (~38% of the cohort), as well as children missing wheezing history at study entry, were excluded from this analysis, it is still possible that parents forgot a history of early transient wheeze that was not active at study entry. If this were the case, our children with incident asthma might be expected to have a pattern of lung function at study entry similar to children with early transient wheeze, and this was not the case. Flow rates at study entry in children who developed new onset asthma were significantly higher than those with early transient or early persistent wheeze (Table E3).

## REFERENCES:

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Table E3: Percent-predicted lung function (mean  $\pm$  se)\* by wheeze status.

Asthma Status <sup>2</sup> (N)	FVC Mean (SE)	FEV <sub>1</sub> Mean (SE)	FEF <sub>25-75</sub> Mean (SE)	FEV <sub>1</sub> /FVC Mean (SE)	FEF <sub>25-75</sub> /FVC Mean (SE)
Never Wheeze (1845)	100.87(0.48)	101.77(0.51)*	106.41(1.09) †	0.88(0.003) †	1.07(0.011) †
Early Transient (78)	100.83(1.28)	98.54(1.35)	93.95(2.9)*	0.85(0.007)*	0.95(0.03)*
Early Persistent (223)	100.34(0.84)	96.27(0.89) †	89.62(1.9) †	0.83(0.004) †	0.89(0.02) †
Late Onset (113)	101.75(0.8)	100.41(0.85)	99.02(1.81)	0.86(0.004)	0.98(0.019)
Others (119)	100.84(1.08)	99.93(1.14)	101.73(2.44)	0.86(0.006)	1.02(0.025)
New Asthma (212)	99.44(1.06)	98.22(1.12)	97.11(2.42)	0.86(0.006)	0.99(0.025)

\* Lung function at study entry of children with or without any history of wheeze was compared with those who developed asthma during follow-up (*New Asthma*) by using ANOVA models,. Least square means and the standard error from the ANOVA models are presented in the table. Pairwise t-tests comparing the mean lung function of different groups to *New Asthma* were adjusted for multiple testing using Tukey adjustment

†p-value<0.05

‡ p-value <0.001