ASTHMA

# Relationship between air pollution, lung function and asthma in adolescents

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**Background:** The interrelationships between air pollution, lung function and the incidence of childhood asthma have yet to be established. A study was undertaken to determine whether lung function is associated with new onset asthma and whether this relationship varies by exposure to ambient air pollutants.
**Methods:** A cohort of children aged 9–10 years without asthma or wheeze at study entry were identified from the Children's Health Study and followed for 8 years. The participants resided in 12 communities with a wide range of ambient air pollutants that were measured continuously. Spirometric testing was performed and a medical diagnosis of asthma was ascertained annually. Proportional hazard regression models were fitted to investigate the relationship between lung function at study entry and the subsequent development of asthma and to determine whether air pollutants modify these associations.
**Results:** The level of airway flow was associated with new onset asthma. Over the 10th–90th percentile range of forced expiratory flow over the mid-range of expiration ($FEF_{25–75}$, 57.1%), the hazard ratio (HR) of new onset asthma was 0.50 (95% CI 0.35 to 0.71). This protective effect of better lung function was reduced in children exposed to higher levels of particulate matter with an aerodynamic diameter <2.5 μm ($PM_{2.5}$). Over the 10th–90th percentile range of $FEF_{25–75}$, the HR of new onset asthma was 0.34 (95% CI 0.21 to 0.56) in communities with low $PM_{2.5}$ (<13.7 μg/m$^3$) and 0.76 (95% CI 0.45 to 1.26) in communities with high $PM_{2.5}$ (≥13.7 μg/m$^3$). A similar pattern was observed for forced expiratory volume in 1 s. Little variation in HR was observed for ozone.
**Conclusion:** Exposure to high levels of $PM_{2.5}$ attenuates the protective effect of better lung function against new onset asthma.

Asthma is a major cause of childhood morbidity and has high social and economic costs.[1] Current research suggests a complex aetiological pathway for asthma,[2] and there is emerging evidence that air pollution is one environmental factor that may be involved in the pathogenesis of the disease.[3] Both indoor pollution[4] and traffic exposure[5] have been associated with an increased risk of asthma in children. In the Children's Health Study (CHS),[6 7] a longitudinal cohort study of air pollution, genetics and respiratory health, we have reported that the genetic risk factors for asthma depend upon exposure to ambient air pollution.[8] For example, we found that the protective effect of a polymorphism in the promoter region of tumour necrosis factor α was attenuated by ambient ozone levels. This suggests that air pollution may overwhelm the protective effects of certain alleles and increase the risk of asthma in a subset of children.

Based on these observations, we suggest that air pollution modifies the risk of asthma associated with other constitutive factors such as lung function which may reflect an integrative index of respiratory health. The evidence supports a protective role for high lung function in asthma development. Flow rates during the first year of life have been associated with the subsequent onset of asthma and persistent wheeze in some[9 10] but not all studies.[11] However, if different environmental exposures such as air pollution attenuate the protective effect of better lung function in some studies, these differences might be expected to occur based on pathophysiology. One class of pollutants of interest is ambient particulate matter which has been associated with small airway remodelling (a hallmark of asthma),[12] low airway flow rates[13 14] and impaired lung function growth.[15] These studies suggest that there may be joint effects of air pollution and lung function on asthma.

To assess the hypothesis that higher lung function is associated with reduced risk for childhood asthma, but that ambient air pollution attenuates this effect, we examined air pollution, lung function and health data from the CHS. Among children without asthma at study entry, we examined the relationship between spirometric measurements of lung volumes and airway flows and the subsequent risk of new onset asthma in communities with different levels of air pollution.

## METHODS

### Study design and cohort

The design, methods and characteristics of the CHS have been described previously.[6 7] Briefly, school children were enrolled into the study in 1993 from 12 communities in southern California (selected on the basis of different ambient pollution levels). At study entry parents or guardians of the children completed a questionnaire regarding children's medical history and sociodemographic factors (for details see Methods in online supplement available at http://thorax.bmj.com/supplemental). This study was approved by the Institutional Review Board of University of Southern California.

To provide a targeted age range (9–10 years of age at baseline) in which to assess the effect of lung function on the risk of asthma from childhood through adolescence, the analysis was restricted to fourth grade cohorts who (1) were free of any wheezing or physician-diagnosed asthma at study

**Abbreviations:** $FEF_{25–75}$, forced expiratory flow over the mid-range of expiration; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; $NO_2$, nitrogen dioxide; $O_3$, ozone; $PM_{10}$, $PM_{2.5}$, particulate matter with an aerodynamic diameter <10 μm and <2.5 μm

entry, (2) could perform adequate lung function manoeuvres at study entry and (3) had at least one follow-up assessment (n = 2057).

### New onset asthma

Children who were disease-free at baseline and reported physician-diagnosed asthma at annual follow-up testing were classified as having new onset asthma. As the follow-up occurred annually, the date of onset was assigned to the midpoint of the interval between the interview date when asthma diagnosis was first reported and the previous interview date. During the interview the children also provided information regarding recent use of any inhaled asthma medication.

### Air pollution data

Ambient levels of ozone ($O_3$), nitrogen dioxide ($NO_2$), particulate matter with an aerodynamic diameter $<10$ μm ($PM_{10}$) and $<2.5$ μm ($PM_{2.5}$), acid vapour and elemental and organic carbon in each of the 12 communities were measured at air monitoring sites from 1994 onwards. Long-term mean pollutant levels (from 1994 to the end of 2003) were calculated for use in the statistical analysis. Owing to a high correlation between $PM_{2.5}$, $NO_2$, acid vapour, $PM_{10}$ and elemental and organic carbon (but not ozone), these can be considered as a correlated non-ozone ''package'' of pollutants with a similar pattern relative to each other across the 12 communities. Communities defined as ''high'' or ''low'' based on any of the non-ozone ''package'' of pollutants were the same for all of the correlated pollutants (for details see Methods section in online supplement available at http://thorax.bmj.com/supplemental).

### Lung function measurement

Data on children's lung function were collected by trained field technicians who visited the schools annually. Maximal effort spirometric tests, standing height and weight were measured. Details regarding the lung function testing protocol have been published previously.[6] These activities covered the period 1993–2004. Three measures of lung function were analysed: forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_1$) and forced expiratory flow over the mid-range of expiration ($FEF_{25–75}$). Sex-specific percentage predicted lung function values were calculated using linear regression (for detail see Methods section in online supplement available at http://thorax.bmj.com/supplemental).

The percentage predicted lung function values were scaled to the 10th–90th percentile range of the corresponding lung function, and also categorised into three groups based on cut-off points that provided an adequate distribution for analyses. The categories were $<90\%$, 90–100% and $>100\%$ of predicted for FVC and $FEV_1$ and $<100\%$, 100–120% and $>120\%$ for $FEF_{25–75}$.

### Sociodemographic and medical history information

Personal information such as ethnicity, birth weight, premature birth, maternal smoking during pregnancy and allergy histories was collected at study entry. A family history of asthma was defined as asthma in any of the biological parents. Body mass index (BMI) was categorised into age- and sex-specific percentiles based on the Centers for Disease Control (CDC) BMI growth charts using 1-month age intervals.[16] Participants with BMI at or above the 85th percentile were classified as overweight. These personal characteristics and household and indoor exposures (pets, pests, humidifier use and household smoking) were considered as potential effect modifiers as well as confounders in the analysis.

### Statistical methods

We fitted Cox proportional hazards models with sex- and age-specific (age defined as integer age at study entry) baseline hazards to investigate the association between new onset asthma and lung function at study entry. Initially, we fitted lung function as both categorical and continuous terms. In the absence of any non-linear association between lung function and new onset asthma (tested by adding quadratic terms for the lung functions in the continuous models as well as by fitting models with categorical lung function terms) based on likelihood ratio tests, we report results using lung function as a continuous term. The hazard ratio (HR) can be interpreted as the change in risk of new onset asthma as the lung function increases over the 10th–90th percentile range of the corresponding lung function. We also fitted proportional hazard models treating annual lung function as 1- or 2-year lagged time-dependent covariates. All models were adjusted for community and race/ethnicity. Additional covariates were considered for inclusion in the model based on whether their inclusion changed the lung function effect estimate by more than 10%. Heterogeneity of associations among subgroups was assessed by comparing appropriate models with and without interaction terms.

To assess the effect of ambient air pollution on the relationship between lung function and new onset asthma, we estimated the heterogeneity of association using community levels of air pollutants measured at one monitor in each community. To address this issue we fitted hierarchical two-stage models to these time-dependent data (for details see Methods section in online supplement available at http://thorax.bmj.com/supplemental).[17]

All analyses were conducted using SAS software (SAS Institute, Cary, NC, USA) Version 9.1. All hypothesis testing was conducted assuming a 0.05 significance level and a two-sided alternative hypothesis.

## RESULTS

### Subject characteristics

Most of the 2057 disease-free children included in this analysis were 10 years of age or less at study entry and non-Hispanic white (table 1). Most children had health insurance and parents with at least a high school education. The median and mean years of follow-up were 8 and 6.5 years, respectively, for the 1993 cohort and 8 and 6.2 years, respectively, for the 1996 cohort (8 years maximum possible for both cohorts). The completeness of the follow-up data was calculated as the ratio of observed and maximum possible years of follow-up. Overall, the children were followed for 79% of the possible time of observation over the 8-year period of the study. The completeness of follow-up did not vary substantially across any of the subgroups (table 1). Based on telephone interviews with the families of subjects with asthma or wheeze at study entry who left the schools, the loss to follow-up was mainly due to employment-related moves of families out of the school catchment area (data not shown). Thus, the loss to follow-up was random and not related to any exposure or disease status.

There was no difference between the children included in the study and those who were excluded owing to insufficient lung function assessments (n = 521) with respect to age, sex, in utero and environmental exposure to smoking, parental education, parental asthma status and health insurance. However, those included in the study were slightly more likely to be non-Hispanic white, to have dogs at home and a higher parental income than those with insufficient lung function assessments (see table E3 in online supplement available at http://thorax.bmj.com/supplemental).

**Table 1** Selected characteristics of participants with no history of physician-diagnosed asthma at study entry

| Selected characteristics at study entry* | N (2057) | Ratio of observed to total possible person-years† |
|---|---|---|
| Age at entry (years) | | |
| 7–9 | 1441 | 0.80 |
| 10 | 557 | 0.79 |
| 11–12 | 59 | 0.67 |
| Race/ethnicity | | |
| Non-Hispanic white | 1094 | 0.80 |
| Hispanic | 651 | 0.79 |
| African-American | 110 | 0.70 |
| Asian | 101 | 0.86 |
| Mixed | 63 | 0.76 |
| Other/unknown | 38 | 0.60 |
| Gender | | |
| Female | 1095 | 0.80 |
| Male | 962 | 0.78 |
| Overweight at entry | | |
| No | 1778 | 0.79 |
| Yes | 279 | 0.77 |
| Parental history of asthma | | |
| No | 1651 | 0.80 |
| Yes | 273 | 0.79 |
| History of allergic rhinitis | | |
| No | 1688 | 0.79 |
| Yes | 322 | 0.78 |
| Humidifier use | | |
| No | 1470 | 0.80 |
| Yes | 497 | 0.77 |
| Maternal smoking during pregnancy | | |
| No | 1700 | 0.80 |
| Yes | 293 | 0.74 |
| Postnatal maternal smoking | | |
| No | 1830 | 0.80 |
| Yes | 189 | 0.74 |
| Household second hand smoking | | |
| No | 1658 | 0.80 |
| Yes | 357 | 0.76 |
| Pests in home | | |
| No | 1455 | 0.76 |
| Yes | 923 | 0.80 |
| Dogs in home | | |
| No | 923 | 0.79 |
| Yes | 1134 | 0.79 |
| Pets in home | | |
| No | 495 | 0.79 |
| Yes | 1562 | 0.79 |
| Health insurance | | |
| No | 358 | 0.78 |
| Yes | 1661 | 0.79 |
| Parental income (US$/year) | | |
| ⩽14 999 | 307 | 0.74 |
| 15 000–49 999 | 749 | 0.79 |
| >50 000 | 697 | 0.81 |
| Parental education | | |
| Less than high school | 295 | 0.77 |
| At least high school | 392 | 0.79 |
| Some college | 822 | 0.79 |
| College and above | 464 | 0.81 |
| Cohort | | |
| 1993 | 1046 | 0.80 |
| 1996 | 1011 | 0.78 |

*Numbers do not add up to 2057 because of missing data.
†Total possible years of observation was 8 years (4th–12th grades).

## Lung function and asthma

There were 212 new cases of asthma resulting in an incidence rate of 16.1/1000 person-years. The incidence of newly diagnosed asthma was inversely associated with measures of airflow at study entry (see table E4 in online supplement available at http://thorax.bmj.com/supplemental). For example, the incidence rate of newly diagnosed asthma increased from 9.5/1000 person-years for children with percentage predicted $FEF_{25–75}$ values ⩾120% to 20.4/1000 person-years for children with $FEF_{25–75}$ values ⩽100%. A similar inverse relationship was observed for $FEV_1$ but was less clear for FVC.

Over the 10th–90th percentile range for $FEF_{25–75}$ (57.1) the hazard ratio (HR) of new onset asthma was 0.50 (95% CI 0.35 to 0.71), table 2. A similar significant inverse association was observed for $FEV_1$. The results from lagged models were very similar to the baseline analysis, except for FVC where a statistically significant inverse relationship was also observed between FVC and new onset asthma. These inverse associations were not confounded or modified by birth weight, premature birth, parental history of asthma, history of allergy, second hand smoke, current and in utero maternal smoking, personal smoking, physical activity, health insurance, overweight or by parental income or education.

## Interrelationship between ambient air pollution, lung function and new onset asthma

The incidence rates across lung function categories differed markedly between "high" (13.7–29.5 μg/m$^3$) and "low" (5.7–8.5 μg/m$^3$) $PM_{2.5}$ communities (table 3). The incidence rate of asthma for $FEF_{25–75}$ ⩾120% in the "high" $PM_{2.5}$ communities was 15.9/1000 person-years compared with 6.4/1000 person-years in "low" $PM_{2.5}$ communities. However, there was little difference in the incidence rate of asthma for $FEF_{25–75}$ 80–100% in the "high" and "low" $PM_{2.5}$ communities. In addition, loss of protection by high lung function against new onset asthma in the "high" $PM_{2.5}$ communities was observed for all of the lung function measures. Over the 10th–90th percentile range of $FEV_{25–75}$, for example, the HR of new onset asthma was 0.34 (95% CI 0.21 to 0.56) in the "low" $PM_{2.5}$ communities, whereas this protective effect was reduced to 0.76 (95% CI 0.45 to 1.26) in the "high" $PM_{2.5}$ communities (table 4). There were no substantial differences in the effect of lung function between "high" and "low" ozone communities.

Using a hierarchical model, we evaluated the effect of individual air pollutants ($NO_2$, $PM_{10}$, $PM_{2.5}$, acid vapour, ozone and elemental and organic carbon) on the association between lung function and asthma (fig 1). The loss of the protective effect from better lung function can be appreciated from the graphs. The modifying effect of $PM_{2.5}$, $PM_{10}$ and organic carbon was statistically significant ($p \leqslant 0.05$) and that of $NO_2$, elemental carbon and acid vapour was marginally significant ($p \leqslant 0.08$). Of all the pollutants, $PM_{2.5}$ appeared to have the strongest modifying effect on the association between lung function with asthma as it had the highest $R^2$ value (0.42). For each 57.1% (10th–90th range) change in $FEF_{25–75}$, the risk of asthma decreased by 0.35-fold in a community with ambient $PM_{2.5}$ levels of 10 μg/m$^3$ whereas this protective effect was attenuated to 0.90-fold in a community with ambient $PM_{2.5}$ levels of 25 μg/m$^3$ (fig 1).

## Sensitivity analysis

To assess the effects of potential misclassification of new onset asthma we limited the definition of incident asthma cases to those who also reported recent use of inhalers. The observed associations were similar to the primary analysis (see tables E5 and E6, model 1, in online supplement available at http://thorax.bmj.com/supplemental). Restricting the analysis to children aged 10 years or less at study entry (see tables E5 and E6, model 2, in online supplement available at http://thorax.bmj.com/supplemental) or children without extreme values of lung function (5th–95th percentile) (see tables E5 and E6, model 3, in online supplement available at http://thorax.bmj.com/supplemental) also did not alter our initial findings. The association also remained unchanged after adjusting for ambient $PM_{2.5}$ (see table E5, model 4, in online supplement available at http://thorax.bmj.com/supplemental)

**Table 2** Association between newly diagnosed asthma and lung function at study entry, and lung function 1 and 2 years before asthma diagnosis

| | Study entry (N = 2057) | 1-year lag (N = 1882) | 2-year lag (N = 1673) |
|---|---|---|---|
| Lung function* | HR (95% CI)† | HR (95% CI)† | HR (95% CI)† |
| FVC (%) | 0.94 (0.68 to 1.32) | 0.66 (0.47 to 0.94)‡ | 0.71 (0.48 to 1.05)¶ |
| $FEV_1$ (%) | 0.68 (0.48 to 0.95)‡ | 0.50 (0.37 to 0.68)§ | 0.57 (0.39 to 0.82)§ |
| $FEF_{25–75}$ (%) | 0.50 (0.35 to 0.71)§ | 0.38 (0.26 to 0.55)§ | 0.49 (0.32 to 0.76)§ |

FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 s; $FEF_{25–75}$, forced expiratory flow over the mid-range of expiration.
*The percentage predicted lung function measures are scaled to 10th–90th percentile values as follows: 25.3% for FVC, 26.2% for FEV and 57.1% for $FEF_{25–75}$.
†Hazard ratio and 95% confidence interval.
‡$p<0.05$; §$p<0.005$, ¶$p<0.10$.

and risk factors of low lung function after birth, ie, preterm birth, birth weight, maternal smoking during pregnancy and parental history of asthma (tables E5 and E6, model 4, in online supplement available at http://thorax.bmj.com/supplemental).

## DISCUSSION

The joint effect of air pollution and lung function in the development of asthma during adolescence has not been characterised previously. The results of this study show that better airflow, characterised by higher $FEF_{25–75}$ and $FEV_1$ during childhood, was associated with a decreased risk of new onset asthma during adolescence. However, exposure to high levels of $PM_{2.5}$ (or $PM_{10}$, $NO_2$, acid vapour, elemental carbon or organic carbon) attenuated this protective association of lung function on the occurrence of asthma.

Although the protective effect of better lung function on the development of asthma has been observed in other studies, the attenuation of this effect with increasing levels of particulate and related non-ozone pollutants is a new observation. The explanation of this pattern of effects is unclear. However, chronic inflammation and resulting airway remodelling is a central pathophysiological characteristic of asthma[18] and, in one necroscopic study, chronic exposure to high levels of particulate air pollution was associated with small airway remodelling characterised by increase in fibrous tissue and smooth muscle in respiratory bronchioles.[12] The authors concluded that those changes could result in chronic airflow obstruction. Furthermore, exposure to a high level of particulate matter and ozone was associated with radiological evidence of bronchiolar disease and mild bronchial wall thickening on CT scans in children 5–13 years of age.[19] In our study it is possible that chronic inflammation in the distal airways induced by air pollution led to remodelling of the airways that modified the protection conferred by better lung function (or associated risk factors) on the subsequent development of asthma.

**Table 3** Incidence rate (IR) with 95% CI of new onset asthma stratified by community-specific annual average $PM_{2.5}$ (and other non-ozone pollutant) levels (1994–2001)*

| | Low $PM_{2.5}$ | High $PM_{2.5}$ |
|---|---|---|
| Lung function | IR (95% CI)† | IR (95% CI)† |
| FVC (% predicted) | | |
| ⩽90 | 19.4 (7.5 to 50.5) | 14.2 (5.1 to 39.6) |
| 90–110 | 16.8 (7.0 to 40.1) | 25.6 (11.1 to 59.2) |
| >110 | 7.9 (2.9 to 21.9) | 16.7 (6.5 to 42.9) |
| $FEV_1$ (% predicted) | | |
| ⩽90 | 23.7 (9.4 to 59.4) | 20.8 (8.0 to 54.0) |
| 90–110 | 15.6 (6.5 to 37.4) | 23.1 (10.0 to 53.7) |
| >110 | 6.5 (2.3 to 18.7) | 18.8 (7.5 to 47.3) |
| $FEF_{25–75}$ (% predicted) | | |
| 80–100 | 21.1 (8.8 to 50.5) | 23.8 (10.2 to 55.6) |
| 100–120 | 11.9 (4.7 to 30.0) | 23.9 (9.9 to 57.7) |
| ⩾120 | 6.4 (2.3 to 18.2) | 15.9 (6.3 to 40.5) |
| Overall IR (95% CI) | 14.2 (7.0 to 28.7) | 18.4 (9.4 to 35.9) |

FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 s; $FEF_{25–75}$, forced expiratory flow over the mid-range of expiration; $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 μm.
*The 12 communities were grouped by annual $PM_{2.5}$ level into six high (13.7–29.5 μg/m$^3$) and six low (5.7–8.5 μg/m$^3$) communities. However, the same grouping and estimates would occur if the communities were grouped by $NO_2$, $PM_{10}$, acids, elemental carbon or organic carbon.
†Adjusted incidence rate of newly diagnosed asthma (per 1000 person-years) for different categories of lung function is reported by high and low $PM_{2.5}$ (non-ozone pollutant) communities, adjusted for community, sex and race/ethnicity.

We have interpreted our results as a protective effect of better lung function that was attenuated by the effects of air pollution. Our data do not support an alternative hypothesis that particulate air pollution increased rates of incident asthma among children with poor lung function at study entry because rates among those with poor lung function were similar in both low and high pollution communities (table 3). This interpretation is also consistent with previous analyses in this cohort in which we found that the reduced risk of asthma associated with the TNFα-308 GG genotype (a promoter variant of tumour necrosis factor) was attenuated by ambient ozone levels.[8] It is therefore likely that evolutionary selection has resulted in lung structure and other characteristics that promote better respiratory health. Better lung function may be a marker for lower susceptibility to airway pathophysiology.

Higher flow rates are well correlated with a lower prevalence of airway hyper-reactivity,[20–22] a phenotype characteristic of asthma which has common genetic determinants with the disease.[23] Furthermore, it has been observed that the age-related decline in the prevalence of airway hyper-reactivity is larger among those with higher $FEV_1$%.[24]

Our results are consistent with the limited number of previous cohort studies that have found that higher flow rates in school children were associated with a lower risk of asthma and wheezing in adults.[25 26] Because our cohort was not recruited at birth, we could not evaluate the effect of lung function very early in life on the risk of asthma. Studies that measured lung function in the first month[10] or first year[11] of life showed that lung function tracked throughout childhood and adolescence. However, the association between early life lung function and subsequent development of wheeze and asthma was not consistent in these studies. In a US study, lung function during the first year of life was associated with subsequent late onset or persistent wheeze but not with transient wheeze.[27] An Australian study reported that lung function in the first month of life was associated with persistent wheeze but not with transient or late onset wheeze.[10]

**Table 4** Risk of new onset asthma by lung function, scaled to the 10th–90th percentile range, stratified by community-specific annual average $PM_{2.5}$ levels (1994–2003)*

| | Low $PM_{2.5}$ | High $PM_{2.5}$ | |
|---|---|---|---|
| **Lung function** | **HR† (95% CI)** | **HR† (95% CI)** | **Interaction p value‡** |
| FVC (% predicted) | 0.65 (0.41 to 1.03)§ | 1.41 (0.87 to 2.26) | 0.02 |
| $FEV_1$ (% predicted) | 0.46 (0.30 to 0.71)¶ | 1.08 (0.66 to 1.76) | 0.01 |
| $FEF_{25–75}$ (% predicted) | 0.34 (0.21 to 0.56)¶ | 0.76 (0.45 to 1.26) | 0.03 |

FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 s; $FEF_{25–75}$, forced expiratory flow over the mid-range of expiration; $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 μm.
*The 12 communities were grouped by annual $PM_{2.5}$ level into six "high" and six "low" communities. However, the same grouping and estimates would occur if the communities were grouped by $NO_2$, $PM_{10}$, acid, elemental carbon or organic carbon.
†Hazard ratio (HR) and 95% confidence interval of newly diagnosed asthma, scaled to the 10th–90th percentile range for each lung function, (25.3% for FVC, 26.2% for $FEV_1$ and 57.1% for $FEF_{25–75}$). All models were adjusted for community and race/ethnicity with age- and sex-specific baseline hazard.
‡Interaction p value based on likelihood ratio tests.
§p<0.10; ¶p<0.001.

It is possible that different constitutive factors such as genetic predisposition[28] and environmental exposures such as maternal smoking or other air pollutants[28] or sensitivity to different allergens influenced the pattern of wheeze associated with early deficits of lung function.[10 29] A recent study of a Norwegian birth cohort found that better lung function within days of birth was associated with a lower prevalence of asthma (16.2%) by age 10 compared with those with worse lung function (24.3%) after birth. However, the authors concluded that lung function ascertained within a few days of birth was not a good predictor of asthma at age 10 as the positive predictive value for asthma ranged from 24.3 to 31.3.[9]

The strength of our study was the 8-year follow-up of children in the fourth grade and the collection of their yearly lung function, asthma diagnosis and air pollution exposure in a consistent manner. The observed incidence rate of physician-diagnosed asthma in the present study (16.1 cases/1000 person-years) was similar to the increasing occurrence of asthma in

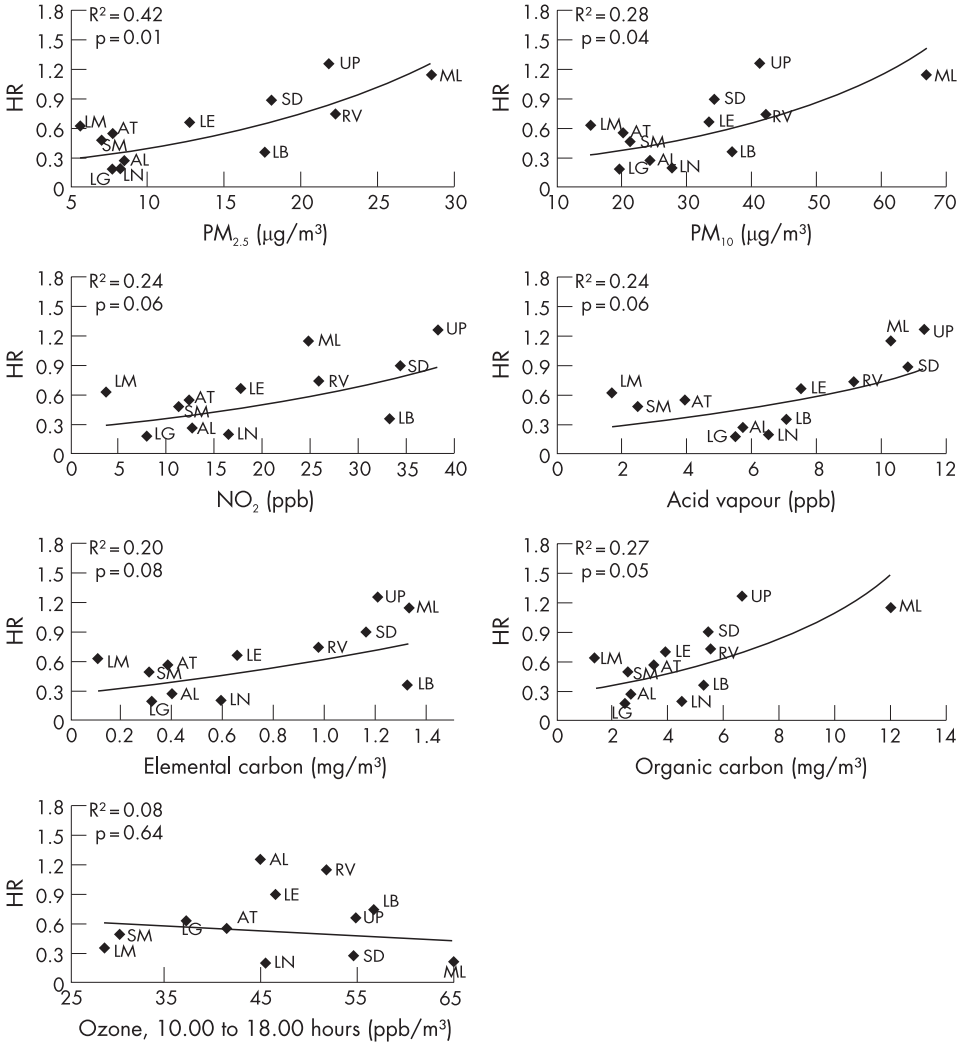


**Figure 1** Community-specific hazard ratio (HR) of newly diagnosed asthma over 10th–90th percentile range (57.1%) of forced expiratory flow over the mid-range of expiration ($FEF_{25–75\%}$) by average levels of different ambient pollutants. $PM_{2.5}$, particulate matter with an aerodynamic diameter <2.5 μm; $PM_{10}$, particulate matter with an aerodynamic diameter <10 μm; $NO_2$, nitrogen dioxide.

recent decades in children.[30–33] The retention rate in this cohort is similar to other longitudinal studies involving children with lung function assessments,[27 34] with an observed follow-up of 79% of the total possible person-years. Furthermore, the 521 children excluded from the study because of insufficient follow-up data did not differ from those included in this analysis with respect to covariates pertinent to the incidence of asthma (see table E3 in online supplement available at http://thorax.bmj.com/supplemental).

As this is not a birth cohort study, 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,[10 27 34] it is possible that the cases of new onset asthma in our study were undiagnosed cases of asthma and had low lung function at study entry. This seems unlikely because children with any history of wheeze or asthma as well as children without a history of wheezing at study entry were excluded (~40% of the cohort). Furthermore, the flow rates at study entry in children who developed new onset asthma were significantly higher than those of children with early transient or early persistent wheeze (see Lung function by wheeze status in online supplement available at http://thorax.bmj.com/supplemental) who could have low lung function[10 11 27] and might be misclassified as ''non-asthmatic'' at study entry by forgetful parents. The observed associations also remained essentially unchanged even after removing those with extreme values (see tables E5 and E6, model 3, in online supplement available at http://thorax.bmj.com/supplemental). Furthermore, if the observed association between flow rates and new onset asthma were mediated through early low lung function, then adjustment for risk factors for low lung function after birth and ambient $PM_{2.5}$ should have attenuated the effects of lung flow on the risk of asthma. However, we did not observe any such effect (see tables E5 and E6, model 4, in online supplement available at http://thorax.bmj.com/supplemental). Tracking of lung function, undiagnosed pre-existing asthma and low lung function at study entry due to ambient $PM_{2.5}$ level are therefore unlikely to explain our results.

Another potential limitation of our study could be the accuracy of new onset asthma as it was based on personal interview of the children; however, a recent study noted that children as young as 7 years can provide information regarding their asthma with an acceptable level of validity and reliability.[35] In our analysis we addressed the possibility that some children might have pre-existing undiagnosed asthma by excluding incident asthma cases diagnosed within the first 2 years of follow-up in the lagged time-dependent analysis. The similarity in the associations between the time-dependent lagged and baseline models makes it unlikely that the observed associations were only due to misclassification of asthma status at cohort entry or during follow-up.

Another potential concern may be that the results of this study are due to chance as we have used three different lung function measurements and tested interaction with ozone and the six correlated non-ozone pollutants. However, we do not think this is the case as the choice of the lung function measurements and the pollutants are based on a priori hypothesis[15] and all the results show a consistent pattern. Furthermore, the lung function parameters and the non-ozone group of pollutants are correlated so a Bonferroni type of adjustment is not appropriate in this setting.

In conclusion, our data suggest that better lung function during childhood provides protection against the development of asthma during adolescence. However, this protective effect of better lung function was attenuated by exposure to higher levels of ambient particulate matter ($PM_{2.5}$ and $PM_{10}$), $NO_2$, acid vapour and elemental and organic carbon. Further research is needed to clarify the mechanism by which air pollution modifies the protective effect of better lung function on the development of asthma.

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Further details are given in the online supplement available at http://thorax.bmj.com/supplemental.

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## REFERENCES

1 **Akinbami L**. The state of childhood asthma, United States, 1980–2005. *Adv Data* 2006:1–24.
2 **Reed CE**. The natural history of asthma. *J Allergy Clin Immunol* 2006;**118**:543–50.
3 **Gilmour MI**, Jaakkola MS, London SJ, *et al*. How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. *Environ Health Perspect* 2006;**114**:627–33.
4 **Delfino RJ**. Epidemiologic evidence for asthma and exposure to air toxics: linkages between occupational, indoor, and community air pollution research. *Environ Health Perspect*, 2002;**110**(Suppl 4), 573–89.
5 **McConnell R**, Berhane K, Yao L, *et al*. Traffic, susceptibility, and childhood asthma. *Environ Health Perspect* 2006;**114**:766–72.
6 **Peters JM**, Avol E, Gauderman WJ, *et al*. A study of twelve Southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. *Am J Respir Crit Care Med* 1999;**159**:768–75.
7 **Peters JM**, Avol E, Navidi W, *et al*. A study of twelve Southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. *Am J Respir Crit Care Med* 1999;**159**:760–7.
8 **Li YF**, Gauderman WJ, Avol E, *et al*. Associations of tumor necrosis factor G-308A with childhood asthma and wheezing. *Am J Respir Crit Care Med* 2006;**173**:970–6.
9 **Haland G**, Carlsen KC, Sandvik L, *et al*. Reduced lung function at birth and the risk of asthma at 10 years of age. *N Engl J Med* 2006;**355**:1682–9.
10 **Turner SW**, Palmer LJ, Rye PJ, *et al*. The relationship between infant airway function, childhood airway responsiveness, and asthma. *Am J Respir Crit Care Med* 2004;**169**:921–7.
11 **Martinez FD**, Wright AL, Taussig LM, *et al*. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;**332**:133–8.
12 **Churg A**, Brauer M, del Carmen Avila-Casado M, *et al*. Chronic exposure to high levels of particulate air pollution and small airway remodeling. *Environ Health Perspect* 2003;**111**:714–8.
13 **Higgins BG**, Francis HC, Yates C, *et al*. Environmental exposure to air pollution and allergens and peak flow changes. *Eur Respir J* 2000;**16**:61–6.

14 **Balmes JR**, Chen LL, Scannell C, *et al*. Ozone-induced decrements in $FEV_1$ and FVC do not correlate with measures of inflammation. *Am J Respir Crit Care Med* 1996;**153**:904–9.
15 **Gauderman WJ**, Avol E, Gilliland F, *et al*. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;**351**:1057–67.
16 **CDC**. *SAS code for calculating percentiles and Z-scores*. http://www.cdc.gov/nccdphp/dnpa/growthcharts/sas.htm.
17 **Berhane K**, Gauderman W, Stram D, *et al*. Statistical issues in studies of the long term effects of air pollution: the Southern California Children Health Study (with discussion). *Stat Sci* 2004;**19**:414–49.
18 **Vignola AM**, Chanez P, Bonsignore G, *et al*. Structural consequences of airway inflammation in asthma. *J Allergy Clin Immunol* 2000;**105**:S514–7.
19 **Calderon-Garciduenas L**, Mora-Tiscareno A, Fordham LA, *et al*. Lung radiology and pulmonary function of children chronically exposed to air pollution. *Environ Health Perspect* 2006;**114**:1432–7.
20 **Ciprandi G**, Cirillo I, Vizzaccaro A, *et al*. Early bronchial airflow impairment in patients with persistent allergic rhinitis and bronchial hyperreactivity. *Respir Med* 2005;**99**:1606–12.
21 **Cirillo I**, Klersy C, Marseglia GL, *et al*. Role of $FEF_{25\%–75\%}$ as a predictor of bronchial hyperreactivity in allergic patients. *Ann Allergy Asthma Immunol* 2006;**96**:692–700.
22 **Litonjua AA**, Sparrow D, Weiss ST. The $FEF_{25–75}$/FVC ratio is associated with methacholine airway responsiveness. The Normative Aging Study. *Am J Respir Crit Care Med* 1999;**159**:1574–9.
23 **Clarke JR**, Jenkins MA, Hopper JL, *et al*. Evidence for genetic associations between asthma, atopy, and bronchial hyperresponsiveness: a study of 8 to 18-year-old twins. *Am J Respir Crit Care Med* 2000;**162**:2188–93.
24 **Ulrik CS**, Backer V. Longitudinal determinants of bronchial responsiveness to inhaled histamine. *Chest* 1998;**113**:973–9.
25 **Toelle BG**, Xuan W, Peat JK, *et al*. Childhood factors that predict asthma in young adulthood. *Eur Respir J* 2004;**23**:66–70.
26 **Jenkins MA**, Hopper JL, Bowes G, *et al*. Factors in childhood as predictors of asthma in adult life. *BMJ* 1994;**309**:90–3.
27 **Morgan WJ**, Stern DA, Sherrill DL, *et al*. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;**172**:1253–8.
28 **Young S**, Arnott J, O'Keeffe PT, *et al*. The association between early life lung function and wheezing during the first 2 yrs of life. *Eur Respir J* 2000;**15**:151–7.
29 **Rhodes HL**, Thomas P, Sporik R, *et al*. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. *Am J Respir Crit Care Med* 2002;**165**:176–80.
30 **Beckett WS**, Jacobs DR Jr, Yu X, *et al*. Asthma is associated with weight gain in females but not males, independent of physical activity. *Am J Respir Crit Care Med* 2001;**164**:2045–50.
31 **Norrman E**, Nystrom L, Jonsson E, *et al*. Prevalence and incidence of asthma and rhinoconjunctivitis in Swedish teenagers. *Allergy* 1998;**53**:28–35.
32 **Ronmark E**, Jonsson E, Platts-Mills T, *et al*. Incidence and remission of asthma in schoolchildren: report from the Obstructive Lung Disease in Northern Sweden studies. *Pediatrics* 2001;**107**:e37.
33 **Strachan DP**, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996;**312**:1195–9.
34 **Sears MR**, Greene JM, Willan AR, *et al*. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;**349**:1414–22.
35 **Olson LM**, Radecki L, Frintner MP, *et al*. At what age can children report dependably on their asthma health status? *Pediatrics* 2007;**119**:e93–102.


# LUNG ALERT

## High index of suspicion required when screening new entrants for tuberculosis

▲ Laifer G, Widmer AF, Simcock M, *et al*. TB in a low-incidence country: differences between new immigrants, foreign-born residents and native residents. *Am J Med* 2007;**120**:350–6.

In this Swiss study, the authors divided 385 patients with suspected tuberculosis (TB) into three groups: immigrants, foreign-born residents (from moderate- to high-incidence countries) and native residents. Immigrants displaying an abnormal chest radiograph on entry to the country were compared with the other two groups who had suspected TB. Each of the groups was assessed for clinical signs and symptoms of TB, laboratory markers of inflammation and sputum culture.

The results showed that new immigrants who were later diagnosed as having active TB, either on the basis of culture results or response to treatment, failed to display traditional clinical signs and symptoms (17% of immigrants had night sweats, compared with 39% of native residents) and mounted a lower inflammatory response systemically. Seventy three per cent of immigrants had a normal C reactive protein level, with the mean being 17 g/l compared with a mean of 67.1 g/l in foreign-born residents and 90 g/l in native residents. The immigrant population group also yielded fewer positive sputum cultures but had a higher proportion of multi-drug resistant strains. It appeared that the main factor leading to a diagnosis of TB in the immigrant group was an abnormal chest radiograph.

The authors concluded that a chest radiograph alongside rapid diagnostic tests, including sputum smear and PCR, seemed to be most effective at reaching the correct diagnosis rapidly. The authors do point out that the differences in clinical features seen may be due to selection bias because all new entrants were screened, whereas only residents who presented with disease were included in the study. Nonetheless, it is important to carefully work up new entrants with abnormal chest radiographs—a message particularly important in countries with low incidence rates for TB. The authors suggest that post-migration follow-up in addition to active testing should be reinforced to prevent the slippage of positive individuals through the net of passive testing.

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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 $FEV_1$and $FEF_{25-75}$) and ratios ($FEV_1$/FVC and $FEF_{25-75}$/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 $FEF_{25-75}$) 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:


1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133-8.
2. Haland G, Carlsen KC, Sandvik L, Devulapalli CS, Munthe-Kaas MC, Pettersen M, et al. Reduced lung function at birth and the risk of asthma at 10 years of age. *N Engl J Med* 2006;355(16):1682-9.
3. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: Follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172(10):1253-8.
4. Turner SW, Palmer LJ, Rye PJ, Gibson NA, Judge PK, Cox M, et al. The relationship between infant airway function, childhood airway responsiveness, and asthma. *Am J Respir Crit Care Med* 2004;169(8):921-7.
5. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349(15):1414-22.

Table E3: Percent-predicted lung function (mean ± se)[*] by wheeze status.

| Asthma Status[2] (N) | FVC Mean (SE) | $FEV_1$ Mean (SE) | $FEF_{25-75}$ Mean (SE) | $FEV_1$/FVC Mean (SE) | $FEF_{25-75}$/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

# The Relationship between Air Pollution, Lung Function and Asthma in Adolescents

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Online Data Supplement

## METHOD

Fourth, seventh, and tenth grade children were enrolled into the study in 1993 from 12 communities in southern California, (selected on the basis of different ambient pollution levels). In 1996, an additional fourth grade cohort from the same communities and schools was added to the study. The average participation rate of students in each classroom was 81%. At study entry parents or guardians of the children completed a questionnaire, which provided demographic information, characterized history of prior respiratory illness and its associated risk factors, and household characteristics. At study entry and in each subsequent year until high school graduation, children provided information on asthma symptoms, diagnoses of asthma and smoke exposure.

### Study cohort

To provide a targeted age range in which to assess the effect of lung function on asthma risk from childhood through adolescence, this analysis was restricted to the two fourth grade cohorts (n=4,273). Lifetime history of asthma and wheezing at cohort entry was defined using questionnaire responses. Approximately 34% of the children had a history of asthma (n=681) or wheezing (n=763) at study entry. Children with any history of asthma/wheeze were excluded from the primary. To ensure a study population that was free of any previous history of wheeze or asthma, we also excluded children who did not have wheeze information (n=244) at study entry or had a history of serious childhood chest disease (i.e. chest surgery or cystic fibrosis) (n=7). Children who did not perform adequate lung function maneuvers at study entry (n=206) and subjects with less than one follow-up assessment (precluding incident asthma diagnoses, n=315) were excluded from the analysis of this study. These exclusions resulted in a total of 2,057 children classified as 'disease free' at baseline (Table 1).

### Sociodemographic and medical history information

Ethnicity was defined as non-Hispanic white, Hispanic, African American, Asian, and mixed/other ethnicities. Selected aspects of children's early medical histories such as birth weight, preterm birth and duration of gestation and any special care at birth were collected at baseline from the parents. Parental history of asthma and allergy was collected at baseline. Family history of asthma and allergy was defined as any biological parent having been diagnosed with asthma. Parents also provided history of any allergies for their children. We categorized BMI into age- and sex-specific percentiles based on the Centers for Disease Control (CDC) BMI growth charts using one-month age intervals (11). Participants with BMI at or above the $85^{th}$ percentile were classified as overweight. Participation in team sports was used to assign children's physical activity levels.

### Air-pollution data

Air-pollution–monitoring stations were established in each of the 12 communities in 1993. These stations have been measuring average hourly levels of ozone ($O_3$), nitrogen dioxide ($NO_2$) and particulate matter with an aerodynamic diameter of less than 10 μm ($PM_{10}$) since their establishment. Two-week integrated-filter samples for measuring acid vapor and the mass and chemical makeup of particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) were also collected. Acid vapor included both inorganic acids (nitric and hydrochloric) and organic acids (formic and acetic). For statistical analysis, we used total acid computed as the sum of nitric, formic and acetic acid levels. Hydrochloric acid was excluded from this sum, since levels were very low and close to the limit of detection. We also determined the levels of

elemental carbon and organic carbon using method 5040 of the National Institute for Occupational Safety and Health.[1] We computed annual averages on the basis of average levels in a 24-hour period in the case of $PM_{10}$ and nitrogen dioxide, and a two-week period in the case of $PM_{2.5}$, elemental carbon, organic carbon and acid vapor. For ozone, we computed the annual average of the levels obtained from 10 a.m. to 6 p.m. (the eight-hour daytime average) and of the one-hour maximal levels. We also calculated long-term mean pollutant levels (from 1994 through 2003) for use in the statistical analysis of the lung-function outcomes. As relative position of the communities in respect to any given pollutant did not vary substantially between years, the long term average was the proper metric to be used in the analysis.

We have previously shown that the average levels of study pollutants of the 12 communities of this study varied substantially between the communities, but there was little year-to-year (1994-2001) variation in levels within any one community(2). Similar to our earlier report, average level of $O_3$ was not correlated with any of the other pollutants though a significant correlation was observed between all other study pollutants during the period 1994-2003 (Table E1). Thus, $PM_{2.5}$, $NO_2$, acid vapor, $PM_{10}$ and elemental and organic carbon are a correlated non-ozone 'package' of pollutants with a similar pattern relative to each other across the 12 communities. The annual ranking of the communities into 'high' (six communities) and 'low' (six communities) based on annual average of ozone or any of the non-ozone 'package' of pollutants remained consistent throughout the calendar years between 1994 and 2003. Communities defined as 'high' or 'low' based on any of the non-ozone 'package' of pollutants were the same for all of the correlated pollutants. Thus the communities stratified into 'high' and 'low' based on the $PM_{2.5}$ level should be considered 'high' and 'low' for all of the non-ozone pollutants. However, we have defined them as high/low $PM_{2.5}$ because $PM_{2.5}$ showed the strongest effect in statistical associations between lung function and new onset asthma (Figure 1).

Table E1. Correlation of mean air-pollution levels from 1994 through 2003 across the 12 communities*

| Pollutant | $NO_2$ | Acid Vapor | $PM_{10}$ | $PM_{2.5}$ | Elemental Carbon | Organic Carbon |
|---|---|---|---|---|---|---|
| | | | | R values | | |
| Ozone (10a.m.-6p.m.) | -0.10 | 0.36 | 0.17 | 0.15 | -0.04 | 0.12 |
| $NO_2$ | | 0.86 | 0.67 | 0.81 | 0.94 | 0.64 |
| Acid Vapor† | | | 0.79 | 0.86 | 0.88 | 0.75 |
| $PM_{10}$ | | | | 0.95 | 0.85 | 0.97 |
| $PM_{2.5}$ | | | | | 0.92 | 0.90 |
| Elemental Carbon | | | | | | 0.88 |

* Unless otherwise noted, values are the 24 hour average pollution levels. $NO_2$ denotes nitrogen dioxide and $PM_{2.5}$ and $PM_{10}$ particulate matter with an aerodynamic diameter of less than 2.5 μm and less than 10 μm, respectively. All pairwise correlations were significant except between ozone and other pollutants.

† Acid vapor is the sum of nitric, formic and acetic acid.

**Lung function measurement**

To determine the predicted lung function values, i.e., FVC, $FEV_1$ and $FEF_{25-75,}$ we fitted a gender-specific linear regression model for log-transformed observed lung function values with the known predictors from previous literature.[2,3] The selection of the best prediction model

was based on the attained $R^2$. The best model for predicting lung function included race ("White", "Hispanic", "African-American", "Asian", "Mixed" or "Others"), log values for height, body-mass index, the square of body-mass index, any exercise or respiratory tract illness on the day of the test, exposure to secondhand tobacco smoke and indicator variables for field technician and spirometer. The predicted model attained $R^2$ value of 0.80 or better for FVC and $FEV_1$ in both sexes but was much lower for $FEF_{25-75}$, 0.44 for girls and 0.54 for boys. An $R^2$ value above 0.60 or 0.80 could be attained for $FEF_{25-75}$ if the prediction model also included observed FVC or $FEV_1$ values. Previous publications also have noted similar low $R^2$ values for $FEF_{25-75}$ [4,5] when the prediction model does not include any lung function terms. The percent predicted lung function was computed by dividing the observed lung function measurement by the predicted values and was expressed in percentage (%). A percent predicted value of less than 100% meant that the child's observed lung function was lower than the expected value. The percent predicted lung function values were similar in both sexes at study entry (Table E2). The percent predicted values and ratios in this study were similar to earlier published reports.[3, 4] The $FEV_1$/FVC values ranged from 64-100% with less than 8% of children having baseline value less than 80%. The $FEF_{25-75}$ values ranged from 31.7% to 212.8% though 5%-95% of the data ranged from 68.4%-140.1%.

**Ambient air pollution, lung function and asthma**

To assess the effect of ambient air pollution on the relationship between lung function and new asthma, we needed to consider the possible effect of the communities as all children within a community had the same exposure levels. To address this issue we fitted two stage models to this time dependent data.[6] Letting $\lambda(t)$ be the expected hazard rate for asthma in this population and $\lambda_{bs/sex\text{-}age}(t)$ be the sex- and age-specific baseline hazard, then the first stage proportional hazard model[24] has the following form:

Stage 1: $\lambda(t) = \lambda_{bs/sex\text{-}age}(t) \exp\{b_{cLF}Z + \gamma W\}$ ……(1)

where, $b_{cLF}$ corresponds to 12 community-specific slopes of lung function on asthma risk. This model is further adjusted for different individual level covariates, W (such as race/ ethnicity). The first stage model is followed by an ecologic regression model in the form:

$b_{cLF} = \delta_0 + \delta X_c + \eta_c$ ……(2)

The parameter $\delta_0$, the mean of the within-community slopes $b_{cLF}$, serves as an aggregated effect estimate of lung function across communities. However, our parameter of interest is $\delta$, which characterizes the modifying effect of the long-term average pollution levels ($X_c$) on the relationship between lung function and asthma. Note that the second stage model (2) accounts for heterogeneity in the community specific slopes via $\eta_c$. The second stage "ecologic" regression is weighted by the inverses of the variances of $b_{cLF}$.

Using this framework, we fitted separate models for seven pollutants; $O_3$ (10 a.m.–6 p.m. daily average ozone), and averages of $PM_{10}$, $PM_{2.5}$, $NO_2$, acid vapor (sum of nitric, formic and acetic acid), and elemental and organic carbon. The averages were based on available daily (or bi-weekly) pollutant levels from 1994 to 2003. The effect of ambient pollution on the relationship between lung function and new onset asthma was graphically presented by plotting the pollutant on the X-axis and community specific hazard ratio over the 10th-$90^{th}$ percentile range of lung function on the Y-axis. The exponential regression line is drawn through the predicted values derived from the stage two equations.

Table E2: Descriptive statistics of lung functions at study entry (age 7-9 years) for Children's Health Study participants without any history of physician-diagnosed asthma.

| Sex | N | Variable | Mean (%) | Standard Dev (%) | Median (%) | Lower Quartile (%) | Upper Quartile (%) | Minimum (%) | Maximum (%) |
|---|---|---|---|---|---|---|---|---|---|
| Girls | 1095 | FVC | 100.6 | 10.7 | 100.5 | 94.1 | 107.4 | 50.4 | 138.6 |
| | | $FEV_1$ | 100.6 | 11.0 | 100.8 | 93.7 | 108.1 | 35.6 | 136.6 |
| | | $FEV_1$/FVC | 89.3 | 5.3 | 89.3 | 86.2 | 92.3 | 64.2 | 100.0 |
| | | $FEF_{25-75}$ | 102.8 | 23.4 | 101.9 | 87.3 | 117.5 | 31.6 | 212.8 |
| | | $FEF_{25-75}$/FVC | 110.6 | 26.1 | 109.1 | 91.4 | 127.2 | 37.1 | 217.3 |
| Boys | 962 | FVC | 100.5 | 9.8 | 100.5 | 93.6 | 107.1 | 60.9 | 135.0 |
| | | $FEV_1$ | 100.5 | 10.2 | 100.3 | 93.9 | 106.8 | 68.9 | 141.8 |
| | | $FEV_1$/FVC | 87.4 | 5.0 | 87.4 | 84.4 | 90.3 | 64.0 | 100.0 |
| | | $FEF_{25-75}$ | 102.3 | 21.5 | 100.7 | 87.1 | 116.5 | 36.6 | 178.5 |
| | | $FEF_{25-75}$/FVC | 101.2 | 23.3 | 99.4 | 85.0 | 114.1 | 36.2 | 202.1 |

Table E3: Comparison of selected characteristics of Children's Health Study participants between those with (n=2,057) and without (n=521) sufficient lung function assessment

| | N (2057) | % | N (521) | % | P-value |
|---|---|---|---|---|---|
| Age at Entry | | | | | |
| 7-9 Years | 1441 | 70.0 | 326 | 62.6 | 0.38 |
| 10 Years | 557 | 27.1 | 164 | 31.5 | |
| 11-12 Years | 59 | 2.9 | 31 | 5.9 | |
| Race/ethnicity | | | | | |
| Non-Hispanic white | 1094 | 53.2 | 249 | 47.8 | 0.04 |
| Hispanic | 651 | 31.7 | 170 | 32.6 | |
| African-American | 110 | 5.4 | 40 | 7.7 | |
| Asian | 101 | 4.9 | 16 | 3.1 | |
| Mixed | 63 | 3.1 | 19 | 3.6 | |
| Other/unknown | 38 | 1.9 | 27 | 5.2 | |
| Gender | | | | | |
| Female | 1095 | 53.2 | 282 | 54.1 | 0.86 |
| Male | 962 | 46.8 | 239 | 45.9 | |
| Parental history of asthma | 273 | 13.3 | 76 | 14.6 | 0.41 |
| History of allergy | 371 | 18.0 | 88 | 16.9 | 0.92 |
| History of allergic rhinitis | 322 | 15.7 | 102 | 19.7 | 0.61 |
| Humidifier use | 497 | 24.2 | 107 | 20.5 | 0.60 |
| Maternal Smoking during pregnancy | 293 | 14.2 | 93 | 17.8 | 0.63 |
| Postnatal maternal smoking | 189 | 9.2 | 82 | 15.7 | 0.17 |
| Household second-hand smoking | 357 | 17.4 | 132 | 25.3 | 0.17 |
| Pests in home | 1455 | 70.7 | 343 | 65.8 | 0.51 |
| Dogs in home | 1134 | 55.1 | 235 | 45.1 | 0.04 |
| Pets in home | 1562 | 75.9 | 352 | 67.6 | 0.07 |
| Health insurance | 1661 | 80.8 | 92 | 17.7 | 0.39 |
| Parental Income* | | | | | |
| ≤14,999 | 307 | 17.5 | 127 | 29.6 | 0.05 |
| 15,000-49,999 | 749 | 42.7 | 188 | 43.8 | |
| >50,000 | 697 | 39.8 | 114 | 26.6 | |
| Parental Education* | | | | | |
| Less than high school | 295 | 14.9 | 100 | 20.1 | 0.26 |
| High school or greater | 1678 | 85.1 | 397 | 79.9 | |
| Cohort | | | | | |
| 1993 | 1046 | 50.9 | 291 | 55.9 | 0.19 |
| 1996 | 1011 | 49.1 | 230 | 44.1 | |

*Numbers don’t add up to 2057 due to presence of missing data.

Table E4: Cumulative incidence rate, person years of follow-up and number of newly diagnosed cases of asthma, by lung function categories.

| Lung Function | Person Years | New Asthmatics | Cumulative Incidence Rate (per 1000 person year) |
|---|---|---|---|
| FVC(%Predicted)* | | | |
| <=90 | 1942.0 | 28 | 14.4 |
| 90-110 | 8656.6 | 157 | 18.1 |
| >110 | 2437.5 | 25 | 10.2 |
| $FEV_1$(%Predicted) | | | |
| <=90 | 1858.6 | 36 | 19.4 |
| 90-110 | 8776.1 | 150 | 17.1 |
| >110 | 2425.3 | 25 | 10.3 |
| $FEF_{25-75}$ (%Predicted) | | | |
| 80-100 | 5987.8 | 122 | 20.4 |
| 100-120 | 4071.3 | 62 | 15.2 |
| >=120 | 2844.1 | 27 | 9.5 |
| Total | 13130.6 | 212 | 16.1 |

*Percent predicted is calculated as the percentage of observed lung function values over predicted.

Table E5: Association of lung function categories at study entry with new onset asthma among CHS children, adjusted relative risk (HR) and 95% confidence intervals (95% CI)*

| Lung Function | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | RR | 95%CI | RR | 95%CI | RR | 95%CI | RR | 95%CI |
| FVC% | 0.87 | (0.60-1.27) | 0.81 | (0.51-1.28) | 0.90 | (0.61-1.32) | 0.95 | (0.67-1.34) |
| FEV% | 0.64 | (0.44-0.94)† | 0.57 | (0.37-0.87)† | 0.63 | (0.43-0.92)† | 0.67 | (0.47-0.96) † |
| $FEF_{25-75}$% | 0.53 | (0.35-0.79)‡ | 0.47 | (0.29-0.75)‡ | 0.46 | (0.30-0.70)‡ | 0.50 | (0.34-0.72) ‡ |

*All Cox models are adjusted for race/ethnicity and communities with separate baseline hazards for gender and age at entry.
† P-val<0.05
‡P-val<0.005
Model 1: The asthma definition is restricted to children with inhaler use.
Model 2: The analysis is restricted to children less than 10 years of age at study entry.
Model 3: The analysis is restricted to $5^{th}$ to $95^{th}$ percentile of lung function.
Model 4: The analysis is adjusted for preterm birth, birth weight, maternal smoking during pregnancy, family history of asthma and ambient $PM_{2.5}$.

Table E6: Risk of new onset asthma for $FEV_1$ scaled to $10^{th}$-$90^{th}$ percentile range, stratified by community specific annual average $PM_{2.5}$ level*

| Model | Low $PM_{2.5}$ | | High $PM_{2.5}$ | | P-value |
|---|---|---|---|---|---|
| | HR | 95%CI | HR | 95%CI | |
| Model 1 | 0.44 | (0.28-0.70) † | 1.10 | (0.68-1.78) | 0.05 |
| Model 2 | 0.41 | (0.14-0.69) † | 1.07 | (0.62-1.87) | 0.05 |
| Model 3 | 0.38 | (0.21-0.71) † | 0.85 | (0.47-1.55) | 0.04 |
| Model 4 | 0.41 | (0.25-0.67) † | 1.05 | (0.63-1.75) | 0.02 |

*All Cox models are adjusted for race/ethnicity and communities with separate baseline hazards for gender and age at entry.

† P-val<0.0001

Model 1: The asthma definition is restricted to children with inhaler use.

Model 2: The analysis is restricted to children less than 10 years of age at study entry.

Model 3: The analysis is restricted to $5^{th}$ to $95^{th}$ percentile of lung function.

Model 4: The analysis is adjusted for preterm birth, birth weight, maternal smoking during pregnancy and family history of asthma.

REFERENCES

1. Anonymous. Elemental carbon (diesel exhaust) No. 5040. *In* C. N. I. f. O. S. a. Health, editor. NIOSH manual of analytical methods. 1999.

2. Gauderman WJ, Avol E, Gilliland F, *et al*. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;**351**:1057-1067.

3. Peters JM, Avol E, Gauderman WJ, *et al.* A study of twelve Southern California communities with differing levels and types of air pollution. II. Effects on Pulmonary Function. *Am J Respir Crit Care Med* 1999;**159**:768-775.

4. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;**159**:179-187.

5. Pistelli R, Brancato G, Forastiere F, *et al*. Population values of lung volumes and flows in children: effect of sex, body mass and respiratory conditions. *Eur Respir J* 1992;**5**:463-470.

6. Berhane K, Gauderman W, Stram D, *et al*. Statistical issues in studies of the long term effects of air pollution: The Southern California Children Health Study (with discussion). *Stat Sci* 2004;**19**:414-449.