Sex differences in factors associated with childhood and adolescent onset wheeze; analysis of a longitudinal birth cohort

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Online supplement for METHODS

Study Members

All study participants are members of the Dunedin Multidisciplinary Health and Development Research Study, a longitudinal investigation of health and behavior in a complete birth cohort (7, 21, 24, 28-36, 49). The study members were born in Dunedin, New Zealand, between April 1972 and March 1973 Of these, 1037 children (91% of those eligible by residence; 52% male) participated in the first follow-up assessment at age 3, constituting the base sample of the remainder of the study. Cohort families represent the full range of socioeconomic status in the general population of New Zealand's South Island and are primarily Caucasians.

Children were invited to attend the study centre with a parent (usually mother) or guardian every two years between ages 3 and 15, and then at ages 18, 21 and 26 years. The research ethics committee of the Otago Hospital Board approved each assessment. The participants gave written informed consent from the age of 18 years; before that age, a parent or guardian gave written informed consent, and the child gave oral assent.

At each visit from age 7, study members had respiratory questionnaires. Spirometry was performed at each visit between ages 9 and 26 and methacholine challenge was completed at 9, 11, 13, 15 and 21 years. At age 13 and 21, study members underwent skin prick testing. Wheeze was defined as more than two episodes of wheezing lasting for at least one hour in the previous year. For this analysis, only study members who were seen at least once between ages 7 and 26 (n = 1023), and whose age of first wheezing symptoms (if wheezing occurred) could be determined (n = 1022) were included.

Respiratory questionnaires

At age 9 a comprehensive respiratory questionnaire was administered, drawing on questions frequently asked in other validated questionnaires, including occurrence and frequency of symptoms of wheezing and coughing at rest and on exertion, diagnoses of asthma and hayfever, characteristics of the home and bedroom, animal exposure, and other putative risk factors for asthma. These questions were repeated (where appropriate) at ages 11 through 26.

Parental history

At age 7, the guardian attending with the child (usually mother) was asked about the parental history, inquiring whether the child's natural mother or natural father had asthma, hayfever or allergies. The parental history was again requested of the study members attending at age 18. A parent was considered to have a history of atopy if asthma or hayfever was recorded at either the age 7 or age 18 visit. 'Any' maternal history includes all mothers with asthma or hayfever irrespective of paternal history. A similar definition was used for any paternal history. Any parental history included mother, father or both parents with a history of asthma or hayfever. To isolate the independent influence of maternal and paternal history on the development of wheeze, individuals with only a maternal or only a paternal history were identified and compared to study members where neither parent had a history of asthma or hayfever.

Skin allergy prick tests

Skin prick tests were performed in all consenting study members at ages 13 and 21, using the volar aspect of the forearm without specific skin preparation. Use of drugs containing antihistamines was documented, and skin tests invalidated if antihistamines had been used within the previous week. Tests were performed using the standard prick procedure(33), placing droplets of allergen on the skin and using disposable needles to lightly prick the skin without drawing blood. Needles were discarded after pricking each individual droplet of allergen. Skin tests were read at 15 minutes as the size of the resulting weal (to nearest mm).

Allergens tested at age 13 included house dust mite (dermatophagoides pteronyssinus) (Bencard, Middlesex, UK), mixed rye grass pollen, cat fur, dog fur, horse hair, kapok, cladosporium, alternaria, Aspergillus fumigatus, penicillium, and wool (Hollister-Stier, Spokane, Washington), together with positive (histamine) and negative (diluent) controls. At age 21, the same panel of allergens from the same sources were used, and cockroach (Hollister-Stier, Spokane, Washington) was added. A positive skin test was defined as a weal at least 2mm greater than that resulting from the negative control.

Spirometry

Spirometry was performed at each age from 9 to 21 years. At ages 9, 11, 13, 15 and 21, when methacholine challenge was also undertaken, spirometry was undertaken with a Godart water spirometer. Volume calibration was checked regularly with a 3-litre syringe. Study members were asked to inhale fully and then exhale their full vital capacity into the spirometer at a non-forced pace to record slow vital capacity. This was repeated to obtain at least 3 satisfactory and repeatable (to within 5%) measurements. Study members then performed a forced expiratory maneuver to record the forced exhaled volume in 1 second (FEV_1) and forced vital capacity (FVC), again on at least 3 occasions to obtain reproducible data. A Morgan rolling-seal spirometer was used at the age of 18 years, and a Sensormedics body plethysmograph at the age of 26 years. Measurements were made between 1 p.m. and 4 p.m. The predicted values at 26 years of age were based on a study of New Zealand adults (50).

If a bronchodilator was administered as part of the test, either as part of the protocol for all study members (at age 18 and 26) or because of baseline airflow obstruction of such severity that methacholine challenge was not a practical or safe test to perform (see below), the bronchodilator given was salbutamol (5 mg/ml nebuliser solution administered by Hudson updraft nebulizer during 2 minutes of tidal breathing up to age 15, or 2 puffs of 100 μg/puff salbutamol MDI using a valved holding chamber for study members at and after age 18). Change in FEV_1 with bronchodilator was expressed as the difference between the post-bronchodilator and pre-bronchodilator values as a percentage of the prebronchodilator value.

Methacholine challenge

Bronchial challenge was performed in all consenting study members, using an abbreviated protocol (32) modified from Chai et al (51) and validated against the tidal breathing method of Cockcroft et. al (52). After baseline spirometry to establish FEV_1 and FVC, and if the FEV_1/FVC ratio exceeded 70% (75% at ages 9 and 11), methacholine 0.025 mg/ml was nebulised through a Hudson updraft nebuliser (output 0.2 ml/min) and the study member asked to take 5 deep breaths of the aerosol. Spirometry was repeated at 30 sec and 2 min after inhalation. If the FEV_1 had not fallen more than 20% below initial baseline, subsequent inhalations of methacholine were given sequentially in ten-fold increasing concentrations of 0.25, 2.5 and 25.0 mg/ml, with spirometry after each dose. The test was

terminated when FEV_1 declined by more than 20% of baseline value, or the final concentration was reached, or (in a few instances) when symptoms were of concern. The concentration of methacholine causing exactly 20% fall in FEV_1 ($PC_{20}FEV_1$) was determined by interpolation on a log-linear plot of concentration and FEV_1. Methacholine challenge was considered positive if the concentration of methacholine needed to produce a $PC_{20}FEV_1$ was ≤ 8 mg/ml.

Other factors associated with asthma

Breast feeding was determined from questionnaires administered at age 3 and validated in the majority against prospective records maintained by visiting health nurses (31, 35, 36). When the children were seen for review at age nine years, a detailed environmental history was obtained from the accompanying adult, usually the birth mother. The presence of cats, dogs and other animals in or around the house at birth, and at ages 3, 5, 7 and 9 years was documented at that assessment. Birth order was derived from questionnaire data obtained at ages 5 and 9 years. Study members who stated they were a regular smoker at age 15 were defined as being a smoker at that phase. Subsequent smoking history was not used in this analysis. At each age, height without shoes, and weight in light clothing, were measured to calculate an individual's body mass index (BMI) in kg/m^2. Birth length and weight were also recorded.

Statistical analysis

Males and females were analyzed separately. For this analysis, children with recurrent wheezing reported at two or more assessments were classified as "wheezers". The youngest age at which wheezing was reported was used as the age of onset. The oldest age at which non-wheezers were seen was when data were censored. Analyses were repeated defining wheezers as those describing recurrent wheezing at three or more assessments, and also as those who had persistent or relapsing symptoms as previously described (7).

For categorical risk factors, Kaplan-Meier survival analysis was used with univariate analysis based on the log-rank test. For continuous variables, and to calculate univariate hazard rates, Cox regression modelling was used; the proportional hazard assumption was tested using log minus log

plots and by modeling a “time X factor” interaction term. Age-dependent risk was noted if hazard rates for childhood and adolescent-onset wheeze differed significantly.

We examined factors associated with onset of wheeze during childhood (to age 10) and adolescence (after age 10), To examine risk factors for adolescent onset wheeze, individuals who developed wheeze before age 10 were excluded from the analysis. Factors examined, including AHR, spirometry, personal and parental history of atopy, breast-feeding, exposure to parental smoking, maternal smoking during pregnancy, cat or dog ownership in childhood, body mass index (BMI), change in BMI between visits, and personal smoking. To isolate the independent influence of maternal and paternal history on the development of wheeze, individuals with only a maternal or only a paternal history were identified and compared to study members where neither parent had a history of asthma or hayfever. Multiple variable analyses by Cox regression used a backward likelihood ratio ($p \leq 0.05$ in; $p > 0.1$ out). All multiple regression analyses for adolescent onset wheeze were corrected for smoking at age 15. A secondary analysis identified factors associated with the development of wheeze by last follow-up at age 26. Statistical analysis was completed using SPSS version 12 (SPSS Inc. Chicago, Ill).