Protocol

Title of the research project: **Is childhood wheezy bronchitis an early determinant of chronic obstructive pulmonary disease? A longitudinal study**

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Background

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. In the UK ~900,000 people have diagnosed COPD and ~2 million have undiagnosed COPD; it is the fifth leading cause of death (30,000 deaths per annum) and the second most common reason for emergency hospital admission. Patients with COPD present from the 6th decade onwards with a mean age of diagnosis of about 67 years. Direct NHS costs of COPD exceed £800 million, but indirect costs are also substantial with about 24 million working days lost annually.

COPD is defined by lung function, the current international recommendation being a reduced ratio (<0.7) of post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC)[1]. Physiologically COPD is a consequence of accelerated rate of FEV_1 decline. The major risk factor for COPD is tobacco smoking, however the population-attributable fraction for smoking as a cause of COPD is <80%[2] and only a minority (10-20%) of smokers develop clinically significant disease highlighting the importance of individual susceptibility. This project will confirm whether an easily ascertained aspect of childhood medical history increases the likelihood of developing COPD in the 6-7th decades of life.

Many preschool children (20% by 6 years) develop wheezing symptoms (wheezy bronchitis/virus associated wheeze, WB/VAW) during episodes of viral respiratory tract infection but are asymptomatic thereafter[3;4]. Although WB/VAW is believed to have no long term consequences, emerging epidemiological findings suggest that childhood WB/VAW and COPD are closely associated, with several historical cohort studies reporting associations between childhood lower respiratory tract infections and reduced FEV_1 or COPD during adulthood[5;6]. In addition, longitudinal birth cohorts have demonstrated tracking of lung function with reduced neonatal/infant lung function being associated with reduced FEV_1 and FEV_1/FVC up to age 22 years[7].

Evidence also suggests that reduced lung function predates any WB/VAW, making it more likely that a child will exhibit clinical symptoms, such as wheeze, during respiratory tract infection[8]. These observations have led us to hypothesise that: *'The airway developmental trajectory that predisposes children to lower respiratory illnesses also predisposes these children to deficits in adult lung function that increase their likelihood of developing COPD*[9;10].

In this study we will test this hypothesis by following up the Aberdeen-based WHEASE (What Happens Eventually to Asthmatic children: Sociologically and Epidemiologically) cohort[9;11-24]. The WHEASE cohort was recruited from a 1964 cross-sectional primary school survey in Aberdeen. Recruitment included a clinical evaluation of 2511 children by an experienced paediatrician[18].The paediatrician diagnosed 121 children aged 10-15 with asthma (based on a history of wheeze precipitated by factors other than a cold or upper respiratory infection), 167 children were diagnosed with "wheezy bronchitis"/nowadays termed "viral associated wheeze" (based on a history of wheeze only in the presence of infection), never wheezing children were also identified and included in subsequent follow up as control subjects. The cohort has been followed sequentially in 1989 (WHEASE 1, total n=283), 1995 (WHEASE 2, n=326 including 108 with adult onset wheeze), and 2001 (WHEASE 3, n=380 including 56 with adult onset wheeze and 213 never childhood wheezed controls), with the assessments including measurement of FEV_1 and FVC.

In WHEASE 1 at age 34-40, lung function was persistently impaired in those with childhood asthma. In contrast, subjects with childhood WB/VAW had lung function similar to asymptomatic children and significantly less symptoms than those with childhood asthma. However by 2001 (WHEASE 3, age 45-51), when compared with controls, FEV_1 was lower in

those with a history of WB/VAW (mean [95%CI]:-0.18L[-0.38;-0.01]) or childhood asthma (-0.51L[-0.73;-0.30]) and both WB/VAW and childhood asthma groups were associated with a similar accelerated decline in FEV_1 over the previous 12 years -0.15L(-0.28;-0.04) and -0.15L(-0.27;-0.05) respectively[9;20]. These associations were independent of smoking. The results of WHEASE 3 are consistent with the proposal hypothesis and indicate that childhood WB/VAW is associated with an accelerated rate of FEV_1 decline during adult life. If sustained this may be associated with an increased likelihood of COPD.

In this study we will conduct the fourth follow up of the WHEASE cohort now aged 58-63 years with lung function defined COPD as the primary outcome. We anticipate that COPD will be more likely in subjects with a history of childhood WB/VAW. This study will be the longest longitudinal community-based study of childhood wheezing phenotypes worldwide and the first to relate childhood wheezing disease to COPD in the 6^{th}-7^{th} decades.

Aims and research questions

The aim of this study is to follow up the WHEASE cohort 48 years after recruitment and investigate the natural history of childhood wheezy bronchitis/virus-associated wheeze, childhood asthma and early origins of COPD.

Specific research questions are whether compared to those who never wheezed in childhood, adults in their 6-7^{th} decades with a history of childhood WB/VAW are more likely to:

1) develop COPD?
2) have an increased rate of FEV_1 decline?
3) have more respiratory symptoms?

Methods

This is the fourth follow up of a prospective cohort nested within a large randomly selected community-based survey of children recruited and characterised in 1964. All 380 subjects who took part in the WHEASE 3 study in 2001 will be contacted and invited to take part.

If we fail to find subjects using their recorded contact details, NHS Scotland's Community Health Index (CHI) system[25] will be used to trace subjects using NHS databases, this will be conducted by IT Services, University of Aberdeen Data Management Team.

To trace subjects living outwith Scotland the commercial service offered by Data Discovery Ltd, Edinburgh will be used.

Using the CHI system and National Records of Scotland we will identify those participants who are deceased and remove such individuals from our contact list.

We will also use CHI and Data Discovery to try and find those subjects from the original 1964 study with wheezy bronchitis or asthma whom researchers failed to trace in the 1989, 1995, or 2001 WHEASE studies.

Identified subjects will be sent an invitation (+ one reminder a month later if necessary) to participate. As in WHEASE 3 they will be interviewed by the research fellow either in the Chest Clinic, Aberdeen Royal Infirmary or at home. Subjects living outwith the Grampian area will be invited to complete the symptom questionnaire and if possible will be assessed in the clinic if they visit Aberdeen.

The research fellow will:

1. Collect demographic data
2. Measure subjects' height, and weight
3. Administer a modified version of the MRC 1986 Respiratory Symptoms Questionnaire and a generic physical/mental health-status questionnaire (SF-36)
4. Record past and present smoking habits, current medication, exposure to environmental tobacco smoke (ETS) and occupational history
5. Measure pre and post bronchodilator spirometry (FEV_1, FVC, FEF_{25-75}, PEF) 15 minutes after the administration of 400ug inhaled Salbutamol, performed to ATS/ERS standards.
6. Measure fraction of exhaled NO (FENO) using a hand-held device (MINO, Aerocrine)
7. Collect 10ml clotted and 10ml EDTA (ethylene-diamine-tetra-acetic acid) blood samples

The blood samples will be used to quantify IgE (atopic status) and cotinine as an objective measurement of active and passive tobacco smoke exposure[26].

The EDTA 'buffy coat' from which DNA can be extracted will be stored for the purposes of data preservation and sharing.

Surplus blood will be stored in NHS Grampian Biorepository, permissions from the subjects and NOSRES will be sought before their use outwith this project.

Participants will be asked if they would be willing to attend a separate appointment at the Pulmonary Function laboratory for measurement of carbon monoxide gas transfer and transfer coefficient.

Statistical methods: Data analysis will be conducted by the research fellow under the supervision of Dr Fielding. The data from WHEASE 4 will be merged with data from WHEASE 1, 2 & 3. The primary outcome of COPD will be related to childhood wheezing phenotype (WB, no wheeze, asthma,) using logistic regression with adjustment for confounding factors (age, sex, smoking history, socio-economic status). To analyse rate of FEV_1 decline a linear mixed effects model will be applied to lung function data collected during WHEASE 1, 2, 3 & 4 as it utilises the repeated structure of the data. Spirometry-defined COPD status and respiratory symptom data (wheeze, breathlessness on exertion) based on data collected in WHEASE 1,2,3 & 4 will be related to childhood wheezing phenotype (wheezy bronchitis, no wheeze, asthma,) using general estimating equations with adjustment for confounding factors (listed above).

Statistical power: WHEASE 4 utilises the pre-existing cohort and is restricted to the number of subjects studied previously. Extrapolating rates of FEV_1 and FVC decline between WHEASE 2 and 3 suggests that in WHEASE 4 childhood wheezy bronchitis should be associated with an increased likelihood of COPD (FEV_1/FVC ratio<0.7)[1] when compared with childhood controls (29% vs 12% respectively). Assuming a re-contact rate of 80% of the 380 WHEASE 3 participants we will recruit 52 childhood WB, 37 childhood asthmatics, 45 adult onset wheeze and 171 controls, totalling 305 participants. This will give us 80% power to detect the predicted difference in COPD between childhood WB and controls extrapolated from WHEASE 3 (i.e. 29% vs. 12%) at the 5% level of statistical significance. For the secondary outcome of rate of FEV_1 decline, the change in FEV_1 was calculated from existing WHEASE data. The mean (SD) change (reduction) in FEV_1 for the 45 with childhood asthma was 75.7mls (41.4); for the 63 with childhood wheezy bronchitis was 74.7mls (28.2); for the 212 controls was 61.2mls (33.0). With the expected response rate outlined above, using one-way analysis of variance to detect a difference in mean change in FEV_1 for the three groups (childhood asthma, wheezy bronchitis, controls) assuming common standard deviation of 33.4mls, a total sample size of 259 will have 81% power to detect these differences at the 5% significance level.

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