Does age of onset of asthma influence the effect of cigarette smoking on lung function?

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Worldwide prevalence of cigarette smoking in asthma ranges from 9% to 35% (1, 2). In the United States, about 21% of people with asthma smoke compared to 17% of the general population (3). Adverse effects of cigarette smoking in asthma include worse symptoms, increased chronic mucus hypersecretion and more exacerbations as well as an impaired therapeutic response to corticosteroids compared to never-smokers with asthma (1, 4, 5). Co-morbidities occur more frequently in people with asthma who smoke with higher rates of cardiovascular disease, pneumonia and lung cancer (4). Lung function is reduced (1, 4, 6) and a greater proportion of smokers with asthma develop persistent airflow obstruction. Potential pathways for the development of persistent airflow obstruction in asthma include sub-maximal lung growth and airway remodelling in childhood and/or accelerated rate of decline in lung function in adulthood. Asthma in childhood, particularly in those with severe disease, is a risk factor for impaired lung function in adulthood (7, 8). Several longitudinal population-based studies report accelerated decline in lung function in adults with asthma, particularly among cigarette smokers (9-12). Little is known however, about the effects of cigarette smoking on lung function in adulthood among people with childhood-onset persistent asthma, in particular, whether airway caliber is reduced by the effects of asthma in childhood and by the additional or synergistic effects of cigarette smoking in adulthood.

In this issue of the *Journal*, Hancox and colleagues (13) report the results of an important study that investigated the influence of childhood asthma and cigarette smoking on the development of airflow obstruction in adulthood using data from the Dunedin Multidisciplinary Health and Development Study. The study recruited 1037 individuals born in 1972/73 and monitored

health and behavior outcomes at regular intervals up until the age of 38 years. Information obtained included the diagnosis of asthma based on parental-reported or self-reported data, pre-and post-bronchodilator spirometric measurements (FEV_1/FVC ratios, FEV_1, FVC) at ages 18, 26, 32 and 38 years and cumulative active and second-hand tobacco smoke exposure histories. A strength of the Dunedin study is the high rates of participation in the longitudinal assessments over a lengthy-period of time. Persistent airflow limitation at age 38 was defined using a lower limit of normal set at 5th centile cut-points for post-bronchodilator FEV_1/FVC ratios among never-smokers with no history of asthma. The population was divided into four sub-groups: childhood-onset persistent asthma (n=91), late-onset asthma (n=93), asthma in remission (n=85), and non-asthmatic (n=572).

In the Dunedin study (13), active smoking history and childhood-onset asthma were both associated with reduced FEV_1/FVC ratios at 38 years of age. Of particular interest, a history of cigarette smoking was not associated with lower FEV_1/FVC ratios in the group with childhood-onset persistent asthma unlike the other sub-groups with late-onset asthma, asthma in remission or non-asthmatics, in whom cumulative smoking history was associated with lower FEV_1/FVC ratios. Approximately one third of participants with childhood-onset asthma had persistent airflow obstruction irrespective of a history of cigarette smoking. The findings were similar using GOLD criterion for persistent airflow obstruction (FEV_1/FVC ratio <70%). Interestingly, the lack of an adverse effect of cigarette smoking on the decline in lung function in childhood-onset persistent asthma was contrary to the author's original hypothesis (13).

Although important, the study by Hancox and colleagues (13) has some potential limitations. The diagnosis of asthma was based on self-reported data without objective confirmatory tests and some participants may have been misdiagnosed. A cut-off age of >13 years of age was used to define late-onset asthma, whereas other studies have used a higher cut-off at 18 years or older (14). As the pack-years history of 11.5 years at 38 years was relatively low, an interaction between cigarette smoking and childhood onset asthma may develop as the cohort progresses into later life due to increased exposure to tobacco smoke, particularly as 28.8% of the childhood-onset persistent asthma participants are still current smokers.

Despite these limitations, the results from the Dunedin study are of considerable interest. The finding that active smoking does not increase the risk of persistent airflow obstruction in young adults whose asthma started in childhood is supported by previous research. Children with persistent asthma recruited to the Melbourne Asthma Cohort who smoked as adults had a similar decline in lung function at 50 years of age as never-smokers with asthma (8). The Tucson Epidemiological Study of Airway Obstructive Disease (15) and the European Community Respiratory Health Survey (11) found that cigarette smokers with late-onset asthma had an increased risk of developing persistent airflow obstruction and a greater decline in lung function respectively compared to smokers with early-onset asthma. The Tasmanian Longitudinal Health Study, which included participants with both early-onset and late-onset asthma, found a synergistic effect on the development of persistent airflow obstruction of smoking, atopy and current asthma (12).

The study by Hancox and colleagues (13) was not designed to investigate mechanisms for the lack of an effect of cigarette smoking on lung function in childhood-onset persistent asthma. The variation in susceptibility to the adverse effects of tobacco smoke on lung function between people with asthma that first develops in childhood or adulthood is so far unexplained. Differences between age-related phenotypes in one or more of the following risk factors may be relevant including the effects of early-life events on lung structure, asthma-induced airway inflammation and remodelling, atopic status, onset and duration of treatment with inhaled corticosteroids, environmental exposures including second-hand smoke, genetic factors or other processes (5, 11, 12, 14).

In conclusion, Hancox and colleagues (13) study challenges the concept that cigarette smoking adversely effects lung function in asthma irrespective of the age of onset. The finding also highlights the need to consider age of onset of asthma as a potentially important variable when assessing the effects of cigarette smoking on clinical outcomes, airway inflammation and therapeutic responses in asthma and the asthma-COPD overlap syndrome. Finally, smoking cessation has a central place in management irrespective of the age of onset of asthma due to the harmful effects of cigarette smoking on the health of people with asthma.

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