

In conclusion, we have shown that in adult asthmatics who have a preserved FEV<sub>1</sub>, the presence of persistent small airway dysfunction was associated with poorer control, perhaps suggesting the presence of a defined small airway asthma phenotype.



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In asthmatics with preserved FEV<sub>1</sub>, small airway dysfunction was associated with poorer long-term control <http://ow.ly/yAWgY>

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# Reduced lung function and the risk of out-of-hospital sudden cardiac death

To the Editor:

Although some previous studies have shown that reduced lung function is related to cardiovascular mortality little is known about the relationship between lung function tests and the risk of sudden cardiac death (SCD) among the general population [1–5]. This prospective population-based study was designed to

determine if impaired lung function (forced expiratory volume in 1 s (FEV<sub>1</sub>)) is a risk factor for out-of-hospital SCD in the general male population.

The study population was a representative sample of males living in the city of Kuopio, Finland and its surrounding rural communities, who were 49–67 years of age at baseline examinations performed between 1991 and 1993. The study was approved by the Research Ethics Committee of the University of Kuopio (Kuopio, Finland) and each participant gave written informed consent. The study reported here is based on data obtained from 1441 participants who had data from lung function test measurements and did not have chronic obstructive pulmonary disease (COPD), asthma or lung cancer at baseline. The current analysis was based on males with complete spirometry data, whereas the whole population is described elsewhere [6]. During the 20-year follow-up period, a total 68 out-of-hospital SCDs occurred. Lung function was measured by FEV<sub>1</sub> using standard spirometry at baseline. There were no losses to follow-up.

A death was determined SCD when it occurred either within 1 h after the onset of an abrupt change in symptoms or within 24 h after onset of symptoms when clinical findings did not reveal a noncardiac cause of sudden death [6]. Risk factors for out-of-hospital SCD were analysed using Cox multivariate models. Cox models were adjusted for age and other demographic and clinical factors previously reported to be predictive of SCD by considering their clinical relevance. The multivariate model was further adjusted for smoking, alcohol consumption, systolic blood pressure, body mass index, serum low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, prevalent myocardial infarction, type 2 diabetes, and C-reactive protein. The analysis was repeated among smokers (n=401) and nonsmokers (n=849) separately. Relative risks with 95% confidence intervals, adjusted for clinical risk factors, were estimated as antilogarithms of the coefficients from multivariable models. Analyses were also performed on a model including males with lung diseases.

The mean value for FEV<sub>1</sub> was 96.6% predicted (range: 15.4–226.7% pred). Males who died due to SCD were older, had higher systolic and diastolic blood pressure, had higher serum levels of HDL cholesterol and triglycerides, were more likely to have prevalent coronary heart disease, previous myocardial infarction, hypertension and diabetes, and smoked more as compared with those who did not die due to SCD. Among 849 nonsmokers there were 36 SCD cases, whereas among 401 smokers 32 cases of SCD occurred. After adjusting for age, low FEV<sub>1</sub> (lowest quintile: <71.8% pred) was associated with a 5.6-fold increased risk of SCD (95% CI 2.32–13.71; p<0.001) as compared to the highest quintile of FEV<sub>1</sub> (≥118.9% pred). After further adjustment for established risk factors, the risk was a 3.5-fold increased risk for SCD among males in the lowest quintile. After additional adjustment for maximal oxygen uptake the relative risk for SCD was 2.90 (95% CI 1.16–7.23; p=0.02). When further adjusted for smoking status (current, former or never), in addition to pack-years, the results remained statistically significant (relative risk 3.3, 95% CI 1.33–8.07; p=0.009). We found that the C-index for discrimination changed from 0.794 (95% CI 0.739–0.846) to 0.815 (95% CI 0.783–0.844) after adding FEV<sub>1</sub> into the model, and integrated discrimination improvement was 0.018 (95% CI 0.005–0.030; p=0.005).

This prospective study shows that FEV<sub>1</sub> is associated with an increased risk of out-of-hospital SCD in the general population. The current study demonstrates that lung function tests provided prognostic value beyond that predicted by common cardiovascular risk factors among males with no history of COPD, asthma and lung cancer. Our findings indicate that airflow obstruction is an important risk factor for SCD in smokers (relative risk 5.7, 95% CI 1.17–27.56; p=0.031). Although systemic inflammation probably contributes to the association between the impairment of lung function and cardiovascular diseases (CVDs), factors including the capture and elimination of external toxic agents may also play a role in the prevention of CVDs [7]. It has been shown that C-reactive protein upregulates the production of pro-inflammatory cytokines and tissue factors by monocytes and increases the uptake of LDL by macrophages, interacting with other inflammatory mediators to create foam cells that in turn serve as building blocks for vulnerable atherosclerotic plaques [8, 9]. However, in this study, the association between FEV<sub>1</sub> and SCD remained significant, although the level of C-reactive protein was taken into account. Poor lung function with bronchial wall oedema can lead to airway obstruction inducing myocardial ischaemia [10, 11]. It has also been suggested that the increased risk may be associated with alcohol intake, which has been shown to influence lung function leading to SCD [12]. However, our main findings were independent of alcohol intake. A limitation of this study may be residual confounding due to unmeasured variables [5]. Another limitation of study was that we included only middle-aged males. Finally, we have no data on changes in health habits and medication during the follow-up period, which is well known issue in epidemiological studies.

These findings emphasise the importance of FEV<sub>1</sub> as potentially useful in risk stratification for out-of-hospital SCD in the general population, although further studies are needed.



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Reduced lung function is a robust predictor of out-of-hospital sudden cardiac death in middle-aged males <http://ow.ly/A0SjL>

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# Autonomic dysregulation: a mechanism of asthma death

To the Editor:

Therapeutic advances in the management of asthma have led to a gradual but sustained reduction in mortality [1, 2]. However, the death of otherwise healthy young individuals remains a tragic and all too frequent occurrence. The unheralded demise of two of our patients with previously minimally troublesome asthma led us to reconsider the mode of death in such patients. Numerous studies and retrospective reports have attributed such mortality to preventable factors such as inadequate severity assessment, discontinuity of medical care, poor concordance to prescribed therapies and poor management of acute asthma exacerbations [3, 4]; others have attributed fatalities to significant behavioural, socioeconomic or psychosocial factors including smoking, denial, depression and alcohol abuse [1, 5, 6].

Whilst these associations are undeniably important they do not adequately explain the observed clinical picture of precipitous deterioration, loss of consciousness, and death. ROBIN *et al.* [7] reported two patients with an abrupt demise, one during a telephone conversation and with no prior asthma-related symptoms. Grubb *et al.* [8] followed a teenage boy with a history of long-standing asthma after repeated near fatal asthma episodes requiring resuscitation. Our similar experience of two unexpected fatalities caused us to