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Early View

Research letter

Relationship between supernormal lung function and long-term risk of hospitalisations and mortality: a population-based cohort study

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Relationship between supernormal lung function and long-term risk of hospitalisations and mortality: a population-based cohort study

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Take home message: Supernormal lung function is associated with fewer cardiovascular and respiratory events and a survival benefit independent from major risk factors.

Cardiovascular and respiratory diseases are major contributors to global deaths[1]. Although low lung function is a risk factor for early death, like hypertension and hypercholesterolaemia[2], evaluation of lung function in primary care is not prioritised as highly as blood pressure or cholesterol measurements[3]. Also, public health authorities have remained silent on major health challenges other than smoking relevant for development and preservation of normal lung function from birth to old age. It is now increasingly evident that low lung function in childhood may affect general health throughout life[4-8]. It therefore seems likely that improvement of lung function on a population-scale may be associated with lower morbidity and mortality. We therefore tested the hypothesis that supernormal lung function is associated with lower morbidity and mortality.

We included 108,246 individuals aged 20-100 years from the Copenhagen General Population Study, an ongoing Danish contemporary population-based cohort recruited in 2003-2015[9-11]. All participants completed questionnaire, underwent physical examination, and provided blood for biochemical analyses. Pre-bronchodilator forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were measured[12]. The upper and lower limit of normal (ULN and LLN) for FVC and FEV_1 were defined as the highest or lowest 5th percentile of the predicted value, calculated as the mean value ±1.645 standard deviations according to internally derived reference equations[10,12]. Normal lung function was defined as FVC≥LLN and ≤ULN, and supernormal lung function as FVC>ULN. Individuals with below normal lung function, i.e. FEV_1<LLN and/or FVC<LLN, were excluded.

Information on acute admissions and vital status was obtained from the national Danish Patient Registry and Danish Civil Registration System, respectively, recorded until December 2018. Information on cause of death was obtained from the national Danish Causes of Death Registry recorded until December 2016. Admission and death due to respiratory disease (International Classification of Diseases [ICD]-10:J00-J99) and cardiovascular disease (ICD-10:E00-E99) was

based on the underlying cause. Any acute admission included also other diseases besides respiratory and cardiovascular. Death due to cancer (ICD-10:C00-C99) was included as a negative control outcome.

Cox regression was used to determine risk of admission and death during follow-up. Age was used as the underlying timescale, and hence automatically adjusted for in the analyses, while accounting for delayed time-entry (i.e. left truncation meaning individuals are at risk only from study entry). Analyses were adjusted for well-known major respiratory and cardiovascular risk factors obtained at baseline examination, that is, age (as timescale), sex, measured body mass index (BMI, kg/m^2), measured waist-hip ratio, smoking status (never, former, or current), cumulative tobacco consumption (pack-years), socioeconomic status based on education after school (no education, high school, other education up to 3 years, vocational training, longer education at least 3 years, and university education) and annual household income (converted as 1 Danish Krone to 0.13 Euro [EUR]: <26,000 EUR, 26,000-52,000 EUR, 52,000-78,000 EUR, 78,000-104,000 EUR, and >104,000 EUR), leisure-time physical activity (none or light activity <2 hours/week, light activity 2-4 hours/week, light activity >4 hours/week or heavy activity 2-4 hours/week, and heavy activity >4 hours/week or regular exercises per week), blood pressure, cholesterol, alcohol consumption, and diabetes. Analyses were performed using STATA/SE 13.1 for Windows (StataCorp, College Station, Texas, US), and a two-sided P-value<0.05 was considered significant.

Among 108,246 individuals from the general population, 88,478 (82%) had normal lung function, 5,948 (5%) had supernormal lung function, and 13,820 (13%) had below normal lung function. Individuals with supernormal lung function had mean FVC of 5.21 L (corresponding to FVC 130% of predicted), whereas individuals with normal lung function had mean FVC of 3.95 L (FVC 101% of predicted). Compared to individuals with normal lung function, those with supernormal lung function were slightly younger, taller, had lower cumulative tobacco consumption, and less active

smoking (Figure 1, Panel A). Although highly statistically significant due to the large sample-size, no clinically relevant differences could be observed for well-known major respiratory and cardiovascular risk factors, including BMI, low physical activity, blood pressure, cholesterol, alcohol consumption, and diabetes.

During up to 15 years follow-up (median [interquartile range]:9.2 years [5.2]), we observed 63,225 acute admissions (7,452 respiratory; 15,044 cardiovascular) and 8,234 deaths (341 respiratory; 1,408 cardiovascular). Compared to individuals with normal lung function, multivariable adjusted hazard ratios (HRs) for individuals with supernormal lung function were 0.93(95% confidence interval:0.90-0.97) for any acute admission, 0.80(0.71-0.90) for respiratory admission, and 0.91(0.85-0.99) for cardiovascular admission (Figure 1, Panel B). Corresponding HRs were 0.84(0.76-0.93) for all-cause mortality, 0.49(0.25-0.98) for respiratory mortality, and 0.57(0.42-0.79) for cardiovascular mortality. Median survival was 2.3 years longer in those with supernormal versus normal lung function. The two groups did not differ in cancer mortality with corresponding HR of 0.91(0.75-1.11).

Results were similar in sensitivity analyses. When supernormal lung function was defined by calculating the predicted values according to Global Lung Initiative reference equations[13], multivariable adjusted corresponding HRs were 0.85(0.76-0.96) for all-cause mortality, 0.33(0.12-0.89) for respiratory mortality, and 0.56(0.39-0.82) for cardiovascular mortality. Corresponding HRs were 0.82(0.73-0.93), 0.44(0.19-0.99), and 0.66(0.47-0.93) when supernormal lung function was defined with FEV_1 instead of FVC, and were 0.85(0.76-0.94), 0.40(0.19-0.86), and 0.55(0.40-0.77) when supernormal lung function was defined as FVC in the upper 5th age, sex, and height adjusted percentile without use of reference equations. Corresponding HRs were 0.86(0.72-1.04), 0.13(0.10-3.67), and 0.71(0.43-1.18) in never-smokers, and were 0.81(0.71-0.93), 0.59(0.29-1.21), and 0.49(0.33-0.73) in ever-smokers without evidence of interaction.

In a Danish contemporary population-based cohort with 108,246 randomly selected adults followed for up to 15 years, we found that supernormal lung function is associated with fewer cardiovascular and respiratory events and a survival benefit independent from major risk factors. To our knowledge, this is the first study investigating supernormal lung function in the general population.

Individuals with supernormal lung function did not differ clinically from individuals with normal lung function with regard to age, sex, height, and major respiratory and cardiovascular risk factors, suggesting that other factors, possibly related to lung development, may explain the difference in lung function. In support of the lung development hypothesis, it has been suggested that individuals with supernormal lung function are those with a high peak in early adulthood[4]. Also, it has been shown that children with persistently high or low lung function seem to follow the same lung function trajectory up until early and late adulthood, and early life factors were the most important determinants of these lung function trajectories[14,15].

Strengths of the present study include a large contemporary general population cohort with randomly selected individuals, and information on clinically relevant morbidity and mortality outcomes without any losses to follow-up.

A potential limitation of the present study is that body plethysmography was not used to determine lung capacity, as it is not feasible to apply this highly specialised method in large-scale population-based cohorts, whereas spirometers are readily accessible and used in clinical practice. We did also observe similar results when supernormal lung function was defined with FEV_1 instead of FVC, which suggests that supernormal lung function could in principle have been defined with other lung function measures.

The benefit of having a supernormal lung function will likely be less prioritised than the detrimental effects of a low lung function. Nonetheless, the present study could be viewed as a first step in

exploring the relevance of development and preservation of best possible lung function from birth to old age for public health. Our results suggest that supernormal lung function is associated with fewer cardiovascular and respiratory events and a survival benefit independent from major risk factors.

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Competing interests: YÇ reports personal fees from Boehringer Ingelheim, AstraZeneca, and Sanofi Genzyme outside of the submitted work. JV reports personal fees from GlaxoSmithKline, Chiesi Pharmaceuticals, Boehringer Ingelheim, Novartis, and AstraZeneca, outside of the submitted work. JV is supported by the NIHR Manchester BRC. PL reports grants from AstraZeneca and GlaxoSmithKline and personal fees from Boehringer Ingelheim, AstraZeneca, Novartis, and GlaxoSmithKline outside of the submitted work. BGN and SA have nothing to disclose. The views expressed are those of the authors.

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FIGURE LEGEND

Figure 1. Baseline characteristics and risk of acute hospital admission and mortality in individuals with supernormal versus normal lung function in the general population. Based on the Copenhagen General Population Study. *Panel A:* Data presented as mean (SD), or number (percent). Numbers may not add up due to rounding. P-value for comparison calculated using Student's t-test or Pearson's chi-squared test. Cumulative tobacco consumption includes only smokers. *Panel B:* Hazard ratios (HRs) with 95% confidence intervals (CIs) were obtained from Cox regression with left truncation and age as the underlying timescale. Multivariable adjusted analyses included major respiratory and cardiovascular risk factors obtained at baseline examination, that is, age (as timescale), sex, body mass index, waist-hip ratio, smoking status, cumulative tobacco consumption (pack-years), socioeconomic status based on education after school and annual household income, leisure-time physical activity, blood pressure, cholesterol, alcohol consumption, and diabetes. FEV_1=forced expiratory volume in 1 second. FVC=forced vital capacity.

A. Baseline characteristics according to normal and supernormal lung function in individuals in the general population

	Normal lung function (n=88 478)	Supernormal lung function (n=5948)	P-value
Age – years	57.7 (13.2)	56.7 (13.4)	<0.001
Male sex – no. (%)	39 578 (45)	2698 (45)	0.35
Anthropometric measurements			
Weight – kg	76.7 (14.8)	75.4 (13.2)	<0.001
Height – cm	171 (9)	173 (10)	<0.001
Body mass index – kg/m^2	26.1 (4.1)	25.1 (3.4)	<0.001
Waist – cm	90 (13)	87 (11)	<0.001
Hip – cm	102 (8)	101 (7)	<0.001
Waist-hip ratio	0.87 (0.09)	0.86 (0.08)	<0.001
Lung function			
FEV_1 – L	3.07 (0.81)	3.83 (0.92)	<0.001
FEV_1 % predicted – %	98 (11)	120 (14)	<0.001
FVC – L	3.95 (0.98)	5.21 (1.08)	<0.001
FVC % predicted – %	101 (11)	130 (11)	<0.001
FEV_1/FVC	0.78 (0.06)	0.73 (0.07)	<0.001
Smoking information			
Never-smokers – no. (%)	38 953 (44)	2680 (45)	0.12
Former smokers – no. (%)	35 938 (41)	2554 (43)	<0.001
Current smokers – no. (%)	13 262 (15)	692 (12)	<0.001
Unknown smokers – no. (%)	325 (<1)	22 (<1)	0.98
Cumulative tobacco consumption – pack-years	19.2 (18.7)	15.0 (15.3)	<0.001
Poor socioeconomic status – no. (%)	14 676 (17)	677 (11)	<0.001
Low physical activity – no. (%)	4847 (5)	230 (4)	<0.001
Cholesterol – mmol/L	5.6 (1.1)	5.5 (1.0)	<0.001
Systolic blood pressure – mmHg	141 (21)	139 (20)	<0.001
Diastolic blood pressure – mmHg	84 (11)	83 (11)	<0.001
Alcohol – units/week	10 (10)	10 (9)	<0.001
Diabetes – no. (%)	3381 (4)	127 (2)	<0.001

B. Risk of acute hospital admission and mortality in individuals with supernormal versus normal lung function in the general population