

# Association of lung function with physical, mental and cognitive function in early old age

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## **Abstract**

Lung function predicts mortality, whether it is associated with functional status in the general population remains unclear. This study examined the association of lung function with multiple measures of functioning in early old age. Data are drawn from the Whitehall II study; data on lung function (forced expiratory volume in one second, height FEV<sub>1</sub>), walking speed (over 2.44 m), cognitive function (memory and reasoning), and self-reported physical and mental functioning (SF-36) were available on 4443 individuals, aged 50-74 years. In models adjusted for age, one standard deviation (SD) higher height-adjusted FEV<sub>1</sub> was associated with greater walking speed (beta=0.16, 95% CI: 0.13, 0.19), memory (beta=0.09, 95% CI: 0.06, 0.12), reasoning (beta=0.16, 95% CI: 0.13, 0.19), and self-reported physical functioning (beta=0.13, 95% CI: 0.10, 0.16). Socio-demographic measures, health behaviours (smoking, alcohol, physical activity, fruit/vegetable consumption), BMI and chronic conditions explained two-thirds of the association with walking speed and self-assessed physical functioning and over 80% of the association with cognitive function. Our results suggest that lung function is a good “summary” measure of overall functioning in early old age.

**Keywords:** ageing, lung function, cognitive function, physical function

Lung function is known to increase up to the mid-twenties and then diminish with age<sup>1;2</sup> as static recoil pressure of the lungs decreases leading to lowered forced expiratory flow and vital capacity. There is evidence, from at least two strands of research, to show that poor lung function is associated with poor functional status. One, research suggests that lung function predicts poor cognitive outcomes<sup>3-7</sup> and dementia<sup>8</sup>; perhaps due to changes in the central nervous system through processes such as subclinical vascular disease, resulting from inflammation, oxidative stress or cardiovascular risk factors,<sup>9</sup> or hypoxia-induced changes in neurotransmitter metabolism.<sup>10;11</sup> Two, Chronic Obstructive Pulmonary Disease (COPD) is associated with complex chronic comorbidities,<sup>12</sup> even in middle-aged patients.<sup>13;14</sup> There is also some evidence to support the hypothesis that pulmonary function is associated with physical function in the general population.<sup>14-16</sup>

Lung function,<sup>1;17-20</sup> like cognitive<sup>21</sup> and physical function<sup>22</sup>, declines with age. Whether lung function is a causal risk factor for cognitive and physical functioning is difficult to establish using observational data, as is the case in most of the studies in this domain. Nevertheless, the interrelationship between different aspects of functioning is important as the decline in lung function might be a forerunner of decline in physical and cognitive function. If this is the case, then determinants of lung function and decline might provide important targets of intervention. In this study we examine the relationship of lung function with cognitive and physical in early old age. As the data come from an observational study and the analysis cross-sectional we cannot infer causality. However, by examining the association of lung function with both cognitive and physical functioning we hope to gain better understanding of the importance of lung function for ageing outcomes.

## Methods

Data are drawn from Phase 7 (2002-2004) of the Whitehall II study, set up in 1985-1988 on 10,308 (67% men) individuals, aged 35-55 years.<sup>23</sup> All participants gave consent to participate and the University College London ethics committee (UCLH Committee Alpha, #85/0938) approved this study.

## Lung Function

Participants were allowed to opt out of spirometry testing if they were coughing up blood or had a pneumothorax, severe angina, heart attack, stroke, pulmonary embolism, aneurysm, a perforated ear drum or hernia, recent surgery (ear, eye, stomach, chest), or blood pressure >180/96 mmHg on the day; excluding 25.5% of participants.

Lung function was measured using a portable flow spirometer (MicroPlus Spirometer, Micro Medical Ltd, Kent, UK), administered by a trained nurse. We assessed *Forced Vital Capacity (FVC)* and *Forced Expiratory Volume in 1 second (FEV<sub>1</sub>)* based on standardised methods.<sup>24</sup> The largest FVC and FEV<sub>1</sub> values from the three manoeuvres was used in the analysis. As lung volumes are related to body size and standing height is the most important correlating variable, the lung function measure was corrected for height by dividing by the square of the subject's standing height and multiplying by the square of the sample mean height, 1.77 m in men and 1.63 m in women.<sup>25</sup> This standard correction procedure ensures that the observed variation in lung function is due to factors other than body size.

## Functioning

**Walking speed:** Walking speed was measured over a clearly marked 8-ft (2.44m) walking course using a standardized protocol.<sup>26</sup> Participants wore either low-heeled close-fitting footwear or walked barefoot with instructions to “walk to the other end of the course at

your usual walking pace, just as if you were walking down the street to go the shops. Walk all the way past the other end of the tape before you stop.” Three tests were conducted and the fastest walk (2.44 metres/minutes) was used in the analysis.

**Cognitive Function:** Two tests were used. The first was a test of *short-term verbal memory*, assessed with a 20-word free recall test. Participants were presented a list of 20 one or two syllable words at two second intervals and were then asked to recall in writing as many of the words in any order and had two minutes to do so. The second was a test of *reasoning*, the *Alice Heim 4-I (AH4-I)* test, composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty<sup>27</sup>. It tests inductive reasoning and with only 10 minutes allocated to the test it is also a measure of processing speed.

**Self-assessed health functioning** was assessed using the Short Form 36 (SF-36) General Health Survey Scales.<sup>28</sup> The SF-36 is a 36-item questionnaire on general health status that can be summarized into physical and mental components scores (PCS and MCS) to assess physical and mental functioning.<sup>29</sup> Physical functioning declines with age but mental functioning has been shown to improve with age.<sup>30</sup>

### **Covariates**

The covariates were *age*, *sex*, *ethnicity* (white or non-white), *education* (lower primary or lower, lower secondary, high school, first university degree or higher), *occupational position*, *health behaviours*, *Body Mass Index (BMI)* and *chronic conditions*. Occupational position, classified as high, (administrative grades), intermediate (professional or executive grades) and low (clerical or support grades) position) is a comprehensive marker of socioeconomic circumstances and is related to salary, social status and level of responsibility at work. As of August 1992 the salary range among high grade employees was £25 330 - £87 620 and among low grade employees £7 387 – £11 917.<sup>23</sup>

*Smoking* status was self-reported (never, ex, or current smoker). *Alcohol* consumption was assessed as number of alcoholic drinks (“measures” of spirits, “glasses” of wine, and “pints” of beer) consumed in the last week and converted to number of alcohol units (1 unit=8g alcohol) consumed per week.<sup>31</sup> This measure was highly skewed and was log transformed for the analysis. *Diet* was assessed via a question on the frequency of fruit and vegetable consumption (8-point scale, ranging from ‘seldom or never’ to ‘two or more times a day’), converted to frequency of consumptions per week.<sup>32</sup> *Physical activity* was assessed using 20 items on frequency and duration of participation in different physical activities (e.g., walking, cycling, sports) that were used to compute hours per week of moderate and vigorous activity. *Body Mass Index* (BMI) was calculated as weight in kg/height in meters squared. Weight was measured in underwear to the nearest 0.1 kg on Soehnle electronic scales. Height was measured in bare feet to the nearest 1mm using a stadiometer with the participant standing erect with head in the Frankfort plane.

Chronic conditions included as covariates were *coronary heart disease* (CHD), *diabetes*, *stroke* and *respiratory illness*. CHD events included non-fatal myocardial infarction (MI) and ‘definite’ angina. MI was determined using data from ECGs, cardiac enzymes and physician records following MONICA criteria.<sup>33</sup> Angina was assessed based on the participant’s reports of symptoms,<sup>34</sup> with corroboration in medical records for nitrate medication or ECG abnormalities. Diabetes assessment was based on fasting glucose ( $\geq 7.0$  mmol/L) or 2-hour postload glucose ( $\geq 11.1$  mmol/L) or previous use of anti-diabetic medication or reported doctor diagnosed diabetes. Both stroke and respiratory illness (chronic bronchitis, emphysema, asthma, allergy resulting in lung or breathing problems, sinusitis) were assessed using self-reports at Phases 1, 3, 5 and 7.

## Statistical Analysis

For the descriptive analysis height-corrected FEV<sub>1</sub> values were divided into tertiles separately for men and women. Its association with covariates was examined using chi-square or a one way analysis of variance. Subsequently, age and all measures of functioning were standardized to z scores (mean=0 and standard deviation (SD)=1) separately in men and women. As all predictors and outcomes in the regression analyses that follow were continuous measures, we used standardized z-scores (mean = 0, standard deviation = 1) in the analysis. Standardised regression coefficients represent the change in the outcome variable, expressed as a fraction of the standard deviation, per 1 standard deviation change in the predictor variable. Standardised regression estimates allow comparison of the associations of the predictor with different outcome measures;<sup>35</sup> in our case first the association of age with different measures of functioning and then that of lung function with measures of physical, cognitive and mental functioning. We first examined the association between a SD greater age and standardized measures of lung, cognitive, physical and mental functioning using linear regression. These analyses were successively adjusted for ethnicity, sex, education, occupational position, health behaviours (tobacco and alcohol consumption, diet, physical activity), BMI and chronic conditions.

The next set of analysis examined the association between FEV<sub>1</sub> and functioning using linear regression. We used five blocks of covariates to explain this association using the following formula  $100 \times (\beta_{\text{unadjusted}} - \beta_{\text{controlling for the covariate}}) / \beta_{\text{unadjusted}}$ .<sup>36</sup> These blocks were age, ethnicity & sex, education and occupation, health behaviours and BMI, and the final block was chronic conditions. As a next step all these covariates were entered together in order to estimate the attenuation in the association between lung function and measures of cognitive, physical, and mental functioning.

## Results

A total of 6483 participants came to the medical examination and 4829 of these undertook the lung function tests, our analysis is based on 4443 (3111 men and 1332 women) participants with complete data; those not in the analysis were older (62.1 vs.60.7 years,  $p<0.0001$ ). The age of those included in the analysis ranged from 50.5 to 73.6 years, table 1 shows all covariates to be associated with FEV<sub>1</sub> (all  $p\leq 0.03$ ). The analysis in this study used height-corrected FEV<sub>1</sub> but replacing it with height-corrected FVC did not much change the results (available from the first author).0

Figure 1 presents the cross-sectional associations, modelled to show effects of a SD increment in age on functioning, standardized to allow comparability. The interaction terms showed no sex differences in the association between age and functioning (all  $p\geq 0.09$ ) allowing us to combine men and women in the analysis although lung function was standardized separately in men and women due to differences in lung volume. The standardised beta represents the change in the functioning measures, expressed as a fraction of the standard deviation, per 1 standard deviation change in age. The standard deviations were 5.9 years for age, 0.6 litres (0.5 in women) for FEV<sub>1</sub>, 2.4 for memory, 10.8 for reasoning, 0.3 metres/minute of walking speed, 8.4 on the physical and 8.8 on mental functioning score. These SDs allow the reader to convert the standardised results back to regression coefficients. For example, 1 SD increase in age (corresponds to 5.9 years) was associated with lower scores on lung function (beta=-0.38, 95% CI: -0.41, -0.36), Figure 1. In men this corresponds to 0.23 litres (.38 multiplied by the standard deviation, here 0.6 litres) and in women 0.19 litres lower FEV<sub>1</sub>.

One SD increase in age was also associated (Figure 1) with lower memory (beta=-0.25, 95% CI: -0.28, -0.22), reasoning (beta=-0.23, 95% CI: -0.26, -0.20), walking speed (beta=-0.20, 95% CI: -0.23, -0.17), physical functioning (beta=-0.16, 95% CI: -0.19, -0.13)

but higher scores on mental functioning (beta=0.22, 95% CI: 0.19, 0.25) implying that the older participants had better mental functioning. The association with age was strongest for lung function, adjustment for multiple covariates did not much change this association (beta=-.37, 95% CI: -0.40, -0.34), see Figure 1. The association between age and all functioning measures was robust to adjustment for the covariates, results in tabular form available on request.

Table 2 presents the association of lung function with walking speed, cognitive function and self reported physical and mental functioning, again standardized to z-scores. The non-significant interaction term between sex and FEV<sub>1</sub> (all  $p \geq 0.10$ ) allowed men and women to be combined in the analysis. One standard deviation higher FEV<sub>1</sub> was associated with greater memory (beta=0.17 (95% CI: 0.15, 0.20)), reasoning (beta=0.23 (95% CI: 0.20, 0.26)), walking speed (beta=0.21 (95% CI: 0.18, 0.24)) and physical functioning (beta=0.17 (95% CI: 0.14, 0.20)) but lower mental functioning (beta=-0.07 (95% CI: -0.10, -0.04)). Age explained the largest part of this association, 47% for memory, 30% for reasoning, 24% for walking speed, 24% for physical functioning, and all of it for mental functioning (129%). All covariates taken together explained less of the association of lung function with the measures of physical functioning, walking speed (62%) and self-assessed physical functioning (65%), compared to the measures of cognitive function, memory (82%) and reasoning (91%).

## Discussion

This study, based on a large non-patient sample of adults aged 50-74 years, shows lung function to be associated with both cognitive and physical functioning, associations only partly explained by age. Our results also show lung function to have a pervasive association with a range of socioeconomic, behavioural and health measures. These results extend

previous knowledge on the value of lung function as a good “summary” measure of health and functional status.

Life expectancy is increasing at the rate of five or more hours per day in the developed world.<sup>37</sup> The challenge posed by population ageing is to ensure that the extra years of life will be of good quality and free from high-cost dependency. Thus, functioning – physical, mental and cognitive – is increasingly examined as an outcome in the ageing literature. Positive health trajectories are related to higher quality of life, longer independence and considerably lower medical and social care costs. Chronological age is a good indicator of ageing but it does not capture the variability in exposure and response to environmental insults that could well be better captured in lung function tests, even in populations not composed of COPD patients.

Previous research has shown poor lung function to be associated with poor cognitive outcomes<sup>3-7</sup> and dementia.<sup>8</sup> Three mechanisms have been proposed to explain this association: (1) lung function as a risk factor, (2) poor lung function as a consequence of dementia or impaired cognition and (3) the common cause hypothesis.<sup>8</sup> Many studies have examined the first explanation,<sup>3-8;38</sup> inferring causality due to the analytic method<sup>3</sup> or longitudinal design of the study.<sup>4;5</sup> It is clear that the association between lung and cognitive function is not restricted to old age or to sick populations. Studies show this association in mid,<sup>6</sup> and late midlife.<sup>7</sup> Spirometry tests in children aged 7 are associated with cognition in analysis adjusted for multiple covariates,<sup>39</sup> perhaps reflecting shared neural and endocrine regulatory processes as well as common response to environmental exposures.

There is evidence of the impact of COPD on the non-pulmonary system, even in non-elderly populations where it was shown to be associated with lower extremity functioning, exercise performance, skeletal muscle strength and self-reported limitation in basic physical actions.<sup>40</sup> Research on COPD increasingly views it not simply as a disease of the lungs but as

a chronic inflammatory syndrome accompanied by complex chronic comorbidities.<sup>12;41</sup> Our results show lung function to be associated with both an objective (walking speed) and a subjective (self-reported) measure of physical function was robust and all the covariates taken together explain only two thirds of this association. This is a new finding and it is possible that the association stems from the shared pathophysiological processes that lead to declines in pulmonary and physical function.

There are a number of caveats to the results reported here. The Whitehall II study is based on a white collar cohort and thus is not representative of the general population. Furthermore, a quarter of those who came to the medical examination did not do the spirometry. Finally, it is clear that cross-sectional studies are not ideal, they under-estimate the effect of age due to healthy survivor effect<sup>42</sup> and over-estimate it due to cohort effects such as changes in environmental exposures, nutritional factors and childhood infections as younger individuals have been shown to have better lung function compared with 50 years ago.<sup>2</sup>

### ***Conclusions and implications***

Our study, as most others on lung function and functioning cannot answer questions on causality but provides evidence to suggest that lung function in early old age, because it reflects the impact of environmental insults over the lifecourse, might be a good indicator of “ageing”. In our data, adjustment for demographic, socioeconomic, behavioural and health measures fully attenuated the association between lung function and cognition, measured via a test of memory and reasoning, but the association with objective and subjective physical functioning remained robust to these adjustments. The finding that physical activity is associated with a slower decline in pulmonary function offer new ways of thinking about prevention of age related decline in functioning.<sup>43;44</sup> Further research using longitudinal data

is required to understand the mechanisms linking decline in lung function to health functioning in the general population.

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Table 1. Sample characteristics as a function of tertiles of Forced Expiratory Volume (FEV<sub>1</sub>) in 3111 men and 1332 women.

		<b>lowest tertile N=1481 69% men</b>	<b>mid tertile N=1481 71% men</b>	<b>highest tertile N=1481 70% men</b>	<b>p</b>
FEV <sub>1</sub> <sup>†</sup> Men (litres)	M (SD)	2.55 (0.43)	3.28 (0.14)	3.84 (0.26)	<0.001
FEV <sub>1</sub> <sup>†</sup> Women (litres)	M (SD)	1.60 (0.31)	2.18 (0.11)	2.65 (0.22)	<0.001
Age	M (SD)	63.45 (5.89)	60.74 (5.64)	58.02 (4.86)	<0.001
University degree	N (%)	395 (26.7%)	438 (29.6%)	557 (37.6%)	<0.001
High grade	N (%)	611 (41.3%)	701 (47.3%)	782 (52.8%)	<0.001
Non-white	N (%)	224 (15.1%)	62 (4.2%)	14 (0.9%)	<0.001
Current smokers	N (%)	148 (10.0%)	116 (7.8%)	73 (4.9%)	<0.001
Alcohol (Units /week)	GM(SDL)	6.55 (3.35)	7.85 (3.13)	8.94 (2.87)	<0.001
Consumption of fruit & vegetable(/week)	M (SD)	8.69 (4.27)	9.29 (4.34)	9.56 (4.31)	<0.001
Physical activity(Hours/week)*	M (SD)	3.61 (3.34)	3.91 (3.22)	3.85 (3.41)	=0.03
Body Mass Index	M (SD)	26.80 (4.57)	26.59 (4.19)	26.15 (4.01)	<0.001
Self reported Respiratory illness	N (%)	255 (17.2%)	180 (12.2%)	149 (10.1%)	<0.001
Self reported Stroke	N (%)	27 (1.8%)	26 (1.8%)	11 (0.7%)	= 0.02
Diabetes	N (%)	198 (13.4%)	112 (7.6%)	83 (5.6%)	<0.001
Coronary Heart Disease	N (%)	157 (10.6%)	84 (5.7%)	48 (3.2%)	<0.001
Memory (Range 0-20)	M (SD)	6.33 (2.41)	6.90 (2.41)	7.32 (2.34)	<0.001
Reasoning, AH4-I (Range 0-65)	M (SD)	41.39 (11.67)	44.58 (10.51)	47.01 (9.45)	<0.001
Walking speed (metre/minute)	M (SD)	1.27 (0.30)	1.36 (0.29)	1.39 (0.28)	<0.001
Physical Functioning (SF 36)	M (SD)	47.80 (9.04)	49.93 (7.94)	50.89 (7.76)	<0.001
Mental Functioning (SF 36)	M (SD)	52.84 (8.64)	52.80 (8.55)	51.06 (9.15)	<0.001

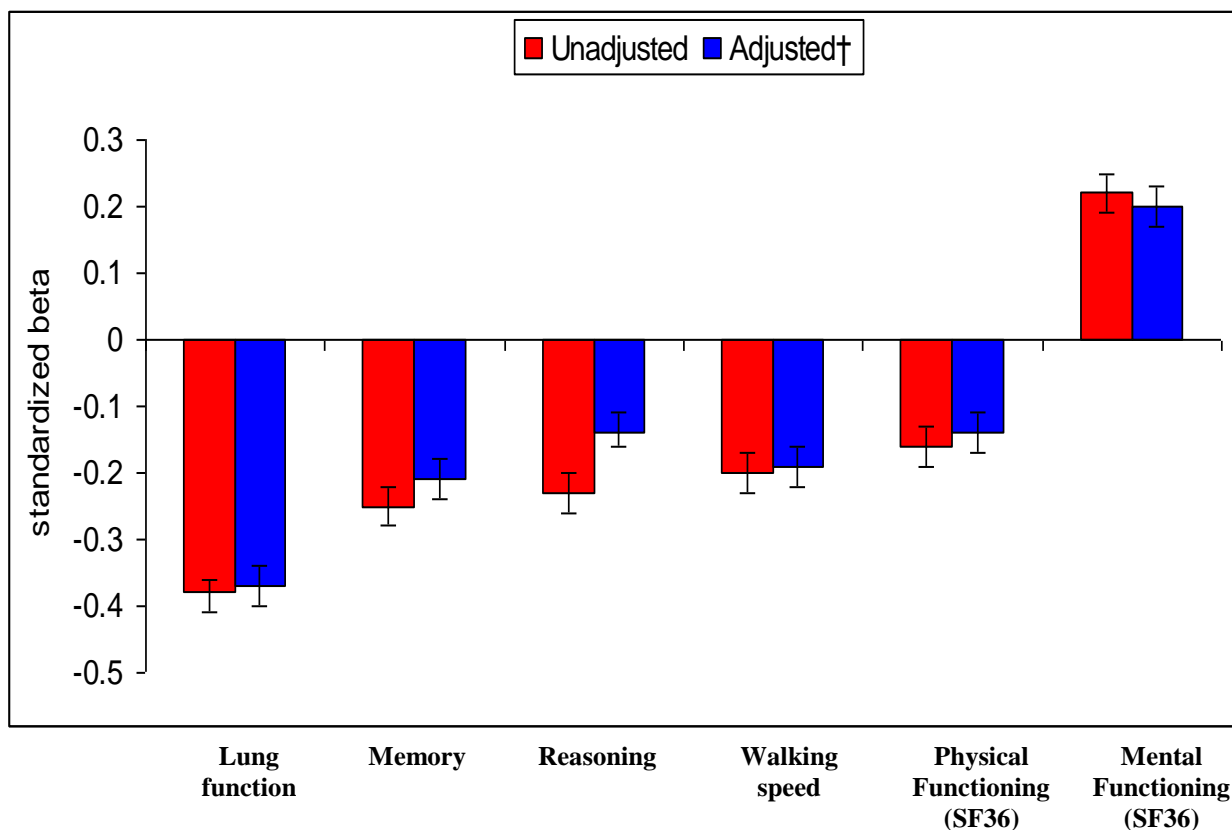
<sup>†</sup>FEV<sub>1</sub> values corrected for height by dividing by own height<sup>2</sup> and multiply by mean height<sup>2</sup> of 1.77 m in men and 1.63 m in women.

M: Mean; SD: Standard Deviation.

GM: Geometric mean; SDL: Standard deviation of logged values.

\*Moderate and vigorous physical activity.

Figure 1. Association\* of a standard deviation increase in age with lung, cognitive, physical, and mental functioning.



\*Expressed as a standardised beta, each coefficient represents the change in the functioning measures, expressed as a fraction of the standard deviation, per 1 standard deviation change in age. The standard deviations were 5.9 years for age, 0.6 litres (0.5 in women) for FEV<sub>1</sub>, 2.4 for memory, 10.8 for reasoning, 0.3metres/second of walking speed, 8.4 on the physical and 8.8 on mental functioning score.

† Adjusted for sex, ethnicity, smoking, alcohol consumption, physical activity, fruit and vegetable consumption, diabetes, coronary heart disease and self-reported stroke and respiratory illness.

Table 2. Explaining the association between lung function and physical, mental and cognitive function.

	Memory		Reasoning AH4-I		Walking speed		Physical Functioning (PCS, SF-36)		Mental Functioning (MCS, SF-36)	
	beta <sup>†</sup> (95% CI)	%Δ <sup>‡</sup>	beta <sup>†</sup> (95% CI)	%Δ <sup>‡</sup>	beta <sup>†</sup> (95% CI)	%Δ <sup>‡</sup>	beta <sup>†</sup> (95% CI)	%Δ <sup>‡</sup>	beta <sup>†</sup> (95% CI)	%Δ <sup>‡</sup>
Height-corrected FEV <sub>1</sub>	0.17 (0.15, 0.20)		0.23 (0.20, 0.26)		0.21 (0.18, 0.24)		0.17 (0.14, 0.20)		-0.07 (-0.10, -0.04)	
+ age	0.09 (0.06, 0.12)	47%	0.16 (0.13, 0.19)	30%	0.16 (0.13, 0.19)	24%	0.13 (0.10, 0.16)	24%	0.02 (-0.01, 0.05)	129%
+ ethnicity, sex	0.15 (0.12, 0.18)	12%	0.15 (0.12, 0.18)	35%	0.18 (0.15, 0.21)	14%	0.16 (0.13, 0.19)	6%	-0.07 (-0.10, -0.04)	0%
+ education & occupation	0.14 (0.11, 0.17)	18%	0.16 (0.13, 0.18)	13%	0.19 (0.16, 0.22)	10%	0.16 (0.13, 0.19)	6%	-0.06 (-0.09, -0.03)	14%
+ health behaviours <sup>±</sup> & BMI	0.15 (0.12, 0.18)	12%	0.18 (0.15, 0.21)	30%	0.17 (0.15, 0.20)	19%	0.15 (0.12, 0.18)	12%	-0.08 (-0.10, -0.05)	-6%
+ chronic conditions <sup>‡</sup>	0.17 (0.14, 0.20)	0%	0.22 (0.19, 0.25)	4%	0.20 (0.17, 0.23)	5%	0.14 (0.11, 0.17)	18%	-0.07 (-0.10, -0.04)	0%
<b>+ all</b>	<b>0.03 (-0.01, 0.06)</b>	<b>82%</b>	<b>0.02 (-0.01, 0.05)</b>	<b>91%</b>	<b>0.08 (0.05, 0.11)</b>	<b>62%</b>	<b>0.06 (0.03, 0.09)</b>	<b>65%</b>	<b>-0.001 (-0.03, 0.03)</b>	<b>99%</b>

BMI: Body Mass Index; PCS: Physical Component Score; MCS: Mental Component Score.

<sup>†</sup>From standardized values, separately in men and women.

<sup>±</sup>Smoking, alcohol consumption, physical activity, fruit and vegetable consumption.

<sup>‡</sup>Diabetes, Coronary Heart Disease and self-reported stroke and respiratory illness.

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