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What is the predictive value of established risk factors for total and cardiovascular disease mortality when measured before middle-age? Pooled analyses of two prospective cohort studies from Scotland

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Abstract

Aims—To examine the association of physiological, behavioural and social characteristics in pre-middle-age with future total and cardiovascular disease (CVD) mortality.

Methods and Results—Risk factor data on 1503 individuals aged 16-35 years at baseline were collected in two prospective cohort studies using standard protocols. Their association with total and CVD mortality ascertained during 40 years of follow-up was summarised using Cox proportional hazards regression. A median follow-up of 39.6 years gave rise to 255 deaths (103 from CVD). In age- and sex-adjusted analyses, impaired lung function (one standard deviation (SD) increases in forced expiratory volume in one second: hazards ratio 0.69; 95% confidence interval 0.55, 0.86; and in forced vital capacity: 0.76; 0.59, 0.98), current cigarette smoking (4.16; 2.22, 7.80), and higher alcohol consumption (one SD increase in standard units consumed: 1.20; 1.02, 1.41) were associated with CVD. In fully-adjusted analyses associations generally held. For total mortality, these factors plus obesity and socioeconomic disadvantage were predictive.

Conclusion—A range of risk factors measured before middle-age were related to risk of total and CVD mortality up to four decades later, indicating that public health interventions should be implemented earlier in the life course than is currently the case.

Keywords

cardiovascular diseases; mortality; epidemiology; risk factors; lifecourse

Introduction

While it has been well documented that rates of cardiovascular disease (CVD) are declining, this condition remains the leading cause of death and morbidity in industrialised countries.

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(1) CVD is also a prominent public health problem in low/middle income societies, with predictions that it will become the leading cause of death by 2020.(1, 2) A series of studies of middle- and older-aged populations have identified a range of well-documented risk factors for CVD and total mortality. These include smoking,(3) alcohol consumption,(4) high blood pressure,(3) high cholesterol,(5) obesity and overweight,(6-8) reduced stature, (9-11) physical inactivity,(3, 6, 12, 13) lung function(9, 14) and socioeconomic disadvantage.(11, 15)

With very few studies having measured these risk factors before middle-age, much less is understood about their predictive capacity, if any, earlier in life. More evidence about risk factor–CVD relationships in younger populations may point to the value of implementing interventions to reduce disease burden earlier in the life course than is currently the case.(16) Furthermore, given that several of these factors – physical activity, alcohol intake, cholesterol, weight – are influenced by chronic diseases common in middle- and older-age populations, earlier assessment of risk indices may lead to more accurate estimates of their association with CVD and all-cause mortality.

The few studies that do have mortality surveillance in cohorts of younger people in which established risk factors were captured, suggest that smoking,(17-19) elevated blood pressure, (18, 20, 21) adverse lipid profiles,(18, 21, 22) obesity/overweight,(23-26) short stature,(27) and socioeconomic adversity(28) confer an increased risk of subsequent CVD and total mortality; in one study, neither alcohol intake nor physical activity were predictive.(29) However, few of these studies made adjustment for socio-economic circumstances, a potentially important confounding factor. Further, to our knowledge, the predictive value of other variables known to be risk factors in middle- and older-aged populations – reduced lung function and larger heart size(30) – is unknown in younger adults.

In the following two prospective cohort studies from Scotland, risk factors were measured in study participants between the ages of 14 and 92 years. We have previously presented results for middle- and older-aged study participants.(4, 15, 28) For the first time, we report risk factor—disease association for men and women aged 16-35 years with extended (maximum 42 years) mortality surveillance, incorporating adjustment for socio-economic status. In doing so, we address the afore described methodological shortcomings and paucity of data in this area.

Methods

Study participants

Data are drawn from two well characterised prospective cohort studies established in the 1960s and early 1970s in Scotland, collectively referred to as the Midspan studies.(31) The ‘Main’ study was conducted between 1965 and 1968 and comprised 3931 male and female factory employees examined during routine cardiorespiratory screening in central Scotland, plus 762 individuals identified from the Register of Electors living on the island of Tiree and their mainland relatives (all aged 14-92 years at study induction).(32) In the ‘Collaborative’ study, 7028 employees screened in workplaces across Glasgow, Grangemouth and Clydebank were enrolled between 1970-73 when aged 21-75 years.(33)

Study protocols were almost identical in both cohorts and similar to those subsequently utilised in the original Whitehall(34) and General Post Office studies.(35) Described in detail elsewhere,(31, 32) these protocols consisted of a self-administered questionnaire and medical examination. Enquiries were made about current and past regular cigarette smoking and responses were grouped into never smokers, ex-smokers, and current smokers (pipe and cigar smokers who had never smoked cigarettes [n=33] were added to the group of never

cigarette smokers). Study participants also estimated their usual weekly consumption of spirits, beer and wine, and responses were converted to 10 millilitres (approximately 8 grams) UK units of ethanol. Socio-economic status was based on occupational social class and car ownership (Main study) or car use (Collaborative). Social class was based on the 1960(36) (Main study) and 1966(37) (Collaborative study) versions of the Registrar General's classification scheme of occupations, and grouped as non-manual (I, II and III non manual) or manual (III manual, IV and V).

Anthropometric measurements were self-reported in the Main study and measured directly in the Collaborative study. After conversion to metric units, height (metres) and weight (kilograms) were used to derive body mass index (BMI) in kg/m^2, which was categorised into normal and underweight ($<25\ kg/m^2$), overweight ($25 - < 30 kg/m^2$) and obese ($\geq 30\ kg/m^2$) based on World Health Organization definitions.(38) Measurements of diastolic and systolic blood pressure were made using a London School of Hygiene sphygmomanometer while the participant was seated during screening examination.(39) Based on these data, study participants were classified as hypertensive (diastolic blood pressure >= 90 mmHg and/or systolic blood pressure >= 140 mmHg).(40) Whole plasma cholesterol, available in the Collaborative Study only, was ascertained using autoanalyser techniques(41) on a 10ml fasting blood sample.(42) Forced expiratory volume during the first second of exhalation (FEV1) and forced vital capacity (FVC) measurements were made using the Garthur Vitalograph respiratory function test, with the two highest expirations recorded. Raw values were used in the present analyses.(12) Questions on respiratory function were take from the Medical Research Council respiratory questionnaire, and participants were classified as having bronchitis according to the established criteria.(43) Cardiothoracic ratio, an index of cardiac enlargement, was estimated from chest X-ray film(44) and was based in the ratio of cardiac (measured by a line connecting the right and left borders of the heart at the points of maximum curvature(32)) and thoracic diameter measurements.

Mortality ascertainment

Participants were ‘flagged’ for notification of mortality until embarkation (15 individuals were alive when last traced; median 10.8 years of follow-up) or the end of 2006 with the General Register Office of Scotland and other Registrar General offices covering the whole of the UK. Cause of death was classified according to the International Classification of Disease (ICD) (versions 9(45) and 10(46)) into cardiovascular disease (ICD9 390–459; ICD10 G45, I00-I99, M30.0, M30.3 and R58) and malignant cancers (ICD9 140-208; ICD10 C00-C97). Notification was virtually complete and coding of causes of death by the registrar and independent physicians have been shown to be concordant.(47)

Statistical analyses

The current analyses are based on the subset of 1503 (1129 in Main, 374 in Collaborative) study participants aged 16-35 years. Data were missing for height (1 observation); BMI (7); blood pressure (14), cardiothoracic ratio (58); smoking status (5); and social class (64). For mortality analyses, missing data were multiply imputed using the variables listed in Table 1 under the missing at random assumption using the chained equations procedure,(48) with 10 imputations corresponding to 10% (147) of observations with incomplete data.(49)

As indicated, the protocols used in each study were, for the most part, identical. However, prior to pooling the data, we examined risk factor—disease associations across the two studies in preliminary analyses and these were similar. Having also determined that the proportional hazards assumption had not been violated, calendar time in years from baseline study measurement to death was modelled using Cox proportional hazards regression.(50) Study participants were censored at death, date of embarkation, or 31 December 2006 –

whichever came first. For height, BMI, components of blood pressure, blood cholesterol, lung function and cardiothoracic ratio, hazard ratios (HRs) per unit increase in standard deviation (SD) increase were utilised as there was little evidence of departure from linearity. With no evidence that the risk factor—mortality relations differed between men and women (all $p>0.20$), HRs were sex- and age-adjusted, followed by adjustment for socioeconomic status, and finally controlled for all risk factors. All analyses were conducted using STATA (Version 9.1; College Station, Texas, USA).

Results

In table 1 we present the baseline characteristics of participants in both studies. The large majority of participants in the Collaborative study were male; the Collaborative study participants were somewhat older at baseline that those in the Main study. Combining the cohorts, there were 1,100 (73.2%) men and 403 women aged 16-35 years (mean 27.9 years) at study induction. Around three-quarters of this study sample were normal or underweight, just under one quarter were hypertensive, almost two thirds were current smokers, half were in a manual social class and almost two thirds were not regular drivers.

A total of 55,525 person-years of follow-up (median follow-up 39.6 years), gave rise to 255 deaths (194 in Main, 61 in Collaborative), 103 (82 and 21, respectively) of which were ascribed to CVD. In table 2 we present the relations of pre-middle age risk factors with total mortality. In age- and sex-adjusted analyses, obese study participants experienced greater mortality risk than their normal-weight counterparts. The suggestion of a modest elevated risk in the overweight group resulted in some evidence of an incremental effect across these weight categories (p for trend: 0.025). Lower FEV1 and FVC, current smoking, higher alcohol consumption, manual social class and being without a car were also associated with elevated mortality rates. There was a suggestion that increased systolic blood pressure and bronchitis conferred elevated risk, but associations were of borderline statistical significance and the latter was based on very few deaths in the exposed group. These gradients were very little altered on adjustment for markers of socioeconomic position (car use/ownership and social class). On mutual adjustment, the associations with total mortality for obesity, FEV1, current smoking and alcohol intake remained at conventional levels of statistical significance.

In table 3 we depict the associations between risk factors pre-middle age and later CVD mortality. Lower FEV1 and FVC, current smoking, and higher alcohol consumption were associated with later risk CVD mortality after controlling for age and sex. There was also a suggestion of elevated CVD rates in persons with higher measured systolic and diastolic blood pressure, those who met the definition for hypertension, and in the lower occupational social classes although statistical significance was not seen. When we further adjusted for socioeconomic position there was again little evidence of attenuation of these effects estimates, although mutual adjustment led to some confidence intervals including unity. Hazards ratio across the smoking groups remained incremental (p for trend: <0.001).

We carried out sub-group analyses of only Collaborative study participants, who had blood cholesterol measurements at baseline (374 individuals). Higher cholesterol was weakly associated with both total mortality (61 deaths) (HR 1.23; 95% CI: 0.94 - 1.60) and CVD mortality (21 deaths) (HR 1.38; 95% CI: 0.88 - 2.16) in multiply-adjusted analyses and statistical significance was not attained. We found very similar results comparing effect estimates for all other variables in the multiply-adjusted model including and excluding plasma cholesterol.

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We also examined the relation of all the above risk factors with mortality due to cancers from all sites (87 deaths). Lower diastolic blood pressure, poorer lung function, current smoking, higher alcohol consumption and lower socio-economic status were all predictive in age- and sex- adjusted analyses. Some attenuation was apparent following mutual adjustment (results not shown but available upon request). To assess any effect modification due to high smoking prevalence in this population, we performed analyses separately for current and non-current smokers. Effect estimates were similar in each group. Further, all analyses were repeated on the subset of study members with no missing data (n= 1,356) and, again, results were found to be very similar to those reported here using imputed data.

Discussion

The main findings of this study were that reduced lung function (as indexed by FEV1 and FVC), cigarette smoking, higher alcohol consumption, obesity and socioeconomic disadvantage (total mortality only for the latter two) when measured before middle-age were associated with mortality due to all-causes and CVD. Some attenuation of these relations was seen after mutual adjustment.

Comparison with other studies

Our findings accord with other studies examining the influence of early adulthood smoking and later mortality risk.(17-19) For instance, in another Scottish-based study, smoking in adolescence and early adult life was strongly associated with future total mortality.(17) To our knowledge, the present study was the first to examine the influence of another behaviour, alcohol intake, before middle-age on later mortality risk. Consistent with studies of middle and older-aged populations,(4) though contrasting with a study of younger adults,(29) positive associations between increased alcohol consumption and risk of mortality were found. Similarly, in older-aged groups, there is strong evidence linking reduced lung function with non-respiratory mortality such as CVD.(14) However, while respiratory disease in late adolescence/early adulthood has previously been linked with future cardiovascular mortality in men,(51) this is the first study examining the predictive value of directly measured lung function within the normal range in younger people. In the present analyses, a one standard deviation higher FEV1 was associated with around a 30% reduction in the total and CVD mortality. Corresponding results for FVC were a 20-25% reduction, although this effect disappeared on mutual adjustment; this is likely to be due to collinearity with FEV1. The underlying mechanisms are unclear but may be due to hypoxia-induced increased sympathetic activity, blood viscosity, or inflammation,(52) and our findings may point to consideration of monitoring of lung function from early adulthood. Whereas the few studies with measurement in middle- and older aged groups reveal positive associations with coronary heart disease,(30, 44) cardiothoracic ratio in early adulthood was not found to predict mortality herein.

A small groups of studies, usually less well characterised than our own, have examined the link between measured blood pressure in late adolescence/early adulthood, often determined at entry to university, and CVD up to 50 years later. In general, these studies report stronger and more robust effects than those herein.(18, 20, 21) In a long term follow-up of university alumni in Scotland,(20) for instance, positive associations between CVD and individual blood pressure components were apparent.

In middle-aged cohorts, height generally reveals an inverse association with CVD such that increased stature is cardioprotective.(9-11) One explanation for this effect is reverse causality due to ‘shrinkage’, whereby existing but occult illness at study induction leads to osteoporotic vertical collapse and this in turn raises mortality risk. Examining cohorts of individuals who had their height measured earlier in life when co-morbidity is less

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prevalent, to a degree, circumvents this problem. Taking this approach we found a weak stature—CVD association, an observation that contrasts with the few other studies of early adult height and CVD which report stronger inverse associations.(27) In accordance with other studies, obesity measured early in life was predictive of all-cause mortality,(7, 26) and, less strongly, CVD.(7, 25, 26)

Study strengths and limitations

The Midspan Main and Collaborative studies have some advantages over other studies. First, the range of baseline risk factors was wider than most other cohorts, allowing us to examine mortality associations for selected pre-middle-age risk factors for the first time. Second, we have almost complete mortality coverage so minimising concerns regarding selection bias. The study is not, of course, without its shortcomings. First, we were not able to examine the predictive capacity of emerging risk indices such as coagulation or inflammatory factors,(53, 54) nor that of other lifestyle factors such as physical activity or fitness. Second, risk factors 'track' across the life course, such that people who are classified as high risk earlier in adulthood tend to be those who are at high risk by middle-age.(26, 55) It is therefore plausible that the apparent influence of risk indices measured earlier in adulthood may be mediated, partially or in full, by those measured later. In the present study we did not have repeat measurement of risk factors with which to test this important hypothesis. Third, despite long-term follow-up, there are relatively small numbers of deaths which limits the power to ascertain effects. Fourth, since most of these data are based on samples of employees, they may not be representative of the general population (which includes unemployed individuals). For instance, the strength of the risk factor–disease association might be underestimated in our sample given that it is a relatively homogenous group with narrower variance (the phenomenon of the healthy worker effect). Fifth, the information on measures such as smoking and alcohol intake were self-reported, which may lead to underestimation of the effects of these behaviours; (56, 57) however for the purposes of their categorization, this approach is more than adequate. (58)

In conclusion, selected risk factors measured before middle age predicted total and CVD morality. It may be that public health interventions which aim to reduce disease burden should be implemented earlier in the life course than is currently the case.

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Table 1

Baseline characteristics of study participants in Main, Collaborative, and both cohorts combined (N=1503)

		Main		Collaborative		Combined	
Numbers [% (N)]		75.1	(1129)	24.9	(374)	100.0	(1503)
Sex [% (n)]	**Men**	66.7	(753)	92.8	(347)	73.2	(1100)
	Women	33.3	(376)	7.2	(27)	26.8	(403)
BMI category [% (n)]	**Underweight/normal**	75.3	(850)	60.4	(226)	71.6	(1076)
	Overweight	20.8	(235)	35.6	(133)	24.5	(368)
	Obese	3.3	(37)	4.0	(15)	3.5	(52)
	Missing [a]	0.6	(7)	0.0	(0)	0.5	(7)
Hypertensive	**No**	73.6	(831)	82.4	(308)	75.8	(1139)
	Yes	25.2	(284)	17.7	(66)	23.3	(350)
	Missing [a]	1.2	(14)	0.0	(0)	0.9	(14)
Bronchitis	**No**	98.8	(1115)	98.7	(369)	98.7	(1484)
	Yes	1.2	(14)	1.3	(5)	1.3	(19)
Smoking status [% (n)]	**Never-smoker**	32.9	(371)	34.2	(128)	33.2	(499)
	Ex-smoker	5.3	(60)	12.0	(45)	7.0	(105)
	Current smoker	61.4	(693)	53.7	(201)	59.5	(894)
	Missing [a]	0.4	(5)	0.0	(0)	0.3	(5)
Social class [% (n)]	**Non-manual**	35.9	(405)	68.5	(256)	44.0	(661)
	Manual	58.5	(660)	31.6	(118)	51.8	(778)
	Missing [a]	5.7	(64)	0.0	(0)	4.3	(64)
Regular drivers [% (n)] [b]	**Yes**	30.1	(340)	52.9	(198)	35.8	(538)
	No	69.9	(789)	47.1	(176)	64.2	(965)
Age (years) [c]		26.3	(5.7)	32.6	(2.9)	27.9	(5.8)
Height [c]		169.7	(9.2)	174.3	(7.4)	170.8	(9.0)
Diastolic blood pressure (mmHg) [c]		71	(12)	79	(9)	73	(12)
Systolic blood pressure(mmHg) [c]		128	(15)	126	(12)	127	(14)
Blood cholesterol (mmol/L) [c,d]		-	-	5.6	(1.0)	-	-
FEV1 (litres) [c]		312	(101)	357	(87)	323	(99)

	Main		Collaborative		Combined	
FVC (litres)[c]	404	(105)	464	(88)	419	(104)
Cardiothoracic ratio[c]	0.46	(0.04)	0.45	(0.05)	0.46	(0.04)
Alcohol (units[e] per week)[c]	7.1	(11.2)	12.0	(14.4)	8.3	(12.3)

[a] For later analyses, missing data were dealt with using multiple imputation;

[b] Car ownership for Main and car use for Collaborative;

[c] Mean (standard deviation);

[d] Data available for Collaborative only: number at risk=374; number of deaths=61;

[e] UK units: 10ml (~8g) of ethanol

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Table 2

Hazards ratios (95% confidence intervals) for the relation of risk factors with all-cause mortality (N=1503)

		n deaths	n at risk	Age- and sex-adjusted	Age-, sex- and socioeconomic-adjusted[a]	Mutually-adjusted[b]
BMI category	**Underweight/normal**	163	1,081	1.00 Referent	1.00	1.00
	Overweight	75	369	1.12 (0.84, 1.48)	1.10 (0.83, 1.46)	1.13 (0.85, 1.52)
	Obese	17	53	2.07 (1.25, 3.43)	2.05 (1.24, 3.40)	1.99 (1.14, 3.46)
p-value for trend				0.025	0.034	0.047
Hypertensive	**No**	186	1,149	1.00	1.00	-
	Yes	69	354	1.17 (0.89, 1.55)	1.15 (0.87, 1.52)	-
Bronchitis	**No**	247	1,484	1.00	1.00	1.00
	Yes	8	19	1.98 (0.98, 4.03)	1.72 (0.84, 3.50)	1.35 (0.66, 2.78)
Smoking status	**Never smoker**	48	501	1.00	1.00	1.00
	Ex-smoker	12	105	0.91 (0.48, 1.73)	0.95 (0.50, 1.79)	0.95 (0.50, 1.80)
	Current smoker	195	897	2.18 (1.59, 2.99)	2.06 (1.49, 2.83)	2.05 (1.48, 2.83)
p-value for trend				<0.001	<0.001	<0.001
Social class	**Non-manual**	88	695	1.00		1.00
	Manual	167	808	1.56 (1.20, 2.03)	-	1.16 (0.88, 1.54)
Regular drivers	**Yes**	87	538	1.00	-	1.00
	No	168	965	1.37 (1.05, 1.79)	-	1.16 (0.88, 1.52)
Height	**SD increase**	255	1503	0.86 (0.73, 1.02)	0.91 (0.77, 1.09)	1.02 (0.84, 1.23)
Diastolic blood pressure	**SD increase**	255	1503	0.99 (0.86, 1.13)	1.00 (0.88, 1.14)	0.93 (0.81, 1.08)
Systolic blood pressure	**SD increase**	255	1503	1.10 (0.97, 1.23)	1.08 (0.96, 1.22)	1.13 (0.99, 1.30)
FEV1	**SD increase**	255	1503	0.68 (0.59, 0.78)	0.71 (0.61, 0.82)	0.71 (0.57, 0.88)
FVC	**SD increase**	255	1503	0.74 (0.63, 0.87)	0.78 (0.66, 0.93)	1.06 (0.81, 1.39)
Cardiothoracic ratio	**SD increase**			1.04 (0.92, 1.17)	1.02 (0.90, 1.16)	0.99 (0.87, 1.12)
Alcohol	**SD increase**	255	1503	1.23 (1.11, 1.36)	1.20 (1.08, 1.33)	1.12 (1.00, 1.25)

[a] socio-economic status comprised occupational social class and car use/ownership;

[b] mutual adjustment is for all variables in the table except hypertension (control was made for blood pressure components)

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Table 3

Hazards ratios (95% confidence intervals) for the relation of risk factors with cardiovascular disease mortality (N=1503)

		n deaths	n at risk	Age- and sex-adjusted	Age-, sex- and socioeconomic-adjusted[a]	Mutually-adjusted[b]
BMI category	**Underweight/normal**	64	1,081	1.00 Referent	1.00	1.00
	Overweight	33	369	1.19 (0.77, 1.83)	1.18 (0.76, 1.81)	1.17 (0.75, 1.82)
	Obese	6	53	1.79 (0.77, 4.16)	1.77 (0.76, 4.11)	1.46 (0.57, 3.73)
p-value for trend				0.172	0.196	0.358
Hypertensive	**No**	70	1,149	1.00	1.00	-
	Yes	33	354	1.48 (0.98, 2.24)	1.46 (0.96, 2.21)	-
Bronchitis	**No**	100	1,484	1.00	1.00	1.00
	Yes	3	19	1.74 (0.55, 5.52)	1.57 (0.49, 5.01)	1.18 (0.37, 3.82)
Smoking status	**Never smoker**	11	501	1.00	1.00	1.00
	Ex-smoker	5	105	1.58 (0.54, 4.57)	1.60 (0.55, 4.64)	1.60 (0.55, 4.66)
	Current smoker	87	897	4.16 (2.22, 7.80)	4.03 (2.15, 7.59)	4.20 (2.22, 7.96)
p-value for trend				<0.001	<0.001	<0.001
Social class	**Non-manual**	37	695	1.00	-	1.00
	Manual	66	808	1.42 (0.94, 2.13)	-	1.04 (0.68, 1.60)
Regular drivers	**Yes**	39	538	1.00	-	1.00
	No	64	965	1.21 (0.80, 1.82)	-	1.01 (0.66, 1.54)
Height	**SD increase**	103	1,503	0.82 (0.63, 1.07)	0.85 (0.65, 1.12)	0.93 (0.69, 1.27)
Diastolic blood pressure	**SD increase**	103	1,503	1.14 (0.93, 1.41)	1.15 (0.94, 1.42)	1.09 (0.87, 1.37)
Systolic blood pressure	**SD increase**	103	1,503	1.16 (0.96, 1.39)	1.15 (0.95, 1.38)	1.17 (0.95, 1.45)
FEV1	**SD increase**	103	1,503	0.69 (0.55, 0.86)	0.71 (0.56, 0.89)	0.72 (0.50, 1.02)
FVC	**SD increase**	103	1,503	0.76 (0.59, 0.98)	0.79 (0.60, 1.03)	1.09 (0.70, 1.69)
Cardiothoracic ratio	**SD increase**	103	1,503	1.06 (0.88, 1.27)	1.05 (0.86, 1.27)	1.01 (0.83, 1.24)
Alcohol	**SD increase**	103	1,503	1.20 (1.02, 1.41)	1.17 (1.00, 1.38)	1.07 (0.90, 1.28)

[a] socio-economic status comprised occupational social class and car use/ownership;

[b] mutual adjustment is for all variables in the table except hypertension (control was made for blood pressure components)