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Results from the 27-year follow up of the cohort “Men born in 1914” from Malmö, Sweden.

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ABSTRACT

Background: Between smokers matched for daily tobacco consumption there are marked variations of the cardiovascular risk. This follow up of the population based cohort “Men born in 1914” from Malmö, Sweden, explored whether this is accounted for by the levels of carbon monoxide (CO).

Methods: Three hundred and sixty-five men without history of cardiovascular disease (CVD) were followed over 27 years. Leg artery disease was defined as a systolic ankle-arm pressure ratio (ABPI) below 0.9 in either leg. Incidence of myocardial infarction (MI), stroke and deaths is based on linkage with regional and national registers. The distribution of CO in blood and expired air, respectively, was divided into quartiles.

Results: There was a significant inverse relation between ABPI and CO in blood and expired air. Incidence of CVD events and deaths increased progressively with degree of CO exposure. Men with CO in the top quartile had significantly increased risks of CVD events (RR: 2.2; 95% CI: 1.00-4.6) and cardiovascular deaths (RR: 3.2, CI: 1.2-8.3), adjusted for daily tobacco consumption and other potential confounders.

Conclusions: In smokers, the prevalence of leg atherosclerosis and incidence of cardiovascular disease is related to the amount of carbon monoxide in blood or expired air.

Key words: Epidemiology; atherosclerosis, carbon monixide, CV disease

INTRODUCTION

The cardiovascular risk associated with smoking has been demonstrated in several cohort studies (1). Yet between smokers matched for daily tobacco consumption there are marked variations of risk that only to some extent can be accounted for by exposure to other cardiovascular risk factors.

Invalid estimates of exposure are potential confounders in studies of incidence in relation to a certain risk factor (2). Furthermore, tobacco smoke contains a vast number of substances, which may have a relationship with the cardiovascular hazards. Estimates of risks should ideally be assessed in relation to the amounts that via the lungs are absorbed into the blood stream (3-5). The vessel wall damaging effects of chronic and acute carbon monoxide (CO) exposure has been demonstrated in animal experiments (6), in humans (7) and in conjunction with acute lethal poisoning (8). Prevalence of cardiovascular disease (CVD) was related blood levels of carbon monoxide, i.e. COHb%, in one cross-sectional study (9). Yet, to our knowledge no prospective studies have been published in which incidence of cardiovascular events in smokers has been compared in groups defined in terms of carbon monoxide exposure.

The “Men born in 1914” from Malmö, in Sweden, is a prospective population based cohort study of the distribution and determinants for cardiovascular disease in men (10). At 68 years of age these men were invited to comprehensive health examinations, which included an evaluation of leg atherosclerosis in relation to established risk factors including carbon monoxide. This cohort has been used to assess whether differences between smokers in terms of the prevalence of asymptomatic atherosclerosis in the leg vessels and the incidence of myocardial infarction, stroke and death is related to carbon monoxide exposure.

MATERIAL AND METHODS

The cohort study “Men born in 1914“, Malmö, Sweden, was designed to identify determinants for cardiovascular and pulmonary diseases in elderly men (10). In short, all men born in even months in 1914 and residing in the city were in 1982/1983, close to their 68th birthday, invited to the baseline examination. Five hundred of 621 invited agreed to participate. The Local Ethics Committee of the University of Lund approved the project and all participants gave their informed consent. Four hundred and seventy-seven men took part in the assessment of leg artery disease by measurement of the systolic arm/ankle pressure ratio, CO in blood or expired air was available for 471 of them. One hundred and six men, who according to the Rose questionnaire had angina or a history of myocardial infarction or stroke, were excluded.

Ankle-arm blood pressure index (ABPI) measurement

The recording system consisted of pulse sensors (mercury-in-Silastic strain gauges) placed on the big toes and thumbs; two Wheatstone bridges with amplifier to record changes in the resistance of the strain gauges; blood pressure cuffs (18x60 cm to measure ankle systolic pressure and 12x35 cm to measure the upper arm systolic pressure); a pressure transducer (Siemens-Elema EMT 746 with amplifier EMT 311) to record cuff pressures; and a six-channel ink-jet recorder (Siemens-Elema; Mingograph) (10, 11). Duplicate recordings were made with the subject in the supine position, and the arithmetic average used. For each leg, an ABPI was calculated by dividing the ankle systolic pressure with the highest upper arm systolic pressure value. The risk factor analysis was based on the ABPI value in the worst leg.

Risk factors at baseline examination

Smoking habits i.e. duration, inhalation and preferred type of tobacco (cigarettes, cheroots, cigars, pipe and or mixed) were assessed by interview using a structured questionnaire. Daily tobacco consumption (in grams per day) was calculated by equating a cigarette to 1g tobacco, a cheroot to 3 g, and a cigar to 5 g. Former smokers are those who had stopped smoking at least one month prior to investigation. Time since quitting was based on three categories: <10 years, 10-19 years and ≥ 20 years. Smokers consuming 1-9 grams/day were labelled mild smokers, 10-19 grams moderate smokers and ≥ 20 grams heavy smokers.

Systolic and diastolic (phase V) blood pressure was measured sphygmomanometrically with the subject in the sitting position after 15 minutes of rest. Blood pressure was recorded to the nearest 5 mm Hg. Men who in the sitting position had a systolic pressure ≥160 mm Hg, a diastolic blood pressure ≥95 mm Hg, and men who used blood pressure lowering medication were classified as hypertensives.

Blood samples were taken after an overnight fast. Plasma cholesterol, triglycerides, and blood glucose in mmol/L were analysed by standard methods (12). Blood glucose ≥6.7 mmol/L and pharmacological treatment for diabetes were used for the definition of diabetes. Plasma cholesterol levels ≥6.5 mmol/L or triglycerides levels ≥2.3 mmol/L were used for the definition of hyperlipidemia. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

Carbon monoxide in blood and expired air

In the mailed invitation were instructions to abstain from food, alcohol and tobacco for 12 hours prior to the examination. Questioning checked compliance. During the initial phase of recruitment (n=129) carbon monoxide was assessed by measurement of CO in

venous blood by gas chromatography according to the method described by Collinson et al (13). For practical reasons it was during the later phase (n=236) replaced by measurement of carbon monoxide (expressed as ppm) in expired air using an Ecolyzer CO Analyzer® (Energetic Science, New York) (14). CO in expired air has both in smokers and non-smokers been demonstrated to closely correlate with CO in blood (15). The reproducibility of CO measurements in expired air was checked using 29 randomly selected men in the present study for a second fasting sample four weeks after the initial one.

Follow-up definition of end-points

Methods for case retrieval and ascertainment of cases has been described in detail previously (10, 16). In short, all were followed from the baseline examination until death or 31 December 1996. Median follow-up time was 13.3 years (range 0.4 -14.3 years). The follow-up analysis is based on a total of 4058 person years. Cause of death, which was established by record linkage with the Mortality Registry of the Swedish National Bureau of Statistics, was in 60% based on necropsy. Cases coded 390 - 438 according to the International Classification of Diseases (ICD) code (eight revised version through 31 December 1986; ninth revised version since 1 January 1987) were counted as cardiovascular (CVD) deaths.

Incidence of myocardial infarction and stroke are based on linkage with The Malmö Heart Infarction Register (17), the Stroke Registry of Malmö (STROMA) (18) and the Swedish Hospital Discharge Register. A CVD event was defined as fatal or non-fatal myocardial infarction (ICD code 410), death due to chronic ischemic heart disease (ICD codes 412 - 414) or stroke [ICD codes 430 (subarachnoid hemorrhage), 431

(intracerebral hemorrhage), 434 (ischemic stroke) or 436 (unspecified stroke)]. In men with more than one CVD event, only the first event was used for the analyses.

Statistical methods

SPSS (version 10.0) was used for all statistical analyses. The CO distribution in blood and in expired air, respectively, was each divided into quartiles and each corresponding quartile of CO in expired air and CO in blood were thereafter condensed into a new variable of CO in quartiles. Distributions of smoking habits, ABPI and other cardiovascular risk factors in groups of CO were expressed in terms of mean and standard deviation or as proportions. Spearman's correlation coefficients were computed for CO in blood and expired air, respectively, and ABPI. Mantel-Haentzel Chi-square test was used to study the linear relationship between daily tobacco consumption and the upper quartile of CO and quartiles of ABPI. A general linear model analysis was used to study the relationship (by test for linear trends) between the upper quartile of CO and quartiles of ABPI, adjusting for potential confounders. Cox's proportional hazards model for multivariate analysis was used to study incidence of CVD event rate, CVD mortality and all-cause mortality in relation to quartiles of CO. Survival plots of the different risk factor categories confirmed the fit of the proportional hazards model. Tolerance for each independent variable was calculated as a test for collinearity (19). Tolerance-values below 0.20 were considered to indicate collinearity problems (19).

RESULTS

Study Cohort

Seventy-six men were never smokers, 160 were former smokers, 41 light smokers (<10 grams/d), 60 moderate smokers (10 - 19 grams/d) and 28 heavy smokers (≥20

grams/d), Table 1. The mean CO concentration in blood and in expired air, respectively, was similar in never and former smokers. In smokers it increased stepwise with increasing daily tobacco consumption.

Reproducibility of smoking habits, tobacco consumption and CO

The reproducibility of the smoking habits, daily tobacco consumption and CO in expired air was checked in 29 randlomly selected men 4 weeks after the initial examination and found to be satisfactory (Kendell's tau-b: 0.97, Spearman correlation coefficient: 0.94 and 0.76, respectively). The initial and follow-up median CO concentration in expired air was rather similar (80; range: 45 - 304 and 71; range: 36 - 296, Wilcoxon rank test, p=0.546).

CO in relation to tobacco consumption and ABPI

In smokers there was a significant but modest relationship between daily tobacco consumption and CO in blood and in expired air (r=0.35, p=0.014, and r=0.28, p=0.028, respectively). In the entire cohort there was a significant inverse correlation between the ABPI and CO in expired air (r= - 0.24, p<0.001), as well as between ABPI and the CO concentration in blood (r= - 0.21, p=0.017). The daily tobacco consumption and percentage having CO-values in the top quartile (i.e., categorization with regard to CO exposure is in 26 men based on CO in blood and in 59 men based on CO in expired air) across quartiles of ABPI is shown in Table 2. Daily tobacco consumption as well as the percentage having CO-values in the top quartile decreased in a statistically significantly stepwise fashion with ABPI. This inverse relationship with CO-exposure remained after adjustment for the amount of tobacco smoked per day and other potential confounders (p for trend 0.024).

Incidence of CVD events and deaths in relation to smoking habits and CO

One hundred and sixty-three men (44.7 %) died during the follow-up, 74 (45.4 %) of them from cardiovascular diseases. One hundred and twelve men (30.7 %) had a CVD event, 29 fatal myocardial infarction or sudden cardiac death, 36 non-fatal myocardial infarction and 47 a stroke (in nine cases with a fatal outcome). The CVD event rate, CVD deaths and all deaths in relation to smoking habits and quartiles of CO are shown in Table 3. The CVD mortality rate in smokers was almost two times that in ex- and never-smokers (p=0.016 and p=0.014, respectively). The relative risk (RR) of CVD events, deaths from CVD and all deaths gradually increased with increasing CO, Table 4. The relative risk of a CVD event was 1.85 [95% confidence interval (CI): 1.08-3.17, p=0.025] times higher in the top CO-quartile than it was in the first quartile. Corresponding risk for death from CVD and total mortality were 3.15; 1.60-6.22, p=0.001, and 1.77; 1.14-2.74, p=0.010, respectively. The increased risk of a CVD event and death from CVD associated with a CO value in the top quartile remained statistically significant after adjustments for amount of tobacco smoked per day and several other potential confounders (RR: 2.16; 1.00-4.65, p=0.050, and 3.19; 1.23-8.29, p=0.017, respectively), Table 4. The adjusted rates of CVD event free survival, mortality from CVD and total mortality associated with CO (in quartiles) are presented in Figure 1. When these models were tested for collinearity, CO and tobacco consumption showed a tolerance of 0.52 and 0.51, respectively, indicating an acceptable degree of collinearity.

DISCUSSION

The systolic ankle-arm pressure index can be considered a semi-quantitative measure of the degree of atherosclerosis distal to the aortic bifurcation (20). Smokers were as expected over-represented among those with the lowest values. Yet, as 36 and 19% of

those with AAI ratios in the two top quartiles were daily smokers and only a minority of the smokers suffered a cardiovascular event, it can be concluded that some smokers are more vulnerable than others. It is our conclusion that among smokers, independent of daily tobacco consumption, the severity of asymptomatic leg athersclerosis as well as the incidence of cardiovascular events and deaths is related to the degree of carbon monoxide exposure.

Tobacco smoke contains a vast number of substances, which could be related to the cardiovascular hazards associated with smoking (3-5). Estimates of risk should ideally be assessed in relation to the amount that via the lungs are absorbed into the blood stream. Among smokers matched for daily tobacco consumption there are marked variations of the amount of carbon monoxide hemoglobin (2, 21). To what extent this may be accounted for by air pollution (22), brand of tobacco, use of filter, inhalation habits and time since last smoked cigarette remains to be evaluated. It can be concluded, however, that cardiovascular risk estimates based solely on the number of cigarettes smoked per day are improved by levels of CO in blood or expired air.

The deleterious of carbon monoxide on the vessel wall has been demonstrated in animal experiments and in conjunction with acute lethal poisoning (6-8). Prevalence of cardiovascular disease was in one cross-sectional study related to plasma levels of CO in blood (9). Yet whether observed associations in this cohort may be related to the health hazards of carbon monoxide per se or whether the amount of carbon monoxide in blood simply reflects the amount of other vessel wall damaging agents remains to be evaluated.

The role of inflammation in the causation of atherosclerosis (23) is strongly supported by both experimental and observational studies (24, 25). Whether the association between smoking and atherosclerosis is mediated via inflammatory mechanisms can only be

speculated about. In another cohort from this urban population it has been demonstrated that plasma levels of fibrinogen, orosomucoid (α_1-acid glycoprotein), α_1-antitrypsin, haptoglobin and ceruloplasmin in smokers are related to CO in blood (26). Values in ex-smokers were similar to those in never-smokers. In a continued follow up of this cohort it was shown that the influence of smoking on incidence of cardiovascular disease and death is related to plasma levels of these inflammatory sensitive proteins. Oxidised low-density lipoprotein (LDL)-cholesterol and other reactive oxygen species play a key role in the inflammatory process leading to atherosclerosis (23). Smoking contributes oxygen radicals via the metabolism of polycyclic aromatic hydrocarbons. The P-450 mixed function oxygenase component system, which is involved in the metabolism of these agents, can be inactivated by carbon monoxide (27).

Some methodological issues should be considered. Vital status at the end of follow up was updated on all by linkage with the regional and national registers (17, 18) the completeness and validity of which has been documented in several other studies (28). Hence, there should be little reason to believe that observed associations with regard to the incidence and mortality from cardiovascular disease could have been confounded by biased retrieval and validation of end-points. The ABPI has in a number of studies been shown to be a valid method for the detection of non-symptomatic stages of leg atheroslcerosis (10, 20). It is our conclusion that the degree/extension of atherosclerotic lesions in the leg arteries in smokers is related to degree of carbon monoxide. However the probability of late stage complications, i.e., plaque rupture with subsequent thrombus formation were similarly related to the degree of exposure to carbon monoxide (29, 30). Several potential confounders were introduced in the multivariate analyses. It remains to be evaluated to what extent differences between groups defined in terms of carbon monoxide exposure with regard to the occurrence of cardiovascular disease could have

been confounded by sub-fractions of cholesterol, cardio-respiratory fitness and coagulation factors. The LDL to HDL-cholesterol ratio is however strongly related to levels of triglycerides, which was one of co-variates in the multivariate assessment of risk. Furthermore, no association has been found between blood lipids and CO in the blood (31). The degree of carbon monoxide exposure should be viewed against circumstances for sampling. All were informed to abstain from tobacco for at least 12h prior to the examination. As the half-life of CO is around 4h it means that many of the smokers during the day are exposed to very high levels. The high to moderate intra-individual correlation of values taken 4 weeks apart can be considered a measure of the validity with which individual exposure has been estimated. Similar to to other population-based surveys findings in this study were based on one blood pressure and one fasting blood glucose reading at a single visit. During the years when this study was performed, the national guideline for hypertension was defined as blood pressure level ≥160/95 mm Hg and diabetes was defined as fasting blood glucose level ≥6.7 mmol/L, which is not today considered as the standard (i.e., ≥140/90 mm Hg and ≥6.1 mmol/L, respectively). However, using the lower cut-off level for hypertension and diabetes would probably introduce a higher proportions of false positive men with hypertension and diabetes.

It is our conclusion that in smokers, independent of daily tobacco consumption, differences with regard to the prevalence of leg atherosclerosis and incidence of cardiovascular disease is related to the amount of carbon monoxide in blood or expired air.

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Table 1. Smoking habits, other cardiovascular risk factors and ankle-arm index (ABPI) in relation to quartiles of carbon monoxide in blood or in expired air among 68-year-old men without history of cardiovascular disease

	CO exposure level[a]				*P* for trend
	Q1	Q2	Q3	Q4	
No of men	97	95	88	85	
CO in blood (in %), range	0.40 - 0.60	0.61 - 0.80	0.81 - 1.30	1.31 - 4.70	NA
CO in expired air (in ppm), range	32 - 60	61 - 79	80 - 141	142 - 554	NA
Smoking habits					
Never, (%)	30.9	33.7	14.8	1.2	<0.001
Former, (%)	68.1	57.9	39.8	4.7	<0.001
Quitted: <10 yrs, (%)	16.5	16.8	8.0	2.4	<0.001
Quitted: 10-19 yrs, (%)	22.7	22.1	17.0	1.2	<0.001
Quitted: ≥20 yrs, (%)	28.9	18.9	14.8	1.1	<0.001
Current, (%)	1.0	8.4	45.4	94.1	<0.001
Tobacco consumption: 1-9 g/d, (%)	1.0	4.2	17.0	24.7	<0.001
Tobacco consumption : 10-19 g/d, (%)	0	2.1	23.9	43.5	<0.001
Tobacco consumption: ≥20 g/d, (%)	0	2.1	4.5	25.9	<0.001
Inhalers (% of current smokers)	0	75.0	79.5	86.3	0.070
Ankle-arm index (ABPI), worst leg	1.05 ± 0.10	1.04 ± 0.11	1.02 ± 0.14	0.98 ± 0.13	<0.001
ABPI <0.9, (%)	6.2	7.4	12.5	17.6	0.007
BMI (kg/m^2)	25.2 ± 3.0	25.6 ± 3.2	25.4 ± 3.6	23.7 ± 3.0	0.003
SBP (mm Hg)	93.7 ± 11.3	93.6 ± 10.2	91.7 ± 10.7	91.6 ± 11.0	0.053
DBP (mm Hg)	156.3 ± 22.6	156.4 ± 20.2	149.9 ± 20.1	149.2 ± 21.3	0.005
Use of BP-lowering medication (%)	20.8	25.3	19.3	11.8	0.090
Cholesterol (mmol/L)	6.1 ± 1.0	6.1 ± 1.0	5.9 ± 1.1	5.9 ± 1.1	0.135
Triglycerides (mmol/L)	1.4 ± 0.6	1.6 ± 0.7	1.6 ± 1.1	1.3 ± 0.6	0.313
Glucose (mmol/L)	5.1 ± 0.8	5.4 ± 1.6	5.3 ± 1.6	5.0 ± 1.0	0.665
Diabetes (%)	2.1	6.3	10.2	2.4	0.556

NA, not applicable; CVD, cardiovascular disease; BMI, body mass index; DBP, diastolic blood pressure SBP; systolic blood pressure. Values are expressed as mean (SD), range or as proportions if otherwise not stated.

[a] Categorization with regard to CO exposure is in 129 men based on CO in blood and in 236 men based on CO in expired air.

Table 2. Distribution of tobacco consumption and top quartile of CO (e.g., the upper quartiles of carbon monoxide (CO) in blood or the upper quartile of CO in expired air) in relation to quartiles of ankle-arm index (ABPI) in the worst leg among 68-year-old men without history of cardiovascular disease

	Quartiles of ABPI				*P* for trend
	Q1	Q2	Q3	Q4	
No of men	92	91	91	91	
ABPI (range)	0.41 - 0.98	0.98 - 1.03	1.03 - 1.08	1.08 - 1.42	NA
Tobacco consumption					
Never plus former smokers, (%)	52.7	60.4	64.1	81.3	<0.001
Current smokers: 1-9 g/d, (%)	13.2	16.5	8.7	6.6	0.063
Current smokers: 10-19 g/d, (%)	18.7	16.5	18.5	12.1	0.307
Current smokers: ≥20 g/d, (%)	15.4	6.6	8.7	0	<0.001
Upper quartile CO[a] (%), unadjusted	38.5	24.2	19.6	11.0	<0.001
Upper quartile CO[a] (%), adjusted[b]	30.8	24.1	18.7	19.7	0.024

Q1 to Q4 refers to the quartiles of ABPI. NA, not applicable.

[a] Categorization is in 26 men based on CO in blood and in 59 men based on CO in expired air. For cut-off levels for each CO, see Table 1.

[b] Adjusted for BMI, tobacco consumption, systolic blood pressure, use of blood pressure lowering medication, and total cholesterol.

Table 3. Incidence of first CVD event (fatal- or non-fatal myocardial infarction, deaths due to chronic ischaemic heart disease or fatal- or non-fatal stroke), cardiovascular deaths or all deaths in relation to smoking habits and quartiles of carbon monoxide (CO) in blood (COHb) or CO in expired air, in 68-year-old men without history of cardiovascular disease.

	Levels of CO exposure[a]				*P* for trend
	Q1	Q2	Q3	Q4	
No of men	97	95	88	85	
First CVD event, number of events	23	27	31	31	
Events per 1000 person-years (95% CI)	21.3 (13.5 – 31.9)	27.7 (18.2 – 40.3)	35.9 (24.4 – 51.0)	38.7 (26.3 – 54.9)	0.014
CVD mortality, number of events	12	17	18	27	
Events per 1000 person-years (95% CI)	10.3 (5.3 – 18.0)	15.8 (9.2 – 25.2)	19.0 (11.3 – 30.0)	31.1 (20.5 – 45.2)	<0.001
All deaths, number of events	36	40	41	46	
Events per 1000 person-years (95% CI)	30.9 (21.7 – 42.9)	37.1 (26.5 – 50.5)	43.3 (31.1 – 58.7)	52.9 (38.7 – 70.6)	0.007
	Smoking habits				
	Never	Former	Current		*P* for trend
No of men	76	160	129		
First CVD event, number of events	22	45	45		
Events per 1000 person-years (95% CI)	26.6 (16.6 – 40.2)	27.2 (19.8 – 36.4)	36.3 (26.5 – 48.6)		0.155
CVD mortality, number of events	11	27	36		
Events per 1000 person-years (95% CI)	12.2 (6.1 – 21.9)	15.0 (9.9 – 21.8)	26.6 (18.6 – 36.8)		0.005
All deaths, number of events	29	67	67		
Events per 1000 person-years (95% CI)	32.3 (21.6 – 46.4)	37.1 (28.7 – 47.1)	49.5 (38.4 – 62.9)		0.023

CVD, cardiovascular; CI, confidence interval.

[a] Categoriazation with regard to CO exposure is in 129 men based on CO in blood and in 236 men based on CO in expired air. For cut-off levels for each CO, see Table 1.

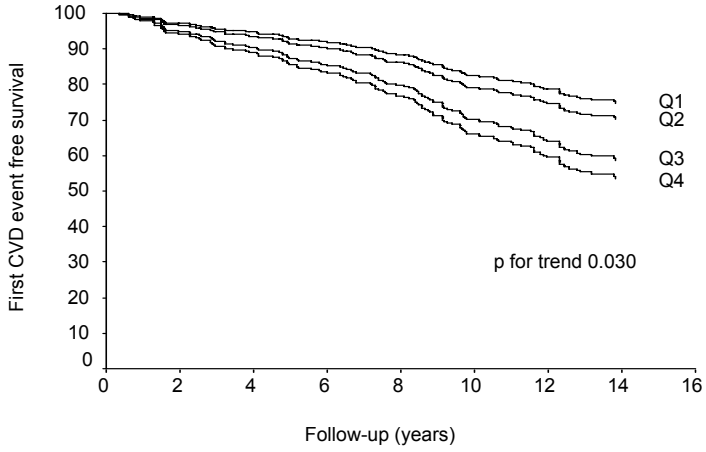
Table 4. Relative risk (RR) (with 95% confidence interval, CI) of first CVD event (fatal- or non-fatal myocardial infarction, deaths due to chronic ischaemic heart disease or fatal- or non-fatal stroke), cardiovascular deaths or all deaths in relation to quartiles of carbon monoxide (CO) in blood (COHb) or quartiles of CO in expired air, in 68-year-old men without history of cardiovascular disease.

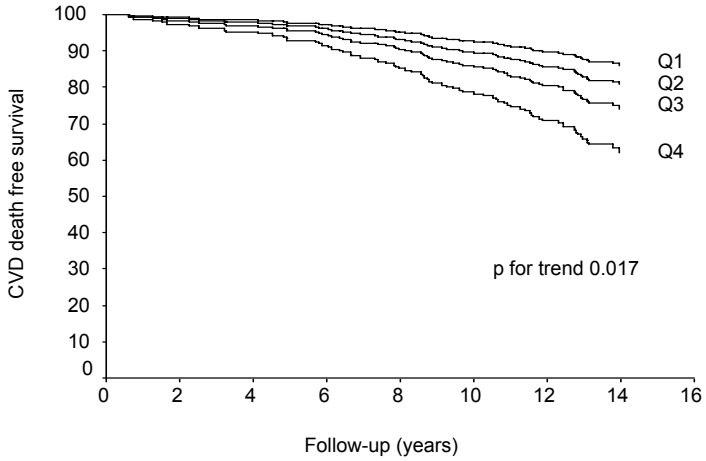
Variable	First CVD event		CVD deaths		All deaths	
	RR	95% CI	RR	95% CI	RR	95% CI
Level of CO exposure[a]						
Fourth vs. first quartile	1.85	1.08 - 3.17	3.15	1.60 - 6.22	1.77	1.14 - 2.74
Third vs. first quartile	1.73	1.01 - 2.96	1.90	0.91 - 3.93	1.43	0.91 - 2.24
Second vs. first quartile	1.32	0.76 - 2.31	1.53	0.73 - 3.21	1.20	0.77 - 1.89
P for trend	0.014		0.001		0.007	
Adjusted for risk factors[b]						
Fourth vs. first quartile	2.16	1.00 - 4.65	3.19	1.23 - 8.29	1.73	0.92 - 3.25
Third vs. first quartile	1.85	1.01 - 3.35	2.02	0.90 - 4.53	1.44	0.87 - 2.38
Second vs. first quartile	1.22	0.70 - 2.14	1.43	0.68 - 3.02	1.14	0.73 - 1.80
P for trend	0.030		0.017		0.081	

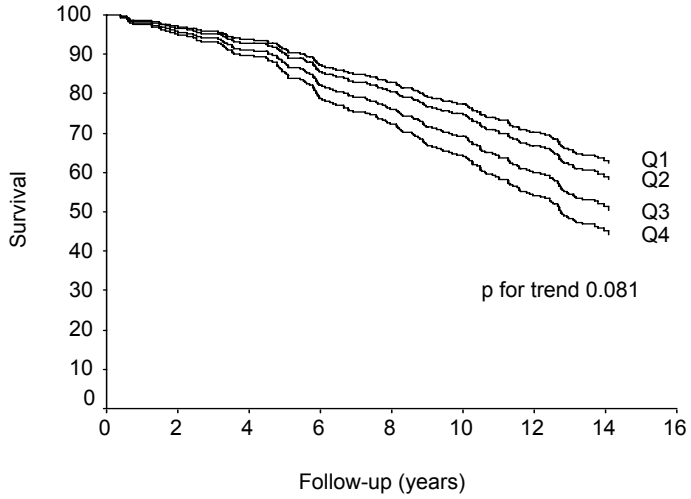
[a] Categorization with regard to CO exposure is in 129 men based on CO in blood and in 236 men based on CO in expired air. For cut-off levels for each CO, see Table 1. Cut-off levels for CO in expired air and CO in blood are shown in Table 1.

[b] Adjusted for BMI, tobacco consumption, systolic blood pressure, use of blood pressure lowering medication, and total cholesterol.

Legend to figure 1. Adjusted first CVD event (upper panel), CVD deaths (middle panel) and total mortality (lower panel) curves of quartiles of CO among 68-year-old men without history of cardiovascular disease (*n*=365). Categorization with regard to CO exposure is in 129 men based on CO in blood and in 236 men based on CO in expired air. For cut-off levels for each CO, see Table 1. The event free survival curves have been adjusted for BMI, tobacco consumption, systolic blood pressure, use of blood pressure lowering medication, and total cholesterol.


First CVD event free survival
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
Follow-up (years)
Q1
Q2
Q3
Q4
p for trend 0.030


CVD death free survival
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
Follow-up (years)
Q1
Q2
Q3
Q4
p for trend 0.017


Survival
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
Follow-up (years)
Q1
Q2
Q3
Q4
p for trend 0.081