

CARDIOVASCULAR MEDICINE

Carboxyhaemoglobin concentration, smoking habit, and mortality in 25 years in the Renfrew/Paisley prospective cohort study

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Objective: To investigate how carboxyhaemoglobin concentration is related to smoking habit and to assess whether carboxyhaemoglobin concentration is related to mortality.

Design: Prospective cohort study.

Setting: Residents of the towns of Renfrew and Paisley in Scotland.

Participants: The whole Renfrew/Paisley study, conducted between 1972 and 1976, consisted of 7048 men and 8354 women aged 45-64 years. This study was based on 3372 men and 4192 women who were screened after the measurement of carboxyhaemoglobin concentration was introduced about halfway through the study.

Main outcome measures: Deaths from coronary heart disease (CHD), stroke, chronic obstructive pulmonary disease (COPD), lung cancer, and all causes in 25 years after screening.

Results: Carboxyhaemoglobin concentration was related to self reported smoking and for each smoking category was higher in participants who reported inhaling than in those who reported not inhaling. Carboxyhaemoglobin concentration was positively related to all causes of mortality analysed (relative rates associated with a 1 SD (2.93) increase in carboxyhaemoglobin for all causes, CHD, stroke, COPD, and lung cancer were 1.26 (95% confidence interval (CI) 1.19 to 1.34), 1.19 (95% CI 1.13 to 1.26), 1.19 (95% CI 1.13 to 1.26), 1.64 (95% CI 1.47 to 1.84), and 1.69 (95% CI 1.60 to 1.79), respectively). Adjustment for self reported cigarette smoking attenuated the associations but they remained relatively strong.

Conclusions: Self reported smoking data were validated by the objective measure of carboxyhaemoglobin concentration. Since carboxyhaemoglobin concentration remained associated with mortality after adjustment for smoking, carboxyhaemoglobin seems to capture more of the risk associated with smoking tobacco than does self reported tobacco consumption alone. Analysing mortality by self reported cigarette smoking underestimates the strength of association between smoking and mortality.

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Epidemiological studies often suffer from underreporting of habits known to be unhealthy or undesirable. In particular, the validity of self reported smoking has been questioned. Studies have used physical measures such as cotinine^{1,2} (in blood, urine, or saliva) or carboxyhaemoglobin^{3,4} to validate self reported smoking habit. The NHANES II (Second National Health And Nutrition Examination Survey) used carboxyhaemoglobin measurements to investigate bias towards reporting multiples of 10 cigarettes a day.⁴ The BUPA study found positive relationships between carboxyhaemoglobin and the amount smoked and amount inhaled.⁵ In this study, carboxyhaemoglobin was used to investigate the relationship with smoking habits and to see how carboxyhaemoglobin concentration is related to mortality from various diseases in the 25 years after screening.

METHODS

The Renfrew/Paisley study was a general population prospective cohort study conducted between 1972 and 1976 on residents of the towns of Renfrew and Paisley in Scotland.⁶ These towns are located near the city of Glasgow in Scotland and are areas of high socioeconomic deprivation with life expectancy figures among the worst in the whole of the UK.⁷ Men and women aged between 45-64 years were invited to take part. The response rate of 78% resulted in 7048 male and 8354 female participants.

Participants completed a questionnaire and attended a clinical examination at specially set up screening centres. The

questionnaire asked about smoking habit, from which smoking categories were derived. These were never smoked, smoked only cigars or a pipe, smoked cigarettes (1-5, 6-14, 15-24, or 25 or more a day) or smoked in the past. Former smokers were defined as not having smoked for at least 12 months before screening; otherwise, they were categorised as current smokers. Current smokers were also asked whether they inhaled. At the screening examination, height was measured without shoes and the forced expiratory volume in one second (FEV₁) was measured with a vitalograph spirometer with the subject standing.⁸ Predicted FEV₁ was calculated from equations derived from a healthy subset of the population for age, height, and sex.⁸ Adjusted FEV₁ was calculated as a percentage of actual FEV₁ to predicted FEV₁. In 1975, about halfway through the Renfrew/Paisley study, co-oximeter measurement of carboxyhaemoglobin concentration in the participants' blood was introduced.

Mortality details are received routinely from the flagging system at the National Health Service Central Register in Edinburgh, the normal method for UK cohort studies. Additionally, death data were obtained from a computerised linkage with deaths in Scotland. For this study, deaths occurring in the 25 year period after screening were defined

Abbreviations: CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; ICD-9, *International classification of diseases*, ninth revision; NHANES II, Second National Health And Nutrition Examination Survey

Table 1 Mean carboxyhaemoglobin percentage by smoking habit in men and women in the Renfrew/Paisley study

Smoking	All		Men		Women	
	No	Mean (SD)	No	Mean (SD)	No	Mean (SD)
Never	2448	1.59 (1.72)	547	1.77 (1.72)	1901	1.53 (1.71)
Former	1206	1.96 (1.87)	876	2.09 (1.94)	330	1.62 (1.64)
Pipe or cigar Cigarettes/day	91	2.63 (2.62)	86	2.52 (2.60)	5	4.42 (2.53)
1–5	162	2.31 (1.94)	36	2.19 (1.58)	126	2.34 (2.03)
6–14	1002	4.39 (2.48)	368	4.13 (2.30)	634	4.54 (2.57)
15–24	1945	5.68 (2.64)	921	5.48 (2.63)	1024	5.86 (2.64)
≥25	710	6.02 (2.86)	538	5.95 (2.84)	172	6.23 (2.90)
All	7564	3.52 (2.93)*	3372	3.81 (2.90)*	4192	3.27 (2.93)*

*p<0.0001 for never and current cigarette smokers.

as being caused by coronary heart disease (CHD) (*International classification of diseases*, ninth revision (ICD-9) codes 410–414), stroke (codes 430–438), chronic obstructive pulmonary disease (COPD) (codes 490–494 and 496), and lung cancer (code 162). Deaths from all causes are also reported.

After the carboxyhaemoglobin measurement was introduced, 7809 participants were screened. Of these, 229 had missing values of carboxyhaemoglobin and there was one obvious outlier. Also excluded from this study were nine participants with missing data on adjusted FEV₁ and six participants who had embarked from the UK during the follow up period. Therefore the complete data of 3372 men and 4192 women (total 7564) were analysed. Trends of carboxyhaemoglobin concentration by amount smoked were calculated by regression analysis for never and current cigarette smokers based on the number of cigarettes smoked a day. Differences between mean carboxyhaemoglobin concentration by inhalation were calculated by using *t* tests. Means of adjusted FEV₁ by quintile of carboxyhaemoglobin were additionally adjusted for smoking with PROC GLM in SAS/STAT, version 6 (SAS Institute, Cary, North Carolina, USA). The smoking adjustment was entered as the number of cigarettes smoked daily by current cigarette smokers, with zero allocated to non-smokers and former cigarette smokers. Trends for adjusted FEV₁ with carboxyhaemoglobin were calculated by linear regression analysis. Cox's proportional hazards models were used to estimate relative rates of mortality by quintile of carboxyhaemoglobin and to calculate the relative rate associated with a one standard deviation

increase in carboxyhaemoglobin concentration with carboxyhaemoglobin as a continuous variable. Adjustments were made for smoking by adding the number of cigarettes smoked daily for current and former smokers, with an additional variable for former smokers (1 if former smoker, 0 otherwise). Cox's models were also used for estimating the relative rates of mortality by smoking category, with adjustments made for carboxyhaemoglobin concentration.

RESULTS

Table 1 presents the mean carboxyhaemoglobin concentration for each smoking category. Never smokers had the lowest carboxyhaemoglobin concentration followed by former smokers. A dose response relationship was seen with number of cigarettes smoked a day, with the pipe or cigar smokers having a mean carboxyhaemoglobin concentration between the 1–5 and the 6–14 cigarettes a day categories. Results were consistent for men and women.

The majority of cigarette smokers reported inhaling (93% of men and 82% of women). For each smoking category and for each sex, inhalers had higher carboxyhaemoglobin concentrations than non-inhalers (table 2). Adjusting for number of cigarettes smoked did not affect the difference in carboxyhaemoglobin concentration between inhalers and non-inhalers (not shown). Overall, among current smokers, inhalers had a mean adjusted carboxyhaemoglobin concentration of 5.63 compared with 4.40 for non-inhalers (*p* < 0.0001).

Carboxyhaemoglobin was strongly related to adjusted FEV₁ in men and women (table 3). Participants with lower carboxyhaemoglobin concentrations had higher adjusted

Table 2 Mean carboxyhaemoglobin percentage for current cigarette smokers according to whether they inhale (1709 men and 1863 women)

Smoking (cigarettes/day)	All		Men		Women	
	No	Mean (SD)	No	Mean (SD)	No	Mean (SD)
1–5						
Inhale	87	2.46 (2.10)	26	2.43 (1.69)	61	2.48 (2.26)
Not inhale	67	2.07 (1.65)	9	1.64 (1.15)	58	2.13 (1.71)
p Value		0.20		0.21		0.35
6–14						
Inhale	767	4.67 (2.42)	303	4.40 (2.28)	464	4.84 (2.49)
Not inhale	180	3.96 (2.46)	38	3.30 (1.77)	142	4.13 (2.59)
p Value		<0.0001		0.004		0.004
15–24						
Inhale	1670	5.98 (2.53)	815	5.75 (2.53)	855	6.21 (2.51)
Not inhale	174	4.56 (2.39)	48	4.38 (2.34)	126	4.63 (2.41)
p Value		<0.0001		<0.0001		<0.0001
≥25						
Inhale	583	6.63 (2.58)	445	6.59 (2.53)	138	6.77 (2.74)
Not inhale	44	5.25 (2.20)	25	5.0 (2.30)	19	5.56 (2.08)
p Value		0.001		0.002		0.07

p Value for difference in means.

Table 3 Mean adjusted forced expiratory volume in one second percentage unadjusted and adjusted for smoking (cigarettes/day) by quintile of carboxyhaemoglobin (COHb) among men and women in the Renfrew/Paisley study

Quintile COHb	All			Men			Women		
	No	Unadjusted	Adjusted	No	Unadjusted	Adjusted	No	Unadjusted	Adjusted
1 (0.1–0.8)	1512	92.2	94.3	533	90.3	92.8	979	93.6	95.2
2 (0.9–2.0)	1622	92.1	93.8	630	89.9	91.8	992	93.7	95.1
3 (2.1–3.7)	1454	89.5	90.0	729	88.1	89.0	725	90.8	91.1
4 (3.8–6.1)	1466	88.5	86.7	738	86.2	84.6	728	90.6	88.8
5 (6.2–24.2)	1510	87.1	84.4	742	86.8	84.2	768	87.0	84.6
p for trend		<0.0001	<0.0001		0.007	<0.0001		<0.0001	<0.0001

FEV₁ and trends were significant even after adjustment for cigarette smoking.

Carboxyhaemoglobin concentration was positively related to all cause mortality, adjusted for age and sex (table 4). Adjustment for smoking considerably attenuated the associations but they remained relatively strong. Relationships with CHD mortality were similar. A less clear relationship was seen between carboxyhaemoglobin and stroke and this was attenuated after adjustment for smoking. Strong relationships were seen with COPD mortality, including after adjustment for smoking, although smaller numbers produced large confidence intervals. Carboxyhaemoglobin concentration was strongly related to lung cancer mortality, even after adjustment for smoking. Tests for interactions between sex and carboxyhaemoglobin concentration were not significant for any of the causes of death analysed (all cause p = 0.10, CHD p = 0.08, stroke p = 0.57, COPD p = 0.09, and lung cancer p = 0.30). When data were analysed by smoking category, the positive relationships with mortality were

similarly attenuated when adjusted for carboxyhaemoglobin concentration (not shown).

DISCUSSION

This analysis has validated the self reported smoking habits in the Renfrew/Paisley cohort by an objective measure. Carboxyhaemoglobin concentrations were strongly related to self reported smoking levels, self reported inhalation, and respiratory function and in addition were related to various causes of death, even after adjustment for smoking.

Since carboxyhaemoglobin concentration is a physical measurement, it can be considered a proxy for risk of disease caused by smoking. In a study of about 1000 Swedish middle aged men, morning carboxyhaemoglobin concentrations were measured.⁹ Concentrations were low for both non-smokers and former smokers. Higher concentrations were reported for current smokers and there was a dose-response relationship as normal daily consumption increased. A large variation in carboxyhaemoglobin concentration was seen

Table 4 Relative rates (RR) and 95% confidence intervals of all cause, coronary heart disease (CHD), stroke, chronic obstructive pulmonary disease (COPD), and lung cancer mortality over 25 years by quintile of carboxyhaemoglobin (COHb) and per standard deviation increase in COHb in men and women in the Renfrew/Paisley study

	COHb quintile (range)	No of deaths	Model 1*	Model 2†
All causes	1 (0.1–0.8)	686	1	1
	2 (0.9–2.0)	727	0.97 (0.88 to 1.08)	0.95 (0.85 to 1.05)
	3 (2.1–3.7)	764	1.22 (1.10 to 1.35)	1.13 (1.01 to 1.25)
	4 (3.8–6.1)	863	1.54 (1.39 to 1.71)	1.28 (1.15 to 1.43)
	5 (6.2–24.2)	942	1.77 (1.60 to 1.95)	1.41 (1.26 to 1.57)
	RR associated with 1 SD increase in COHb			1.26 (1.19 to 1.34)
CHD	1 (0.1–0.8)	213	1	1
	2 (0.9–2.0)	247	1.05 (0.87 to 1.26)	1.03 (0.86 to 1.24)
	3 (2.1–3.7)	276	1.35 (1.13 to 1.62)	1.28 (1.06 to 1.53)
	4 (3.8–6.1)	253	1.37 (1.14 to 1.65)	1.20 (0.98 to 1.46)
	5 (6.2–24.2)	280	1.59 (1.33 to 1.90)	1.34 (1.09 to 1.64)
	RR associated with 1 SD increase in COHb			1.19 (1.13 to 1.26)
Stroke	1 (0.1–0.8)	106	1	1
	2 (0.9–2.0)	86	0.76 (0.57 to 1.01)	0.74 (0.56 to 0.99)
	3 (2.1–3.7)	100	1.13 (0.86 to 1.49)	1.05 (0.79 to 1.38)
	4 (3.8–6.1)	107	1.41 (1.08 to 1.85)	1.18 (0.88 to 1.59)
	5 (6.2–24.2)	89	1.28 (0.96 to 1.70)	1.03 (0.74 to 1.42)
	RR associated with 1 SD increase in COHb			1.19 (1.13 to 1.26)
COPD	1 (0.1–0.8)	12	1	1
	2 (0.9–2.0)	16	1.22 (0.58 to 2.57)	1.15 (0.54 to 2.43)
	3 (2.1–3.7)	24	2.16 (1.08 to 4.33)	1.90 (0.94 to 3.84)
	4 (3.8–6.1)	50	5.10 (2.71 to 9.60)	3.94 (2.03 to 7.66)
	5 (6.2–24.2)	57	6.17 (3.30 to 11.54)	4.42 (2.23 to 8.67)
	RR associated with 1 SD increase in COHb			1.64 (1.47 to 1.84)
Lung cancer	1 (0.1–0.8)	34	1	1
	2 (0.9–2.0)	26	0.69 (0.41 to 1.15)	0.64 (0.38 to 1.06)
	3 (2.1–3.7)	61	1.82 (1.20 to 2.77)	1.43 (0.93 to 2.19)
	4 (3.8–6.1)	109	3.57 (2.43 to 5.26)	2.14 (1.43 to 3.23)
	5 (6.2–24.2)	159	5.41 (3.73 to 7.85)	2.89 (1.92 to 4.34)
	RR associated with 1 SD increase in COHb			1.69 (1.60 to 1.79)

1 SD = 2.93%.

*Model 1 adjusts for age and sex; †model 2 adjusts for age, sex, and smoking.

among people who reported smoking the same amount daily. It was suggested that prospective studies are required to see whether carboxyhaemoglobin measurement is a better measurement than tobacco consumption by questionnaire.

NHANES II found a bias towards reporting the daily amount smoked in multiples of 10 cigarettes a day, which could have been systematic (that is, rounding down) or random.⁴ No similar pattern was seen for carboxyhaemoglobin concentration. It was suggested that biochemical verification and self reported smoking level could be combined when examining smoking–disease relationships. It was also suggested that, since there were errors in self reported smoking, reported relationships between smoking and disease may not have been accurate.

In addition to finding positive relationships between carboxyhaemoglobin and amount smoked, the BUPA study found that carboxyhaemoglobin was related to the risk of mortality from CHD, lung cancer, or chronic obstructive lung disease (defined as ICD-9 codes 416, 491, 492, 496, and 519) independently of smoking category or amount smoked.⁵ Analysis by smoking after adjustment for carboxyhaemoglobin removed the smoking–disease relationship. In the current study, carboxyhaemoglobin concentration remained associated with mortality after adjustment for smoking, suggesting that carboxyhaemoglobin is capturing more smoking related risk than is just self reported smoking. Examples may be unmeasured differences in the way the cigarettes were smoked, such as number of puffs for each cigarette, smoking right down to the butt, or depth of inhalation. The carboxyhaemoglobin concentration could also have been affected by passive smoking, which could have had an increased effect on mortality risk.

Experiments involving smokers showed that carboxyhaemoglobin concentration did not increase during the day as more cigarettes were smoked but remained around each person's mean value.¹⁰ Implications for the current study are that time of day of screening or time since the last cigarette was smoked would not affect the carboxyhaemoglobin concentration measured. The strong relationship between carboxyhaemoglobin and lung function was to be expected, since carbon monoxide is removed from the body by expiration and expiration is less efficient in people with poorer lung function.¹¹

It is known that cigarette smokers who report not inhaling still have raised carboxyhaemoglobin concentrations.³ However, these concentrations are lower than for reported inhalers. In the current study, from a validation viewpoint, carboxyhaemoglobin concentrations were consistently lower in non-inhalers than in inhalers. Further studies of passive smoking in this cohort will be able to use carboxyhaemoglobin concentration to exclude participants who may have misreported their smoking habits.¹²

This research suggests that the smoking mortality risk may have previously been underestimated due to misreporting of

cigarette consumption. Carboxyhaemoglobin concentration may be picking up unmeasured risk in several ways. Firstly, participants could have underreported their tobacco consumption through rounding their response to a pack size or giving an incorrect reply because they know that smoking is harmful. Secondly, carboxyhaemoglobin concentration may be a better measure than just number smoked of the harmful effects of cigarettes, since it is capturing additional unmeasured effects such as depth of inhalation and how much of each cigarette is smoked. In consequence in prospective epidemiological studies the proportion of mortality attributed to smoking in a population would be underestimated through applying the associations observed between reported smoking and mortality.

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