

Carboxyhaemoglobin levels and inhaling habits in cigarette smokers

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Wald, N., Idle, Marianne, and Bailey, A. (1978). *Thorax*, 33, 201–206. Carboxyhaemoglobin levels and inhaling habits in cigarette smokers. In 520 men who currently smoked only cigarettes, carboxyhaemoglobin (COHb) levels were measured as a method of estimating the extent to which cigarette smoke was inhaled and the results were compared with the smokers' own assessment of their inhaling habits. The mean COHb level after standardising for the number of cigarettes smoked before the blood test on the day of the test was 4.0% in self-described non-inhalers. This was much higher than the mean level of 0.7% in 1891 similar non-smokers, but not very different from the standardised mean levels of 5.2%, 5.3%, and 5.6% in men who said they inhaled slightly, moderately, or deeply, respectively. The increasing trend in the COHb levels of men in the four self-described inhaling categories (nil to deep) was small but statistically highly significant. The data from this study may help to explain some of the anomalous epidemiological results regarding the relationship between self-described inhaling habits and the development of diseases associated with smoking, such as coronary heart disease and lung cancer.

There are anomalous results regarding the relationship between self-described inhaling of tobacco smoke and the development of diseases associated with smoking, such as coronary heart disease (CHD) and lung cancer (Doll and Hill, 1952; Schwartz *et al.*, 1961; Doll and Hill, 1964; Schwartz *et al.*, 1966). Most epidemiological studies have found that smokers who say they do not inhale have higher death rates from CHD and lung cancer than non-smokers, and that among cigarette smokers the association between self-described inhaling habits and mortality from both of these diseases has been weak. While, to most people, neither finding is particularly surprising since non-inhalers might be expected to inhale some smoke and the self-reporting of inhaling is likely to be imprecise, both findings have been thought, by some, to cast doubt on the significance of smoking as a cause of either disease (Fisher, 1959; Seltzer, 1968; Burch, 1976). Since carbon monoxide (CO) is present in tobacco smoke and is absorbed from the lung to form carboxyhaemoglobin (COHb), COHb levels can be used to investigate inhaling directly as well as the accuracy of self-described

inhaling. This paper describes the results of a study designed to do this.

Method

Men aged 35–64 years who attend a medical centre in London after 1100 hours for a comprehensive health screening examination complete a questionnaire on their usual and recent smoking habits. All information is collected after arrival at the medical centre, and the men are not forewarned about the survey of smoking habits. The time when each cigarette, cigar, and pipe was smoked since waking is recorded together with the manufacturer's brand. Each man is asked to what extent he usually inhales tobacco smoke, and his reply is recorded as one of the following: 'do not inhale', 'inhale slightly', 'inhale moderately', or 'inhale deeply'. COHb levels are measured twice on a single sample of blood from each man using an IL182 CO-Oximeter, after converting oxyhaemoglobin in the sample to deoxyhaemoglobin by adding sodium dithionite. If the two results differ by more than 0.2% COHb the estimation is re-

peated until this degree of precision is reached. The accuracy of the method is checked periodically by assaying a blood sample using the spectrophotometric method described by Commins and Lawther (1965).

To investigate whether CO is absorbed into the body through the mouth or pharynx, five volunteers who did not normally smoke agreed to smoke three cigarettes, each with a CO yield of 17 mg. One puff was taken every 30 seconds and held in the mouth for five seconds. Subjects were careful not to inhale, and a two-minute interval was taken between cigarettes. Venous blood was taken for COHb assay immediately before the first cigarette and one minute after the third. The subjects were seated throughout the experiment.

Results

The mean COHb level of 1891 men who were non-smokers (including ex-smokers) was 0.7% (SD 0.45). Table 1 shows the mean COHb level among the 579 men who currently smoked only manufactured cigarettes and who smoked brands for which CO yields were available from the Tobacco Research Council. Fifty men (9%) did not smoke such brands and were therefore excluded. The COHb levels are shown according to self-described inhaling habits and the number of cigarettes smoked before the blood test on the day the men were seen at the medical centre. The mean COHb level among all men who had smoked on the day they were seen was higher than that among non-smokers. Even the level among self-

described non-inhalers was substantially higher than that in non-smokers, and it increased progressively with the number of cigarettes smoked before the test. The mean COHb level among cigarette smokers who had not smoked before the blood test on the day of attendance at the medical centre (1.1%) was not very different from that in non-smokers (0.7%). In each inhaling category the mean COHb levels increased with the amount smoked. In order to estimate an average COHb level relating to each of the four inhaling categories, the mean COHb level for men in each self-described inhaling category was indirectly standardised for the number of cigarettes smoked before the test using the COHb levels of men in all four categories as standard. These 'standardised mean COHb levels' were then not biased by the amount actually smoked on the day of the test, and they provided a good indication of the relative amounts of CO inhaled from a constant number of cigarettes. The standardised mean COHb level was 4.0, 5.2, 5.3, and 5.6% COHb in each of the four categories of self-described inhaling, a statistically significant trend (χ^2_1 for trend=14.0, $P<0.001$). These average differences between men in the different self-described inhaling categories were very small in comparison with the difference in COHb levels between all smokers and non-smokers, or even between non-inhalers and non-smokers. The variation in COHb levels from person to person (average standard deviation was 1.8% COHb) within each category of self-described inhaling and each cigarette consumption group was considerably greater than the variation in

Table 1 Carboxyhaemoglobin levels among current male smokers of manufactured cigarettes only, according to self-described inhaling category and number of cigarettes smoked before blood test on day of test

Self-described inhaling category	No. of cigarettes smoked before test									1 or more	
	0	1-	3-	5-	7-	9-	11-	13-	15 or more	Unstandard- ised	Standardised*
Nil											
Mean COHb (%)	1.2	1.7	2.2	3.9	6.7	4.3	6.1	7.5	4.2	3.9	4.0
No. of men	4	4	5	6	2	3	1	2	4	27	—
Slight											
Mean COHb (%)	1.2	2.8	3.3	4.4	5.3	5.4	6.6	7.6	7.4	5.0	5.2
No. of men	12	11	9	8	5	5	7	5	6	56	—
Moderate											
Mean COHb (%)	1.1	2.4	3.6	5.0	5.6	6.3	7.1	5.5	6.7	5.1	5.3
No. of men	32	29	57	64	51	39	27	10	17	294	—
Deep											
Mean COHb (%)	1.0	3.4	4.0	6.2	5.5	5.9	7.2	6.5	7.7	6.1	5.6
No. of men	11	6	15	21	26	18	18	11	28	143	—
All											
Mean COHb (%)	1.1	2.6	3.5	5.2	5.5	6.0	7.1	6.4	7.1	5.3	5.3
No. of men	59	50	86	99	84	65	53	28	55	520	—

*Indirectly standardised for number of cigarettes smoked before test.

Table 2 Carboxyhaemoglobin levels between 1300 and 1600 hours among current male smokers of manufactured cigarettes only, according to self-described inhaling category and number of cigarettes smoked before blood test on day of test (data for men who had smoked their usual number of cigarettes ($\pm 20\%$) for time of day at which they had their blood test)

Self-described inhaling category	No. of cigarettes smoked before test									1 or more	
	0	1-	3-	5-	7-	9-	11-	13-	15 or more	Unstandard- ised	Standardised*
Nil											
Mean COHb (%)	—	1.2	—	5.2	—	3.8	6.1	7.5	4.0	4.8	4.7
No. of men	0	1	0	2	0	2	1	2	2	10	—
Slight											
Mean COHb (%)	—	3.2	4.8	4.2	6.6	5.2	7.0	7.3	7.4	6.0	6.0
No. of men	0	2	2	4	1	1	3	3	6	22	—
Moderate											
Mean COHb (%)	—	2.1	4.0	5.1	5.3	6.4	7.1	6.0	6.2	5.6	5.7
No. of men	0	4	13	13	17	19	16	7	11	100	—
Deep											
Mean COHb (%)	—	6.8	3.4	6.8	5.6	5.6	7.1	7.7	8.3	6.6	6.4
No. of men	0	1	5	4	11	7	6	4	14	52	—
All											
Mean COHb (%)	—	2.9	3.9	5.3	5.5	6.0	7.0	6.8	7.1	5.9	5.9
No. of men	0	8	20	23	29	29	26	16	33	184	—

*Indirectly standardised for number of cigarettes smoked before test, using all men as standard.

mean COHb results between the mean levels of men in the four different inhaling categories. This suggested that an individual COHb level was a poor indication of how a smoker would classify his own inhaling habits.

Table 2 shows, in a similar manner to Table 1, data which were restricted to the 184 men who had blood taken at about the same time of day (namely, from 1300 to 1600 hours), and who had smoked within 20% of their usual or previous day's consumption. The mean standardised COHb levels among men in the four self-described inhaling categories were 4.7, 6.0, 5.7, and 6.4% COHb respectively from nil to deep (χ^2_1 for trend = 4.7, $P < 0.05$).

Table 3 shows that there was no detectable rise in COHb level in five volunteers who did not normally smoke but smoked three cigarettes without inhaling any cigarette smoke as an experiment. This supports previous observations (Rawbone *et al.*, 1976) that CO is not absorbed significantly through the mouth or pharynx.

Discussion

PRESENT FINDINGS

There are two main conclusions which may be drawn from the results of this study. Firstly, cigarette smokers who say they do not inhale in fact nearly always inhale enough smoke into their lungs to raise their COHb level well above that in non-smokers. Secondly, there is a weak but statistically significant association between COHb level and self-described inhaling.

Table 3 COHb levels before and after smoking three cigarettes without inhaling smoke: Results of two COHb assays for each blood sample taken

Subject	COHb (%)	
	Before smoking first cigarette	After smoking third cigarette
1	0.4, 0.4	0.5, 0.4
2	0.7, 0.9	0.8, 0.6
3	0.6, 0.6	0.6, 0.6
4	0.3, 0.4	0.4, 0.4
5	0.7, 0.7	0.7, 0.7
Mean	0.6	0.6

Absorption of CO through the mouth or pharynx does not appear to occur. Therefore COHb must, to some extent, reflect inhaling, although the association will also depend on other factors, such as how each cigarette is smoked and the type and number of cigarettes smoked (Wald *et al.*, 1975; Wald *et al.*, 1977). In all our analyses we allowed for the number of cigarettes smoked before the blood test on the day of the test, so this was not a source of bias when comparing COHb levels among men in the different inhaling categories. We could not, however, estimate the relative contribution of, say, the number of puffs per cigarette and depth of inhaling on COHb levels except to note that in the real absence of inhaling the number of puffs would have little or no influence on COHb levels. The average CO yield of the cigarettes smoked by men was

similar in all four inhaling categories, and therefore this did not account for the differences. For example, in Table 1, the average yields were 18.0, 17.5, 16.7, and 16.8 mg/cigarette from nil to deep.

The smaller proportion of smokers among the men studied (44%) compared to 65% for men aged 35–39 years in the UK as a whole in 1975 (Tobacco Research Council, 1976) can be accounted for partly by the men who attended the medical centre having given up smoking to a greater extent than men in the UK generally (28% of men were ex-smokers at the medical centre and 20% in the UK). This, in turn, was probably due to their being mainly drawn from professional occupations in which reduction in smoking habits has been most marked. In 1975 the proportion of cigarette smokers among the men who attended the medical centre was similar to that of men in social class I (professional occupations) in the UK, namely, 25% and 29% respectively. The relatively high proportion of non-smokers among the men studied should not, however, affect our conclusions, which are based on comparisons of self-described inhaling and COHb levels within the total sample of men studied.

The proportion of self-described non-inhalers (5%) was very similar to the figure of 6% for the general population, and 95% of these men had smoked on the day of the test. Taken together, this indicated that the high COHb levels of self-described non-inhalers was likely to be typical for such smokers in general.

Systematic differences in the pattern of smoking among men in the different self-described inhaling categories might account for differences in their COHb levels. For example, self-described deep inhalers might smoke with shorter intervals between each cigarette than self-described non-inhalers and, as a result, would have higher COHb levels regardless of the extent of inhaling or the number of cigarettes smoked before the test. Furthermore, some men alter their smoking habits on the day they attend the medical centre. The results shown in Table 2 should take account of this since they relate to men who had blood taken at about the same time of day, namely, from 1300 to 1600 hours, and from men who had smoked about the same number of cigarettes (within 20%) as they would normally have smoked by the time of day at which they had their blood test. The positive COHb trend across the four inhaling categories was still evident, but it was statistically less significant for data in Table 2 than for data in Table 1, mainly because the number of men included in the analysis was far fewer. As a further

check on whether the differences in the pattern of smoking might have been a source of bias, the average numbers of cigarettes smoked by men in the different self-described inhaling categories in the three hours before the test were calculated and found to be similar, suggesting that deep inhalers did not smoke more cigarettes just before the test and so have higher COHb levels.

Self-described deep inhalers might also have higher COHb levels than self-described non-inhalers on account of having smoked more cigarettes during the previous day. This is unlikely to be important since most of the COHb from the previous day's smoking would have been eliminated overnight (Wald *et al.*, 1975). Also the COHb levels among men who did not smoke on the day of the test were low (Tables 1 and 2) and similar to those of men in each of the four inhaling categories.

Other factors which affect COHb levels, such as alveolar ventilation and pulmonary transfer factor for CO, are unlikely to account for the differences in COHb level among men in the four self-described inhaling categories since all the men were in good health and their level of physical activity was very similar.

As far as we are aware, the conclusions of this study are not likely to be due to bias, and we can therefore examine how they might help to explain some of the epidemiological results on self-described inhaling habits in relation to coronary heart disease and lung cancer.

EPIDEMIOLOGICAL IMPLICATIONS

A number of epidemiological studies of CHD have recorded information on inhaling. Apart from one study (Schwartz *et al.*, 1966), virtually all have shown that the risk of CHD among smokers who said they did not inhale was significantly greater than among non-smokers (Doll and Hill, 1964; Hammond, 1966; Cederlöf *et al.*, 1975; Reid *et al.*, 1976). The data from the present study indicate that many people who report that they do not inhale in fact do inhale, and the excess risk of CHD observed in such 'non-inhalers' is, therefore, not surprising.

Many studies have shown a relatively weak dose-response relationship between self-described inhaling and mortality from CHD. For example, Doll and Hill (1964) found that the annual death rate from CHD without hypertension was 3.29 per 1000 among non-smokers (50 deaths), 5.09 per 1000 among non-inhalers (60 deaths), and 5.22 per 1000 among inhaling cigarette smokers after standardising for age and amount smoked. Reid and his colleagues (1976) found a stronger relation-

ship; compared with all men in their study the age-adjusted relative risk of death from CHD in non-smokers, non-inhaling cigarette smokers, and inhaling cigarette smokers was 0.78, 0.95, and 1.41, respectively. In the Swedish Prospective Study (Cederlöf *et al.*, 1975) the crude CHD mortality among male cigarette smokers who said that they did not inhale, inhaled slightly, or inhaled deeply was, respectively, 1.2, 1.6, and 1.8 times that of non-smokers. Among men who smoked 16 or more cigarettes daily and said that they did not inhale or inhaled only slightly, the CHD mortality was 1.7 times that of non-smokers; among those who said they inhaled deeply it was 2.4 times higher. However, in the last two studies little allowance was made for cigarette consumption, and it is possible that some of the excess mortality among inhalers might have been due to the greater consumption frequently observed among smokers who say they inhale.

In an analysis of a Danish epidemiological survey (Wald *et al.*, 1973), inhaling as measured by COHb levels in smokers was strongly and statistically significantly associated with the prevalence of CHD and intermittent claudication after adjusting for age, serum cholesterol, and past as well as present cigarette consumption. Self-described inhaling habits were also associated with the two diseases, but much less closely.

These epidemiological observations are consistent with the weak association between self-described inhaling habits and COHb levels. Our results suggest that the weakness of the association is due to the inaccuracy of a smoker's own assessment of his inhaling habits rather than an intrinsically weak association between inhaling and disease.

There is another reason, not related to inhaling, which helps to explain why several studies have demonstrated a relatively small excess risk of CHD among inhalers compared with non-inhalers. Most cases of CHD reported from these studies occurred in persons over the age of 65 years, where the relative risk of CHD in heavy smokers compared to unity in non-smokers is no more than about 1.5, but in younger men it can be as high as 10 or more. It might, therefore, be expected that the relative risk of CHD among inhalers compared with non-inhalers would be less in the old than in the young, and this is indeed the case. For example, Doll and Peto (1976) found that the risk of CHD in inhalers compared with that in non-inhalers among men aged under 65 years was 1.57, but among men aged 65 years or more it was only 1.13.

Several epidemiological studies have also ex-

amined the association between self-described inhaling habits and lung cancer mortality, but many have not adjusted for cigarette consumption (Hammond, 1966; Kahn, 1966). The same two inhaling anomalies found with CHD are also present in data relating to lung cancer, namely, the risk is higher among self-described non-inhaling smokers than among non-smokers, and the association between inhaling and the incidence of lung cancer is weak among light smokers. As with CHD, our results suggest that these observations are not surprising and are consistent with smoking being a cause of both diseases. However, unlike the data relating to CHD, there is an additional anomaly: heavy smokers who say they inhale experience a lower mortality from lung cancer than those who say they do not (Doll and Hill, 1952; Schwartz *et al.*, 1961; Doll and Peto, 1976). Investigations are currently in progress to try to explain this anomaly.

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