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EXPIRED AIR CARBON MONOXIDE, SMOKING, AND OTHER VARIABLES

A COMMUNITY STUDY

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Analysis of the carbon monoxide content of expired air is now a frequently used technique in population studies. Its close correlation with the blood concentration of carboxyhaemoglobin was first demonstrated by Jones, Ellicott, Cadigan, and Gaensler in 1958. Studies in the United Kingdom (Tyrer, 1964) and the United States (Ringold *et al.*, 1962; Goldsmith, Schuette, and Novick, 1963) have shown that it is also associated with cigarette smoking as well as exposure to atmospheric pollution with carbon monoxide. The carbon monoxide in cigarette smoke, present in concentrations of 2% or more, can give rise to carboxyhaemoglobin levels of up to 12% of total haemoglobin in individuals smoking 15 or more cigarettes per day (Goldsmith and Landaw, 1968). There is some evidence that carboxyhaemoglobin levels greater than 5% may have adverse effects on fine visual and aural discrimination (Macfarland, Roughton, Halperin, and Niven, 1944; Beard and Wertheim, 1967; Schulte, 1963). It has been suggested recently that the effect of carbon monoxide might also be involved in the relationship between cigarette smoking and ischaemic heart disease (Goldsmith and Landaw, 1968; Goldsmith, 1969; Astrup, Kjeldsen, and Wanstrup, 1967; Astrup, 1969) and in the relationship between smoking in pregnancy and low birth weight (Astrup, Trolle, Olsen, and Kjeldsen, 1972).

This paper is based on the results of a community study of cardiorespiratory disease in Lambeth in 1967, in which various cardiorespiratory tests were carried out, including carbon monoxide levels of expired air (Holland and Waller, 1971). It gives the experimental details of the latter test and describes the relationship between carbon monoxide levels in expired air, smoking, ischaemic heart disease, and other factors.

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Study Population and Method

During February 1967, 783 adults aged between 35 and 84 years inclusive were examined in the clinical part of a two-stage survey of chronic respiratory and cardiovascular disease in a defined population (North Lambeth). The survey consisted of two main phases:

1. Screening: A brief questionnaire consisting of nine questions from the MRC questionnaire on respiratory symptoms (1960) and the WHO questionnaire on cardiovascular symptoms (Rose and Blackburn, 1968) was mailed to a random sample of 3,022 individuals.

2. Clinical survey: A random sample of four in five of those indicating positive symptoms on the screening questionnaire and one in six of those reporting no symptoms were asked to attend for a clinical examination consisting of:

(*a*) interviews including the full MRC and WHO symptom questionnaires, information on education, occupation, use of medical services, housing conditions, and other psychological and sociological factors;

(*b*) physical measurements—height, weight, and skinfold thickness;

(*c*) an electrocardiogram;

(*d*) tests of ventilatory capacity, forced expired volume in one second, forced vital capacity, peak expiratory flow rate;

(*e*) blood pressure measurement;

(*f*) exhaled air sample for carbon monoxide content;

(*g*) venous blood sample for haemoglobin, packed cell volume, and cholesterol estimation.

Full details of this part of the study are described elsewhere (Adler, Iliffe, Kasap, and Holland, 1971; Holland *et al.*, in preparation).

Samples for estimating expired air carbon monoxide concentrations were collected using a modification of the method of Jones *et al.* (1958). Respondents were asked to inspire deeply, hold their breath for 20 seconds (timed by a stop watch), and then to blow out into one arm of a specially designed T-tube (Wright, 1966). Two bags made of aluminized polyester sheeting were attached to the end and side arm of this T-tube. The first bag (of 300 ml) filled with tidal air and only when this was full did the second bag (of 500 ml) begin to fill. This bag was closed off when full, and was kept for analysis.

Although ideally the tidal air bag should have had a capacity of 800 ml so that the total volume of the physiological dead space would be discarded, it was found that when discarding this volume many subjects with cardiorespiratory disease were unable to produce samples adequate for analysis owing to diminished ventilatory function. If the volume of the tidal air bag was reduced to 300 ml consistent results were still produced, which differed only slightly from true alveolar air samples (Tyrer, 1964). Using this technique, 81% of the men and 76% of the women in the population studied were able to produce samples adequate for analysis.

The group whose CO values were measured was compared with the group whose CO values were not obtained and was found not to differ significantly in social class, type of smoker or amount smoked. There was, however, a significant difference in the average ages of the female groups ($P<0 \cdot 05$), the group who did not produce samples containing a larger than expected number of elderly women. This was mainly due to the fact that the measurement of CO was the most difficult procedure for the respondents to understand and so it could not be attempted in some cases. Indeed the group who did not produce samples admitted to significantly fewer positive symptoms on the screening questionnaire (males, $P<0 \cdot 01$; females, $P<0 \cdot 05$).

The exhaled air samples were analysed using a Beckman non-dispersive infrared gas analyser (IR 315L) incorporating a filter cell. The analysing system was equipped with soda-lime and magnesium perchlorate absorbers to remove carbon dioxide and water from the samples. This overestimates the relative concentration of CO in the expired air sample by a factor of up to 5%. This has not been allowed for in interpreting the findings. Before testing, the analyser was set at zero and calibrated with a known concentration (to within 5%) of carbon monoxide in air (obtained from Rank Precision Industries Ltd.). Samples were usually tested within 4 hours and never more than 16 hours after collection. Each sample was passed through the analyser using hand pressure. Readings were taken when a steady level was reached on the recorder needle. Ambient air carbon monoxide levels were found to be low in both the testing and the sampling rooms (mean level less than 2 parts per million) and no allowance was made for this in evaluating the results.

Aluminized polyester (Scotch pak) bags were chosen because of their relative impermeability compared with polyvinyl bags (Tamplin and Schuette, 1964). Despite this, pin-hole leaks developed with frequent handling in some bags. An independent calibration of the method was made by taking venous blood at the same time from 59

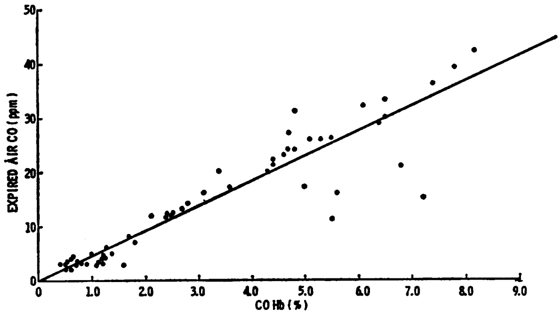

FIGURE The regression line of expired air CO(ppm) on % CO Hb.
Note: Some of the low CO values may have been due to leaking bags.

subjects (chosen at random) for carboxyhaemoglobin estimation at the MRC Air Pollution Research Unit using the spectrophotometric technique of Commins and Lawther (1965). The results given in the Figure show the relationship between percentage carboxyhaemoglobin and indicated expired CO read on a non-dispersive infrared analyser. A definite relationship is seen (correlation coefficient$=0 \cdot 93$) and this has been observed before (Goldsmith and Landaw, 1968; Jones *et al.*, 1958). This relationship was found to be independent of sex, but the expected expired air CO level for a given %COHb was a little lower for the older age groups ($P<0 \cdot 01$). Variations in techniques (e.g. volume of expired air collected, length of time to hold breath, the way in which the infrared analyser is calibrated and used) can result in different relationships between expired air CO and the concentration of CO in the blood; it is thus advisable, when using an expired air method, to calibrate it against a standard method for the determination of carbon monoxide in blood so that absolute concentrations of carboxyhaemoglobin can be estimated (Commins, personal communication).

TABLE IA

DEMOGRAPHIC VARIABLES: OBSERVED EXPIRED AIR CO LEVELS (ppm)

Social Class		Males 35–44	Males 45–64	Males 65+	Males All Ages	Females 35–44	Females 45–64	Females 65+	Females All Ages
I & II	x̄	17·09	17·17	10·27	16·25	16·64	7·28	6·22	11·08
	SD	10·20	12·33	6·12	11·05	14·40	4·44	5·09	10·99
	n	33	42	11	86	25	25	9	59
III M & Nm	x̄	21·52	15·92	7·82	16·59	17·36	11·18	5·00	12·50
	SD	13·37	10·30	3·72	11·82	11·78	10·76	2·56	11·16
	n	46	51	22	119	38	55	15	108
IV & V	x̄	16·67	15·31	9·97	14·31	13·89	11·98	4·88	11·53
	SD	10·59	8·34	6·50	8·93	8·42	9·82	2·42	9·05
	n	33	57	31	121	37	56	17	110
All social classes	x̄	18·78	16·04	9·28	15·66	15·90	10·79	5·22	11·81
	SD	11·83	10·20	5·64	10·64	11·42	9·59	3·18	10·31
	n	112	150	64	326	100	136	41	277

x̄ = mean; SD = standard deviation; n = number; M = manual; Nm = non-manual

TABLE IB

DEMOGRAPHIC VARIABLES AND SMOKING

To assess the independent effects of age, sex, and social class, the following regression equation was used:

$$\text{Log}_{10}(\text{CO}+1) = 1\cdot032 - 0\cdot036 \times \text{female} - 0\cdot005 \times \text{age (yr)} + 0\cdot256 \times \text{smoked in last hour} - \begin{Bmatrix} 0\cdot007 \times \text{L} \\ 0\cdot003 \times \text{Q} \end{Bmatrix} \text{social class} + 0\cdot031 \times \text{ex-smoker} + 0\cdot246 \times \text{present smoker}$$

This equation means, for example, that the value of $\log_{10}(\text{CO}+1)$ is 0·036 less for females than for males, all other things being equal, i.e., that the ratio of CO level in women to CO level in men is about 0·9. The effects of age and smoking were highly significant ($P<0\cdot001$), but sex and social class were non-significant.

Note: Dummy (O,1) variables were used for the independent variables, apart from age. Social class was represented by the orthogonal linear (L) and quadratic (Q) contrasts, classes I and II being coded as L = –1, Q = 1; III M & Nm as L = 0, Q = –2; IV & V as L = 1, Q = 1. CO level is measured in ppm.

ANALYSIS

The relationship between expired air carbon monoxide concentration and some of the variables measured in the clinical examination and extracted from the symptom questionnaires (see Method) was investigated by application of a general linear hypothesis using multiple regression techniques. Since the distribution of CO levels in both males and females was positively skewed, a logarithmic transformation of the CO level ($\log_{10}(\text{CO}+1)$) was used in the analysis. The statistical significance of each variable was tested and deemed non-significant if $P>0\cdot05$ (for exact levels see Tables). Table IB shows the regression line fitted for the demographic variables.

Males and females were considered separately as their smoking habits were very different. Those individuals attending the clinical examination who had smoked in the last hour were found to have significantly higher CO levels irrespective of smoking habits and age. Therefore an extra variable was included in all the analyses, adjusting CO for smoking within the last hour.

RESULTS

Table IA shows the average expired air CO levels for the different age/sex/social class groups calculated from the actual data. The levels for social class III manual and non-manual for each age group were almost exactly the same, so the two classifications were considered together. In each social class group there is a decrease in CO level with age which is more marked in social class III. This is paralleled by a sharper decrease in the percentage of cigarette smokers with age in this social class group. The CO levels of the men are generally greater than those of the women, but this may be accounted for by differences in smoking habits.

Table IIA shows the CO levels for each age/sex/smoking category. The age effect persists in the non-smoking women but the numbers of male non-smokers are too small for valid conclusions to be drawn. The CO levels are higher for the present smokers, especially the cigarette smokers, and this increase is accompanied by an increase in standard deviation. On analysis, age (in years) and type of smoker (for each social class and sex group) were

TABLE IIA
SMOKING HABITS: OBSERVED EXPIRED AIR CO LEVELS (ppm)

Smoking Category		Males				Females			
		Age				Age			
		35–44	45–64	65+	All Ages	35–44	45–64	65+	All Ages
Non-smokers	$\bar{x}$	5·5	6·3	5·5	5·7	5·4	4·5	4·2	4·6
	SD	3·4	1·2	3·5	2·9	4·2	2·0	1·9	2·7
	n	11	3	2	16	24	46	20	90
Ex-smokers	$\bar{x}$	5·6	5·4	5·1	5·4	3·0	6·1	4·6	5·2
	SD	4·8	3·0	2·2	3·3	1·7	4·0	1·8	3·3
	n	12	23	14	49	3	14	8	25
Pipe or cigar only	$\bar{x}$	12·7	7·5	5·9	7·7				
	SD	4·5	3·8	2·0	3·9				
	n	3	11	7	21				
Pipe or cigar and cigarettes	$\bar{x}$	21·9	13·7	14·7	16·7		12·5		12·5
	SD	7·2	6·8	10·1	8·0		10·6		10·6
	n	9	14	3	26		2		2
Cigarette smokers	$\bar{x}$	22·6	20·1	11·2	19·4	19·9	15·6	7·2	16·9
	SD	11·1	9·7	5·5	10·4	10·7	10·5	4·5	10·8
	n	77	99	38	214	73	74	13	160

TABLE IIB
SMOKING HABITS: OBSERVED EXPIRED AIR CO LEVELS (ppm)

No. of Cigarettes Smoked per day		Males				Females			
		Inhalation				Inhalation			
		None	Slight	Moderate	Deep	None	Slight	Moderate	Deep
1—4	$\bar{x}$	4·2	12·2	10·3	13·0	7·0	5·3	3·0	
	SD	1·1	2·2	4·9	—	5·1	1·5	—	
	n	5	5	3	1	20	3	1	
5—14	$\bar{x}$	13·1	16·5	16·9	18·5	12·2	21·2	15·7	17·2
	SD	8·2	13·1	8·5	9·3	6·9	11·1	7·8	10·8
	n	15	11	32	19	19	12	23	9
15—24	$\bar{x}$	11·2	27·4	24·0	21·9	14·5	15·4	21·1	24·0
	SD	5·5	7·2	9·8	10·8	8·3	5·9	11·4	12·3
	n	6	8	30	28	13	10	18	13
25+	$\bar{x}$	12·7	25·0	21·1	24·2	16·3	22·7	29·3	31·0
	SD	6·6	7·8	7·9	11·5	11·8	16·5	7·2	9·8
	n	4	3	15	29	3	4	6	6

TABLE IIC overleaf

found to have highly significant effects on CO level, but the independent effects of social class and sex were non-significant.

The effect of cigarette smoking was studied further by looking at the amount smoked and the degree of inhalation. Table IIB is not age-specific but shows the increase in CO level with amount of cigarettes smoked per day and degree of inhalation. For the men smoking more than 15 cigarettes per day it appears that whether or not they inhaled was more important than the depth of inhalation.

The significance level of each of the smoking characteristics considered is shown in Table IIC. The independent effects of type of smoker, degree of inhalation, and amount are all highly significant in men. In women the independent effect of inhalation is non-significant when amount smoked is taken into account. The non-significant effect in females of pipe-cigar or mixed smoking is due to the very small number of women who smoke pipes or cigars. The independent effect of the number of years of smoking, when age is not taken into account, is non-significant in females but significant in males; the longer the period of smoking, the lower the CO level. However, when age is adjusted for, the independent effect of number of years of smoking is non-significant in both sexes. In both males and females the effect of age persists even after adjusting for smoking habits.

The adverse effects of CO are thought to be closely linked with those of smoking. In investigating

TABLE IIc

SMOKING HABITS: RESULTS OF TESTING FOR SIGNIFICANCE USING A GENERAL LINEAR HYPOTHESIS

Variable Tested	Direction of Association	CO was adjusted, in addition, for	Levels of Significance: Males	Levels of Significance: Females
Whether smoked in last hour	↑	Age; ex, non or present smoker; amount; inhalation; mixed or pipe/cigar; no. of years smoked	***	***
Present smoker Ex-smoker Non-Smoker	↑	Age; smoked in last hour	***	***
Inhalation: deep moderate slight none	↑	Age; smoked in last hour; ex, non, or present smoker; mixed or pipe/cigar; no. of years smoked; amount	***	ns
Other, Mixed or Pipe/Cigar	↑	Age; smoked in last hour; ex, non, or present smoker; no. of years smoked; amount; inhalation	**	ns
No. of years smoked	↓	Smoked in last hour; ex, non, or present smoker; mixed or pipe/cigar; amount; inhalation	**	ns
No. of cigarettes smoked per day 25+ 15—24 5—14 1—4	↑	Age; smoked in last hour; ex, non, or present smoker; inhalation; mixed or pipe/cigar; no. of years smoked	**	***

Dummy variables were used throughout, apart from 'age' and 'number of years smoked', which were measured in years.

ns not significant
** p<0·01
*** P<0·001

TABLE III

OBSERVED MEAN EXPIRED AIR CO (ppm), STANDARD DEVIATION, AND NUMBER IN EACH SYMPTOM GROUP

		Males		Females	
Respiratory Symptoms					
Cough grades⁺	0	14·1 ± 11·2 (134)	ns	10·0 ± 9·8 (164)	ns
	1	17·6 ± 9·4 (66)		14·3 ± 11·6 (45)	
	2	16·2 ± 10·5 (126)		14·6 ± 9·7 (68)	
Phlegm grades⁺	0	15·7 ± 11·6 (162)	ns	10·5 ± 9·5 (178)	ns
	1	17·6 ± 9·6 (69)		14·6 ± 12·1 (53)	
	2	14·2 ± 9·4 (95)		13·8 ± 10·3 (46)	
Persistent cough and phlegm	0	15·5 ± 11·5 (180)	ns	10·5 ± 9·8 (203)	ns
	1	15·8 ± 9·5 (146)		15·3 ± 11·0 (74)	
Persistent cough, phlegm and chest illness	0	16·0 ± 11·1 (268)	ns	11·0 ± 10·0 (243)	↓ **
	1	14·1 ± 7·8 (58)		17·7 ± 10·9 (34)	
Bronchitis I (cough, phlegm, and low FEV)	0	16·2 ± 10·9 (274)	ns	11·5 ± 10·4 (229)	ns
	1	12·8 ± 8·8 (52)		13·4 ± 9·8 (48)	
Bronchitis II (phlegm and breathlessness)	0	15·9 ± 10·9 (290)	ns	11·7 ± 10·4 (257)	ns
	1	14·1 ± 8·3 (36)		12·7 ± 9·7 (20)	
Heart Disease					
Angina	0	15·5 ± 10·6 (284)	ns	12·0 ± 10·4 (233)	ns
	1	16·5 ± 11·0 (42)		11·0 ± 9·7 (44)	
Infarction	0	15·4 ± 10·8 (287)	ns	11·9 ± 10·4 (255)	ns
	1	17·4 ± 9·0 (39)		10·5 ± 8·8 (22)	
Ischaemia (from ECG)					
Normal		16·7 ± 11·0 (201)	ns	13·5 ± 11·2 (155)	ns
Possible		12·3 ± 8·4 (47)		9·5 ± 9·1 (85)	
Probable		15·0 ± 11·5 (27)		10·2 ± 7·5 (19)	
Non-classifiable		15·1 ± 10·1 (51)		10·0 ± 7·9 (18)	

⁺Category 1 consists of those who fall into MRC category 1 but not 2.
ns not significant
** P<0·01

In testing the statistical significance of each symptom, $\log_{10}$ (CO+1) was adjusted for age and whether smoked in last hour.

the relationship between CO and cardiovascular disease, irrespective of smoking habits, no adjustment was made for smoking. Even adjusting only for age and whether smoked in the last hour, there was no significant relationship between CO levels and symptoms of respiratory disease, heart disease, blood indices, and ventilatory function in either sex, except for total haemoglobin level ($P<0\cdot001$), persistent cough, phlegm, and chest illness ($P<0\cdot01$) and FEV/FVC in women ($P<0\cdot05$). Table III shows the observed CO levels for each respiratory symptom and indication of heart disease.

Discussion

In this study, smoking habits and age were the main variables significantly related to expired air CO levels. The higher levels of CO found in cigarette smokers than in pipe and cigar smokers, non-smokers, and ex-smokers confirm the findings of previous studies on particular groups of people, for example, Goldsmith *et al.* (1963) on longshoremen, Ringold *et al.* (1962), and Tyrer (1964). The lower levels in the pipe and cigar smokers are probably due to a decreased degree of inhalation of smoke from tobacco consumed in these forms.

In women, a higher level of haemoglobin was associated with a higher expired air CO level (see Table IV). Taken in conjunction with the association of smoking with CO, this is in agreement with the findings of Pincherle and Shanks (1968) in men. They suggested that the slightly higher levels of haemoglobin which they found in male smokers might be compensatory for the haemoglobin bound as carboxyhaemoglobin. The absence of a significant association between haemoglobin and expired air

Table IV

PREDICTED EXPIRED AIR CO LEVELS FOR GIVEN MEAN Hb LEVELS, ADJUSTED FOR AGE AND WHETHER SMOKED IN THE LAST HOUR

Male			Female		
Hb (g/100 ml)	CO (ppm)		Hb (g/100 ml)	CO (ppm)	
12·5	12·64		11·0	7·00	
15·0	12·36	ns	13·5	8·74	***
17·5	12·05		16·0	10·84	

The regression equations from which these were obtained were:

Log_{10} (CO+1) (males) = 1·210 − 0·005 × age + 0·372 × smoked in last hour − 0·004 × Hb

Log_{10} (CO+1) (females) = 0·708 − 0·006 × age + 0·402 × smoked in last hour + 0·034 × Hb

Note: A dummy (0,1) variable was used to represent 'smoked in last hour'.

Age was measured in years, and Hb in g/100 ml.
ns non-significant
*** $P<0\cdot001$

CO level in the men in this study is understandable. The weighted sample of respondents with chronic respiratory disease might include a substantial number with secondary polycythaemia, which may be independent of present smoking habits.

The decrease in carboxyhaemoglobin concentration which occurs with age in relation to a given smoking exposure has been reported elsewhere (Goldsmith and Landaw, 1968). This age relationship could be due to changes in inhalation habits or decreasing diffusion of carbon monoxide across alveolar surfaces which have become less efficient or diminished in area. Chronic respiratory disease, years of exposure to tobacco smoke or age itself could play a part. Our findings suggest that age is an important factor. This is compatible with the decreasing efficiency of diffusion across alveolar surfaces which is known to occur with age (Cotes, 1965).

The decreasing association of smoking with ischaemic heart disease which occurs with increasing age (Doll and Hill, 1966; Hammond, 1966; Kahn, 1966) provides a parallel. This could be due to changes in inhalation habits or to the decreasing diffusion of constituents of tobacco smoke across alveolar surfaces. Alternatively, susceptibles may have been eliminated from the population of older smokers by death or by giving up smoking. There is an increasing prevalence of ischaemic heart disease with increasing age. It might, therefore, be expected that older people would be more vulnerable to any precipitating factor present in tobacco smoke whereas the converse appears to be the case. If, however, this factor is absorbed less readily in older smokers, the decreasing association might, in part, be accounted for.

We found no correlation between expired air carbon monoxide levels and symptoms or signs of ischaemic heart disease. This may be because smokers with symptoms stop smoking or because those susceptible have died, but this is unlikely to be the sole explanation. Goldsmith (1969) has called the relationship between smoking, coronary heart disease, and carbon monoxide 'a provocative jigsaw puzzle'. It clearly remains incomplete and will continue to provoke.

Summary

The level of expired air CO was measured in adults taking part in a community study of cardio-respiratory disease in Lambeth. Details of smoking habits were also obtained. The high correlation between expired air CO and COHb was confirmed on a random subsample. Those individuals who

had smoked within the hour prior to their CO measurement were found to have significantly higher CO levels irrespective of smoking habits and age. The level of CO was found to increase with increased amount of cigarettes smoked and also with depth of inhalation. The CO level decreased, however, with increasing age. In women a higher level of CO was accompanied by a higher Hb level. No correlation was found between CO levels and symptoms of ischaemic heart disease.

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