Ischaemic heart disease mortality risks for smokers and non-smokers

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SUMMARY Although many studies have shown that smoking is associated with an increased risk of death from ischaemic heart disease (IHD), and that the increase appears to vary with age and amount smoked, there has been little formal specification or estimation of the relationship. In this paper two alternative models are tested, using data for different ages and levels of smoking from four major studies in three countries. One model explains 80% of the variation in mortality in terms of a positive linear function of the number of cigarettes smoked, the parameters of which decrease with age. We estimate that every cigarette smoked per day increases the risk of dying from IHD by as much as 35% at ages 35 to 44, reducing to 2% at ages 65 to 74. The risk attributable to smoking may account for more than 80% of IHD deaths of men aged 35 to 44, and 27% of those of men aged 45 to 64. Although the *relative* risk is highest for younger age groups, the *absolute* risk of death from IHD that is attributable to smoking increases with age. The evidence suggests that both are increasing with time.

In the 1950s and 1960s, several large prospective studies assessed the mortality risks of cigarette smokers. In the United States of America, Hammond and Garfinkel (1969) followed 358 500 males and 445 900 females for six years, Hammond and Horn (1958) followed 187 800 men for three and a half years, Weir and Dunn (1970) followed 68 200 men for up to eight years, and Paffenbarger and Wing (1969) followed 50 000 men for more than 17 years. In Canada, Best (1966) followed 78 000 men for six years and in Britain, Doll and Hill (1964) and Doll and Peto (1976) studied about 34 400 male doctors for 20 years. All these studies indicated that smokers have higher death rates from ischaemic heart disease (IHD) than non-smokers or ex-smokers, and that these rates, relative to those for non-smokers, vary with age and amount smoked. This paper compares the findings of these studies, and synthesises their results in an attempt to quantify the effect on IHD mortality, at different ages, of smoking a given number of cigarettes.

Material and methods

The studies of Hammond and Horn (1958), Best (1966), Hammond and Garfinkel (1969), and Doll

and Peto (1976) all give values of the relative risk (RR) of death from IHD for a wide range of smoking levels and of ages. They also clearly distinguish between non-smokers, ex-smokers, and smokers of pipes and cigars. The RR values for different smoking levels from these four studies are plotted in Fig. 1 and for all smokers in the six studies in Fig. 2. We develop two models to try to explain these RR in terms of s (the number of cigarettes smoked per day) and age.

The first model investigated assumes that the number of cigarettes smoked is linearly (or quadratically) related to RR and has the same effect at all ages; in addition to this an age factor is introduced, so that smokers of different ages are assumed to be at varying basic risk levels, so that

$$RR = b_0 + b_1s + b_2s^2 + c_iA_i + c_jD_j + e \quad \dots (1)$$

where s is the number of cigarettes smoked per day; A_i is an age variable, equal to 1 for age i and otherwise zero; b_s and c_s are coefficients estimated by minimising the sum of the squared residuals e ; D_j is a study variable to account for variation between countries or groups and is equal to 1 for study j and is otherwise zero.

Fig. 1 IHD mortality ratios by number of cigarettes smoked and age, relative to non-smokers of the same age.

Sources (A) Hammond and Horn (1958).
(B) Doll and Peto (1976).
(C) Best (1966).
(D) Hammond and Garfinkel (1969).

In the second model it is assumed that the relative effect of the number of cigarettes smoked per day itself depends on age, so in this model the b coefficient varies with the age of the smoker.

It is assumed that RR is determined by the two variables age and amount smoked, while the absolute IHD mortality rate may vary over time because of other factors. This assumption is discussed later.

Results

In all four studies, smokers' RR tends to increase with the number of cigarettes smoked, at least up to a level of 30 a day (Fig. 1). Another interesting characteristic which is confirmed by all the studies—except in the 30 to 49 age group in the study by Best (1966)—is that RR decreases with age. This is particularly striking for British doctors aged 35 to

Fig. 2 IHD mortality ratios for all smokers by age, relative to non-smokers.

Sources (A) Hammond and Horn (1958).
(B) Doll and Peto (1976).
(C) Best (1966).
(D) Hammond and Garfinkel (1969).
(E) Paffenbarger and Wing (1969).
(F) Weir and Dunn (1970).

44: for example, the very high RR of more than eight for younger British doctors is reduced to less than two at ages 55 to 64 (Fig. 2). These factors are investigated in equation 1 (model 1), with t values given in brackets.

$$\begin{aligned} \text{RR} = & b_0 + 0.051s + 5.72A_{35-44} - 0.23A_{45-54} \\ & (2.5) \quad (2.9) \quad (0.1) \\ & - 0.080A_{55-64} - 0.49A_{65-74} + \text{study effect} \quad \dots (1) \\ & (0.04) \quad (0.2) \end{aligned}$$

Using the first model, RR was found to be linearly related to the number of cigarettes smoked per day ($P < 0.001$); the quadratic term s^2 was not significant, and was dropped from the equation. The results confirm that RR decreases with age and is

significantly higher for the youngest age group. Model 1 explains 61% of the total variation in relative risk. ($\bar{R}^2 = 0.61$).

In the second model (equation 2) the level of smoking effect is postulated to vary with age. This gives a more satisfactory explanation of risk and the model accounts for 79% of the variation in RR ($\bar{R}^2 = 0.79$ and *t* values given in brackets).

$$\begin{aligned} \text{RR} = & 1.0 + 0.35s_{35-44} + 0.030s_{45-54} \\ & (12.5) \quad (1.3) \\ & + 0.044s_{55-64} + 0.022s_{65-74} + 0.003s_{75-84} \dots (2) \\ & (2.3) \quad (1.05) \quad (0.1) \end{aligned}$$

The coefficients in the model show clearly and specifically the risk associated with each cigarette smoked per day. At ages 35 to 44, the risk of dying from IHD is increased by as much as 35% for each cigarette smoked per day; however, the increased risk is only 2% per cigarette at ages 65 to 74 and is quite insignificant (0.3%) at ages over 75.

The decrease in RR with age could be partly due to early deaths of those especially susceptible to the effects of smoking on IHD, who would therefore not be in the population at risk at older ages. This explanation could, however, account for only a small part of the decline in RR with age.

Perhaps a more likely explanation is that the absolute IHD mortality risk includes additive elements of risks P_s , related to smoking, and P_a which is independent of smoking but increases with age. Both risks could interact multiplicatively with other environmental risks, P_e . In its simplest form this would give

$$\text{RR} = \frac{(P_s + P_a) P_e}{P_a \times P_e}$$

At younger ages P_a is small relative to the smoking risk and RR would be large. For example, for ages 35–44, $P_a = P_s/8$ and $\text{RR} = 9$, as we have found. At older ages P_a is larger relative to P_s and RR will be closer to unity. For example, for ages 45–64, $P_a = 1.25 P_s$ and $\text{RR} = 1.8$, as we have found.

Model 2 is compatible with this explanation. The simple example could be adjusted to make P_s proportional to the daily number of cigarettes smoked and P_s itself could increase with age but more slowly than the increase in P_a .

SMOKERS' MORTALITY RISKS: ENGLAND AND WALES 1966–75

The second model has been used to estimate the effects of recent smoking habits on IHD mortality in England and Wales. Data on smoking habits are taken from Lee (1976) and age-specific IHD mortality rates are derived from the Registrar General's mortality figures for the relevant years, using ICD codes 420 and 422 (World Health Organisation, 1957) and 410–414 (World Health Organisation, 1967). The proportion of men in the United Kingdom who smoke, together with the average number of cigarettes smoked, are shown in Table 1 for 1966–70 and 1971–75. The last column gives smokers' RR estimated from equation 2 and shows that a smoker aged 40 is at very high RR: on average, he is more than eight times as likely to die from IHD as a non-smoker of the same age. The 45–64-year-old smoker has an increased risk of more than 75%, the 70-year-old smoker still has a 30% excess risk, but over 75 the extra risk is negligible. The model shows that the RR per cigarette is lower at older ages; in addition older smokers tend to smoke fewer cigarettes per day which further reduces their RR.

Table 1 *Smokers' mortality risks from IHD relative to those of non-smokers (males 1966–75)*

	Age	% Smokers at each age	Cigarettes per day	Relative risk
1966–70	35–44	60	21	8.2
	45–54	56	20	1.6
	55–64	51	18	1.8
	65–74	45	14	1.3
1971–75	35–44	51	24	9.3
	45–54	52	23	1.7
	55–64	45	21	1.9
	65–74	42	16	1.4

The model can be used to estimate the proportion of IHD deaths associated with smoking. Smokers' and non-smokers' mortality risks are estimated as follows:

If $5q_{xt}$ is the IHD five-year mortality rate for age *x*, year *t*

p_{xt} is the proportion of smokers age *x*, year *t*

$5n_{xt}$ is the IHD mortality risk for non-smokers age *x*, year *t*

RR_{xt} is the smokers' mortality risk relative to the non-smokers' then

$$5q_{xt} = [1 + p_{xt} (\text{RR}_{xt} - 1)] 5n_{xt} \quad (7)$$

ATTRIBUTABLE RISK

MacMahon and Pugh (1970) define attributable risk as derived by 'subtracting the rate (usually incidence or mortality) of the disease among exposed persons from the corresponding rate among non-exposed individuals. It is assumed that causes of the disease other than the one under examination had equal effect on the exposed and non-exposed groups'. Following their definition the attributable risk would therefore be $q_x - n_x$ and the proportion attributable to smoking $(q_x - n_x)/q_x$ as given in the last column of Table 2. Estimates are given for age groups for which there was a significant smoking effect.

Between 1966-70 and 1971-75 the IHD mortality risk increased for both smokers and non-smokers of all ages, and the proportion attributable to smoking rose slightly with the increase in average consumption per smoker and despite some reduction in the number of smokers. In 1971-75, 81% of IHD deaths of men aged 35 to 44 were attributable to smoking, 28% at 45 to 64, and 13% at 65 to 74; 13 500 men in England and Wales died of IHD each year because they were smokers.

Using the results in Table 2, we estimate that in 1971-75 32% of IHD deaths in men aged 35 to 64, 13% in men aged 65 to 74, and none in older men were due to smoking. These are close to the estimates of 25%, 10%, and 0% respectively referred to as 'probably conservative' in *Smoking and Health* (Department of Health and Social Security, 1972).

ESTIMATION ERRORS

The relative risks given are subject to estimation error, and the statistical significance of the estimated coefficients is indicated by the *t* values. Errors arise at the sampling stage from data on both cigarette consumption and mortality risks. The Tobacco Research Council state that their data on smoking at different ages are subject to a standard error of about 14%; we have averaged their data over five years, which would reduce this error to about 0.5%.

Another source of error arises from the estimates of RR. All the IHD RRs were estimates from large studies, including 34 400 men in the studies of Doll and Peto (1976) and 360 000 people in those of Hammond and Garfinkel (1969). Each study/smoking/age cell therefore contains several hundred people. However, in the youngest age groups there were few deaths from IHD, particularly among non-smokers. This means that there is likely to be greater variance in the mortality risk estimates for this age range, and introduces the estimation problem of heteroscedasticity. The least squares method of estimation that we have used assumes a common variance for all the data. If this assumption is contravened, the resulting coefficients are still unbiased but are estimated with a higher variance than if the data were homoscedastic. We did not weight estimates by study size, which would have given overwhelming influence to one study, but considered it preferable to base the model variance on the full between study variation.

Discussion

Using the data of the major prospective studies on smoking and IHD mortality from three countries, it appears that the risk of death from IHD in a male smoker relative to that in a non-smoker is approximately linearly related to the number of cigarettes he smokes, and that the slope of this line decreases with age. We have quantified this relationship and used the results to estimate the risk of death from IHD that is attributable to smoking in England and Wales for different age groups, using an epidemiological definition of attributability (MacMahon and Pugh, 1970). Several other factors besides smoking and age are, of course, implicated in the aetiology of IHD and we have tried to standardise for these by using relative rather than absolute mortality. It has been assumed that although mortality from IHD in smokers differs with age and

Table 2 IHD mortality rates and risks per 1000, and proportions of deaths attributable to cigarette smoking (England and Wales, males 1966-75)

Age		Actual IHD mortality rate 5^{a}_{xt}	Non-smokers' risk	Smokers' risk	Proportion attributable to smoking
1966-70	35-44	0.633	0.120	0.975	81
	45-54	2.490	1.864	2.982	25
	55-64	7.045	4.978	9.031	29
	65-74	16.386	14.398	18.815	12
1971-75	35-44	0.646	0.124	1.148	81
	45-54	2.857	2.102	3.554	26
	55-64	7.257	5.105	9.887	30
	65-74	16.534	14.405	19.474	13
DEATHS PER YEAR					
35-74		60 200	26 000	34 200	13 500

over time for reasons outside the scope of this paper, at a given age and level of smoking, and over a fairly short (five-year) time period, it bears the relationship to non-smokers' rates expressed in Table 1. If other possibly relevant factors that we have not been able to consider are correlated with both IHD mortality and level of smoking, then the relative risk will have been overestimated in Table 1 (or underestimated if the correlations are negative). The Framingham Study (1974) considered blood pressure, blood cholesterol, blood sugar, electrocardiographic changes and other factors simultaneously with smoking. It was found that the apparent effect of smoking on IHD was actually enhanced when other factors were included in multivariate analyses, probably because of a negative correlation between smoking and blood pressure; this in turn may be because smokers tend to be less obese than non-smokers. If this is the explanation and the weight difference is *due* to smoking, then the results do not need to be adjusted, but if smoking and low weight are independent, then we have underestimated the effect of smoking on IHD mortality. However, 'stress', diet, alcohol consumption, and level of physical activity also are, or may be, associated with smoking, and we cannot at present allow for the effects of these features on the apparent relationship between smoking and IHD mortality. Uncertainties of this sort make it difficult to say to what extent age-specific associations between smoking and IHD mortality are due to cause and effect. There may well be a difference between true biological and epidemiological 'attributability'. However, there seems little doubt that the effects of smoking on IHD mortality are much larger at younger than at older ages and in this respect our results, using mortality figures, are in line with those of Miettinen *et al.* (1976), based on data from patients with non-fatal myocardial infarction.

Smokers have been at increasing absolute and relative risk in the period studied. The trend towards filter cigarettes does not seem to have reduced the risk of IHD as it may have that of lung cancer. A possible explanation is that men smoking filter cigarettes, especially if these are unventilated, have higher carboxyhaemoglobin levels than those smoking plain cigarettes (Wald *et al.*, 1977). In the studies of British doctors (Doll and Hill, 1964; Doll and Peto, 1976) the relative risk from IHD increased for the last 10 years of the study, for all ages and smoking levels. Hawthorne and Fry (1978) also found that whereas the use of filter cigarettes appears to reduce the risk of bronchitis and lung cancer, it increases the risk of IHD, angina, and cerebrovascular disease. This evidence suggests that cigarette smoking may be of increasing importance in determining IHD mortality risk.

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