Overweight and stroke in the Whitehall Study

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Abstract

Study objective—The aim was to examine the risk of increasing overweight for death from stroke.

Design—This was a prospective cohort study, in which the main outcome measure was the mortality ratio for stroke with increasing body mass index.

Setting—Civil service departments, Whitehall, London.

Subjects—Participants were 17 753 men aged 40 to 64 years.

Measurements and main results—208 stroke deaths were recorded. Men aged 40 to 54 in the most overweight quintile of body mass index had a mortality ratio of 2.01 (95% confidence interval 0.9 to 4.7) compared to the thinnest quintile. The mortality ratio was 1.19 (95% CI 0.7 to 2.0) in men aged 55 to 64. The increase in risk was more apparent in non-smokers: age adjusted mortality ratio 2.58 (95% CI 1.2 to 5.7). When smoking status and overweight were considered in combination a gradient of the age adjusted mortality ratio was observed, from 1.0 in thinner/non-smokers up to 3.15 in fatter/current smokers. On the assumption that smoking and obesity cause strokes, an estimated 60% of strokes could be prevented if these two easily identifiable risk factors could be avoided.

Conclusions—The risks of overweight for death from stroke were more apparent in younger subjects and non-smokers. A substantial proportion of stroke deaths occurring under the age of 80 years would probably be prevented if cigarette smoking and overweight could be avoided.

Although there is good evidence that overweight and blood pressure are causally related, the role of overweight in stroke has been less clear. Overweight might cause strokes through the mechanism of high blood pressure, diabetes, and raised blood lipids, but a clear association has not been described.¹⁻³ Data from the Framingham study have, however, suggested that obesity itself does carry a significantly increased risk of stroke.⁴

Some confusion about the risk of overweight for stroke may have arisen because of the tendency in recent years to make multiple adjustments for a large number of interdependent risk factors. In a previous analysis of the Whitehall cohort which was primarily concerned with glycaemia, a multiple logistic regression coefficient suggesting a non-significant protective effect of overweight for stroke was obtained.⁵ To examine the risks of

overweight itself, adjustment for variables which are also likely mechanisms (for example, hypertension) may be misleading.⁶ Some doubt, furthermore, has recently been cast on the interpretation of the results of statistical models which do not reflect the biological interactions of the risk factors under consideration.^{7 8} For these reasons an analysis avoiding both inappropriate adjustments and statistical modelling seemed worthwhile. The study will, however, take account of cigarette smoking, both because of its complex relation to obesity and stroke,⁹ and because overweight and cigarette smoking are particularly relevant to intervention since they can be easily identified without reference to medical practitioners.

The straightforward analysis of risk factors in clusters does require large case numbers. The cohort of Whitehall civil servants¹⁰ now enables assessment of the risk of overweight and its relationship to cigarette smoking for a substantial number of stroke deaths.

Methods

Details of the Whitehall study have been published^{5 10}; 18 403 male civil servants aged 40-64 years were examined between 1967 and 1969 and their records flagged at the National Health Service Central Registry.

A self administered questionnaire, completed at the screening examination, included details of cigarette smoking. For the present analysis subjects were divided into non-smokers, ex-cigarette smokers, current cigarette smokers, and others (non-responders; pipe or cigar smokers). The latter group was excluded, leaving a total of 17 753 men on which to base this analysis. Subjects were weighed in light clothing and had their height measured with their shoes removed. Body mass index (weight in kg ÷ [height in metres]²) was grouped into quintiles.⁵

Mortality data were available until 31st January 1985, providing a minimum of 15 years of follow up. Total person-years at risk during the follow up period were cross tabulated by smoking status, body mass index quintile, and five year age group. Stroke deaths were defined as those where stroke (International Classification of Diseases, 8th Revision, 430-438) was certified as the underlying cause. This included cerebral infarct and thrombosis, cerebral and subarachnoid haemorrhage, and stroke of uncertain pathology.

Narrow age strata, each with sufficient case numbers, are ideally required to examine the possible confounding or interaction of age on the relation between overweight and stroke. The data were, therefore, stratified into two age groups (40-54 and 55-64 years) for presentation.

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Confidence intervals for unadjusted rate ratios were obtained by first calculating the confidence interval for the ratio of the stroke deaths using the binomial distribution and then dividing these by the ratio of the person-years. Age adjusted rate ratios were calculated as the ratio of directly standardised rates. These age standardised rates were obtained using the total Whitehall study population as standard. Confidence intervals for these adjusted rate ratios were calculated.¹¹ Attributable risks were calculated by first estimating the expected strokes in each of two age groups (40–54 and 55–64 years) if the baseline rates had applied to the whole group; the difference between the expected and observed numbers estimates the avoidable stroke deaths in each age group. These were then added together.

Results

After 15 years of follow up 3427 men had died. Two hundred and eight deaths (6.1%) were attributed to stroke and 1352 (39.5%) to coronary heart disease. A further seven strokes were in the pipe/cigar/non-responder group. Of the 208 stroke deaths, 26 were attributed to subarachnoid haemorrhage (ICD 430) and 42 to intracerebral haemorrhage (ICD 431).

At screening 43% (7601) of the men were current smokers, 38% (6697) ex-smokers, and 19% (3455) had never smoked.

The variation in mortality rates by quintile of body mass index in the two age groups is shown in fig 1. Table I provides the mortality rate ratios relative to the thinnest quintile and suggests there may be differences between the two age groups. However, mortality ratios for all ages have been presented both with and without age adjustment. Failure to adjust for age could overestimate the risks of overweight as there is a small rise in body mass index with age—19% of men aged 40–54 years were in the highest quintile of body mass index compared to 22% of men aged 55–64 years. Conversely, age adjustment could obscure risks if part of the added risk of advancing age is due to the increasingly long exposure to being overweight. The data suggest a steady rise in the hazards of overweight in men under 55 years but a U shaped curve in the older age group. Overall, obesity appears to carry increased risk of stroke.

The age adjusted stroke mortality rate ratio for ex-smokers compared with non-smokers was 1.25

(95% CI 0.8 to 2.0), while that for current smokers was 1.66 (95% CI 1.1 to 2.6).

Because smokers are at increased risk of stroke and also tend to be thinner, the risk of overweight for death from stroke was examined in the different smoking categories. Figure 2 and table II suggest that the risk gradient (but not the actual rate) is greater in those who never smoked. Confidence intervals, however, are wide.

In order to assess the risks for death from stroke of different overweight/smoking status combinations, the lower two and upper three quintiles of body mass index were each grouped together. As age is associated with both stroke risk

Figure 1 Stroke mortality rate by quintile of body mass index in men aged 40 to 54 years and 55 to 64 years.

Figure 2 Stroke mortality rate by quintile of body mass index in the different smoking status groups.

Table I Stroke mortality rate ratio by quintile of body mass index

	Body mass index quintile (kg/m ²)				
	- 22.4	- 24.0	- 25.4	- 27.0	> 27.0
40–54 Years					
Person-years at risk	39 048	37 265	37 436	33 371	33 578
No of stroke deaths	11	14	13	13	19
Rate ratio	(1.0)	1.33	1.23	1.38	2.01
(95% confidence interval)					(0.9 to 4.7)
55–64 Years					
Person-years at risk	17 127	15 629	16 874	17 404	18 984
No of stroke deaths	28	24	23	26	37
Rate ratio	(1.0)	0.94	0.83	0.91	1.19
(95% confidence interval)					(0.7 to 2.0)
All ages					
Person-years at risk	56 175	52 894	54 310	50 775	52 562
No of stroke deaths	39	38	36	39	56
Rate ratio	(1.0)	1.03	0.95	1.11	1.53
(95% confidence interval)					(1.0 to 2.4)
Age adjusted rate ratio	(1.0)	1.01	0.89	0.97	1.30
(95% confidence interval)					(0.9 to 2.0)

and smoking status, the results have been presented in two age groups and, as the rate ratios were generally consistent in the different age strata, after age adjustment (table III). Although numbers are small, the results suggest that overweight is more of a risk in the older age group among non-smokers. The principal conclusion, however, on examining the overall rate ratios in different combinations, is that there is an increased risk in all except the thinner non-smokers. The rate ratio rises to 3.15 in the more obese current smokers.

The attributable risk of a combination of both cigarettes and/or excess weight was calculated (table IV). On the assumption that cigarette

smoking and overweight directly cause strokes and that the stroke death rates reported are valid, around 60% of stroke deaths may be prevented if cigarettes and excess weight could be avoided. For cigarette smoking alone (ex- and current) the attributable risk was 30%. The prevention of stroke by the avoidance of cigarettes and overweight is consistent with a reduction in the all cause mortality rate (table II).

Discussion

These results support the view that overweight increases the risk of stroke. This conclusion is not surprising in view of the strong link between

Table II Stroke and all cause mortality rate ratios by quintile of body mass index in separate smoking status groups

	Body mass index quintile (kg/m ²)				
	- 22.4	- 24.0	- 25.4	- 27.0	> 27.0
<i>Non-smokers</i>					
Person-years at risk	10 479	11 581	10 940	10 815	10 362
No of stroke deaths	3	3	4	6	8
Stroke mortality rate ratio (95% confidence interval)	(1.0)		1.35	2.04	2.84 (0.9 to 9.9)
Age adjusted stroke mortality rate ratio (95% confidence interval)	(1.0)		1.58	2.24	2.58 (1.2 to 5.7)
Age adjusted all cause mortality rate ratio (rate per 1000 person-years)	(1.0) (7.49)	0.73 (5.43)	1.16 (8.67)	1.00 (7.52)	1.44 (10.78)
<i>Ex-smokers</i>					
Person-years at risk	16 686	19 616	22 261	21 173	22 507
No of stroke deaths	13	12	12	17	21
Stroke mortality rate ratio (95% confidence interval)	(1.0)		0.78	1.17	1.35 (0.7 to 2.5)
Age adjusted stroke mortality rate ratio (95% confidence interval)	(1.0)		0.70	0.99	1.07 (0.6 to 1.8)
Age adjusted all cause mortality rate ratio (rate per 1000 person-years)	(1.0) (9.92)	0.89 (8.88)	1.05 (10.38)	1.13 (11.22)	1.18 (11.73)
<i>Current smokers</i>					
Person-years at risk	29 010	21 697	21 108	18 788	19 693
No of stroke deaths	23	23	20	16	27
Stroke mortality rate ratio (95% confidence interval)	(1.0)		1.04	0.94	1.51 (0.9 to 2.5)
Age adjusted stroke mortality rate ratio (95% confidence interval)	(1.0)		1.00	0.87	1.43 (0.8 to 2.6)
Age adjusted all cause mortality rate ratio (rate per 1000 person-years)	(1.0) (18.69)	0.94 (17.56)	0.88 (16.50)	1.00 (18.67)	1.07 (19.94)

Table III Stroke mortality rate and rate ratios (thin/non-smokers as baseline), stratified by age group, body mass index and smoking status

	Body mass index (kg/m ²)					
	Non-smoker		Ex-smoker		Current smoker	
	- 24.0	> 24.0	- 24.0	> 24.0	- 24.0	> 24.0
<i>40-54 Years</i>						
Person-years at risk	17 411	23 532	25 101	42 484	33 801	38 368
No of stroke deaths	3	2	8	15	14	28
Rate/10 000 person-years	1.72	0.85	3.19	3.53	4.14	7.30
Rate ratio (95% confidence interval)	(1.0)	0.49	1.85	2.05	2.41	4.24 (1.3 to 22)
<i>55-64 Years</i>						
Person-years at risk	4650	8584	11 201	23 457	16 906	21 221
No of stroke deaths	3	16	17	35	32	35
Rate/10 000 person-years	6.45	18.64	15.18	14.92	18.93	16.49
Rate ratio (95% confidence interval)	(1.0)	2.89	2.35	2.31	2.93	2.56 (0.8 to 13)
<i>All ages (age adjusted)</i>						
Person-years at risk	22 061	32 116	36 302	65 941	50 707	59 589
No of stroke deaths	6	18	25	50	46	63
Rate ratio (95% confidence interval)	(1.0)	2.20 (0.8 to 5.7)	2.40 (1.0 to 6.0)	2.24 (0.9 to 5.4)	2.43 (1.0 to 5.8)	3.15 (1.3 to 7.5)

Table IV Attributable risk for stroke of a combination of cigarette smoking and excess weight

Age (years)	Expected deaths based on rate of non-smokers with body mass index < 24.0 kg/m ²	Observed deaths	Attributable stroke deaths (percent)
40-54	31	70	39 (56)
55-64	55	138	83 (60)
Total	86	208	122 (59)

overweight and blood pressure.¹² The hazards of overweight, furthermore, are more apparent when either younger age groups or non-smokers are examined separately.

The finding that the risks of overweight are more obvious at a younger age was also reported in the Framingham cohort.⁴ Other stroke studies of adequate power in which stroke cases have been predominantly under the age of 70 have all indicated that overweight is a risk factor for stroke.¹³⁻¹⁷ The risk, however, has not been

apparent in stroke studies in which the events have predominantly occurred over the age of 70.¹⁸⁻²¹ There appears to be a consistent pattern of a reduction in the increased risk of overweight for stroke as age advances. Whether this is also true for non-smokers is not yet clear.

The U shaped curve for body mass index and the risk of stroke in the older age group of this cohort appears to be due to the influence of thin long term smokers. It is noteworthy that in non-smokers the increasing risks of overweight are more apparent in the older age group. An explanation for this could be that the dangers of overweight do not become manifest early in non-smokers because the additional vascular damage caused by smoking is absent.

The results suggest that the danger may be relatively greater in non-smokers (although the absolute excess is less). The explanation for this is probably that smokers, and particularly heavy smokers, are both thinner and at increased risk of stroke compared to non-smokers. This complication is not a problem when examining the non-smokers, although the small number of stroke deaths in this group (24) means that confidence intervals are wide. The varying rate ratios in the different smoking groups suggests that adjusting the risks of overweight for smoking status could obscure real effects, particularly in non-smokers. An overall smoking adjusted ratio would probably only be relevant to other populations with a similar proportion of smokers or ex-smokers. Fortunately these are now rare. For this reason smoking adjusted rate ratios have not been presented. These findings could explain why previous studies have shown a clearer risk of overweight for stroke in women (who tended not to smoke) than in men.⁴

Not all previous studies in younger populations have indicated overweight is a risk factor for stroke. In some this may have been because the investigation was too small.²²⁻²³ In others, multiple adjustments for possible confounding variables are hard to interpret.²⁴ If, as is likely, overweight is causally linked to high blood pressure, diabetes, and hypercholesterolaemia, then adjustment for these variables could obscure the real risk of overweight itself. These variables may actually be the mechanisms through which obesity causes strokes.

Many cohort and case-control studies do indeed positively associate obesity or overweight with stroke.^{13-17 25-28} The association is likely to be causal, as consideration of other risk factors as possible confounding variables fails to provide an alternative explanation. In the Whitehall cohort the risk is apparent in individual age strata and alters little following age adjustment. Cigarette smoking does appear to interact with, but not to confound, the association as the risks of overweight are clearest in non-smokers. Both excessive alcohol consumption and physical inactivity are possible but currently uncertain risk factors for stroke.¹

The evidence that smokers and ex-smokers are at increased risk of stroke is strong,^{9 29} and is supported by our findings. Examining the risk of combinations of smoking and overweight was considered particularly worthwhile because both are risk factors easily understood and recognisable

by the whole population, and over which individuals potentially have control. In this cohort the risk of differing smoking/obesity combinations rises steadily from thin/non-smokers to overweight/current smokers. In a cohort of college students Paffenbarger and Wing found similar results: a stroke morbidity ratio of 2.6 among smoking/obese students compared with their non-smoking/thin colleagues.¹³

Only six of the 208 stroke deaths occurred in people who were relatively thin and claimed to have never smoked. There was a similar finding in a large cohort study of nurses, where only eight of 274 strokes occurred among non-smokers in the thinnest of three body mass index groups.³⁰

The attributable (excess) risk of around 60% suggested by these results implies a considerable potential for stroke prevention. Indeed, any misclassification of true smoking status or total body fat will have tended to underestimate the attributable risk. There is a suggestion that measuring body fat by subscapular skinfold thickness or waist/hip ratio predicts more accurately the risks of stroke.^{17 27}

Although there are advantages in the analysis of data in specific subgroups, there remains the disadvantage of small case numbers in any given group. To confirm some of the findings outlined above, further studies limited to specific subgroups, for example persons who have never smoked, will be required.

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