RESEARCH

Exposure to secondhand smoke and cognitive impairment in non-smokers: national cross sectional study with cotinine measurement

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ABSTRACT

Objective To examine the association between a biomarker of exposure to secondhand smoke (salivary cotinine concentration) and cognitive impairment.

Design Cross sectional analysis of a national population based study.

Setting Stratified random sample of households throughout England.

Participants 4809 non-smoking adults aged 50 years or more from the 1998, 1999, and 2001 waves of the Health Survey for England who also participated in the 2002 wave of the English Longitudinal Study of Ageing and provided saliva samples for cotinine assay and a detailed smoking history.

Main outcome measure Cognitive impairment as defined by the lowest 10% of scores on a battery of neuropsychological tests.

Results Participants who did not smoke, use nicotine products, or have salivary cotinine concentrations of 14.1 ng/ml or more were divided into four equal size groups on the basis of cotinine concentrations. Compared with the lowest fourth of cotinine concentration (0.0-0.1 ng/ml) the odds ratios (95% confidence intervals) for cognitive impairment in the second (0.2-0.3 ng/ml), third (0.4-0.7 ng/ml), and highest fourths (0.8-13.5 ng/ml) were 1.08 (0.78 to 1.48), 1.13 (0.81 to 1.56), and 1.44 (1.07 to 1.94; P for trend 0.02), after adjustment for a wide range of established risk factors for cognitive impairment. A similar pattern of associations was observed for never smokers and former smokers.

Conclusions Exposure to secondhand smoke may be associated with increased odds of cognitive impairment. Prospective nationally representative studies relating biomarkers of exposure to cognitive decline and risk of dementia are needed.

INTRODUCTION

Active smoking may be a risk factor for cognitive impairment and dementia,[1] but whether this applies to exposure to secondhand smoke is not clear. We examined the association between exposure to second-hand smoke and cognitive impairment in a large population based sample of non-smokers.

METHODS

Participants were from the 1998, 1999, and 2001 waves of the Health Survey for England[2] who participated in the 2002 wave of the English Longitudinal Study of Ageing.[3] The core sample of the ageing study is people aged 50 or more in 2002 drawn from the Health Survey for England sample by postcode sector and stratified by health authority and proportion of households in non-manual socioeconomic groups. Of 11 234 people who took part in both studies, 8893 were non-smokers at both time points. We restricted our analyses to the subsample of 5265 non-smokers with measured salivary cotinine levels (73% in 1998, 8% in 1999, and 70% in 2001). We excluded 456 participants (self reported dementia, claimed to be non-smokers, missing values on neuropsychological measures). The remaining 4809 participants formed the sample for our analyses.

Exposure to secondhand smoke and cognitive impairment

We used levels (ng/ml) of salivary cotinine (a metabolite of nicotine) measured in the Health Survey for England as a biomarker for recent exposure to secondhand smoke.[4] Cognitive impairment was assessed using neuropsychological tests incorporated in the English Longitudinal Study of Ageing[5]: attention and processing speed, time orientation, immediate and delayed verbal memory, prospective memory, numeracy, and semantic verbal fluency (see bmj.com for details). As the scoring of each test varied, we obtained a global cognitive function score by summing the standardised scores on each test. We defined cognitive impairment as the lowest 10% of the distribution of cognitive performance.

Statistical analysis

We used multivariable logistic regression models to determine the cross sectional relation between exposure to secondhand smoke and cognitive impairment. We adjusted for known risk factors for cognitive impairment[6,7]: age, sex, ethnicity, highest educational qualification, manual occupational class, fourths of net non-housing wealth, smoking history (never smokers, stopped smoking <10 years ago, stopped smoking

≥10 years or more ago), obesity (body mass index >29.9), alcohol consumption (g/day), physical inactivity, and depressive symptoms (eight item version of the Center for Epidemiological Studies depression scale).[8 9]

In a secondary analysis we examined whether any observed association was mediated by a history of medical conditions thought to be associated with smoke inhalation (diabetes, cardiovascular disease, stroke, untreated and treated hypertension).[10-17] We analysed former smokers and never smokers separately and investigated whether the same pattern of associations was observed if cognition was operationalised as a continuous variable (global cognitive function) in multivariable linear regression models. We also investigated the potential interaction between exposure to secondhand smoke and cardiovascular disease. To take account of potential bias from non-response we used population weights from the English Longitudinal Study of Ageing.[3] We used Stata SE version 9.2 for all analyses.

RESULTS

See bmj.com for the characteristics of participants. Median salivary cotinine levels were low. The patterns of potential confounders observed were in keeping with the general population. The proportion of participants who stopped smoking more than 10 years ago was similar to those who never smoked. Most participants consumed alcohol, and about one in 10 were physically inactive. A large proportion of the study population was obese and had significant depressive symptoms or hypertension.

Non-smokers with valid cotinine measurements (n=4809) were similar to the eligible non-smoking sample from the study of ageing (n=8061) for age (65.1 v 65.7 years), sex (53.2% v 55.3% women), ethnic origin (97.7% v 97.6% white), education (37.6% v 40.0% no qualifications), and occupational class (37.9% v 38.6% manual).

Logistic regression was used to determine the relation between exposure to secondhand smoke and cognitive impairment in non-smokers (see bmj.com). Adjustments were made for age, sex, education, and testing interval, and then additional covariables (see bmj.com). Those with high salivary cotinine levels (0.8-13.5 ng/ml) were more likely to be cognitively impaired (odds ratio 1.44, 95% confidence interval 1.07 to 1.94) than those with low levels (0.0-0.1 ng/ml). Some evidence was found of a linear trend for a dose-response relation (P=0.02). Additional adjustment for medical conditions such as cardiovascular disease had little effect.

Never smokers with high salivary cotinine concentrations (0.8-13.5 ng/ml) were more likely to be cognitively impaired (odds ratio 1.70, 1.03 to 2.80) than those with low levels (see bmj.com). Former smokers with high salivary cotinine concentrations also had an increased odds of cognitive impairment (1.32,

0.92 to 1.91), although this association was weaker than that observed for never smokers.

The same pattern of associations was observed when cognitive function was analysed as a continuous variable across fourths of cotinine concentration for both basic models (P for trend <0.001) and fully adjusted models (P for trend 0.025). The introduction of an interaction term to the fully adjusted logistic regression model indicated that there was no statistically significant interaction between history of cardiovascular disease and exposure to secondhand smoke (P>0.2).

DISCUSSION

High levels of salivary cotinine in non-smoking adults may be associated with increased odds of cognitive impairment. A similar pattern was observed for never and former smokers, and there was no interaction with a history of cardiovascular disease.

We controlled for a wide range of covariables that are potential confounders in cognitive research and incorporated a biomarker for exposure to secondhand smoke (salivary cotinine concentration). The inclusion of former smokers is potentially problematic as historical exposure may be dominated by their previous smoking behaviours, and misclassification of current smoking status may be particularly likely in this group, leading to a residual confounding effect. We carried out analyses separately for former and never smokers, however, and the association between cotinine levels and cognitive impairment seemed stronger in never smokers. We also adjusted for smoking history as a potential confounder, including number of years since stopping smoking. Furthermore, we excluded 205 participants who claimed to be non-smokers but used nicotine products or had salivary cotinine concentrations of 14.1 ng/ml or more.[18] Although cotinine is a sensitive and specific biomarker for recent exposure to secondhand smoke,[19] it does not necessarily reflect exposure over the long period during which cognitive impairment typically develops. We analysed a series of cross sectional data acquired over a mean of 2.6 years and did not find a causal relation. Although we controlled for a wide range of potential confounders the possibility of residual confounding remains. Non-smokers with valid cotinine measurements had a similar sociodemographic profile to the non-smoking sample of the English Longitudinal Study of Ageing, and these variables were controlled for in the analyses, making systematic bias unlikely.

Haight et al (59th annual meeting of the American Academy of Neurology) reported a non-significant trend between self reported exposure to secondhand smoke and risk of incident dementia in never smokers over a six year period. Their sample comprised almost exclusively women, whereas our sample was more heterogeneous. It is possible that their findings were not significant because of the reliance on self reported exposure. Self report measures of secondhand

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Active smoking may be a risk factor for cognitive impairment, although it is not clear whether exposure to secondhand smoke is a risk factor

No previous study has examined the association between biomarkers of exposure to secondhand smoke and cognitive impairment

WHAT THIS STUDY ADDS

In a large diverse sample of non-smoking adults, high levels of cotinine were associated with increased odds of cognitive impairment

A similar pattern of results was observed for never and former smokers, and there was no interaction with a history of cardiovascular disease

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exposure have several important limitations—living with a smoker captures less than half of the variation in cotinine concentration in non-smokers[20] and does not take into account exposure in workplaces and public places. The association we observed between objectively measured cotinine levels and cognitive impairment is consistent with studies suggesting that active smoking may be a risk factor for cognitive impairment and dementia.[1]

Exposure to secondhand smoke is associated with an increased risk of cardiovascular disease,[11 13] and cardiovascular disease may in turn be associated with an increased risk of cognitive impairment and dementia.[21 22] While additional adjustment for medical history made little difference to the fully adjusted model, and no interaction between cotinine levels and a history of cardiovascular disease was observed, it is possible that exposure to secondhand smoke may interact with subclinical cardiovascular disease, as observed by Haight et al (59th annual meeting of the American Academy of Neurology). Another study found that short term exposure to secondhand smoke adversely affects endothelial function in ways that compromise the cardiovascular system.[23]

Given the ongoing international policy debate on exposure to secondhand smoke, this is a topic of major public health significance. Our results provide new evidence to suggest that exposure to secondhand smoke may be associated with increased odds of cognitive impairment.

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Combined effects of overweight and smoking in late adolescence on subsequent mortality: nationwide cohort study

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ABSTRACT

Objective To investigate the combined effects on adult mortality of overweight and smoking in late adolescence.

Design Record linkage study with Cox proportional hazard ratios adjusted for muscle strength, socioeconomic position, and age.

Setting Swedish military service conscription register, cause of death register, and census data.

Participants 45 920 Swedish men (mean age 18.7, SD 0.5) followed for 38 years.

Main outcome measures Body mass index (underweight (BMI <18.5), normal weight (18.5-24.9), overweight (25-29.9), and obesity (≥30)), muscle strength, and self reported smoking (non-smoker, light smoker (1-10 cigarettes/day), heavy smoker (>10/day)) at mandatory military conscription tests in 1969-70. All cause mortality.

Results Over 1.7 million person years, 2897 men died. Compared with normal weight men (incidence rate 17/10 000 person years, 95% confidence interval 16 to 18), risk of mortality was increased in overweight (hazard ratio 1.33, 1.15 to 1.53; incidence rate 23, 20 to 26) and obese men (hazard ratio 2.14, 1.61 to 2.85; incidence rate 38, 27 to 48), with similar relative estimates in separate analyses of smokers and non-smokers. No increased risk was detected in underweight men (hazard ratio 0.97, 0.86 to 1.08; incidence rate 18, 16 to 19), though extreme underweight (BMI <17) was associated with increased mortality (hazard ratio 1.33, 1.07 to 1.64; incidence rate 24, 19 to 29). The relative excess risk due to interaction between BMI and smoking status was not significant in any stratum. Furthermore, all estimates of interaction were of small magnitude, except for the combination of obesity and heavy smoking (relative excess risk 1.5, −0.7 to 3.7). Compared with non-smokers (incidence rate 14, 13 to 15), risk was increased in both light (hazard ratio 1.54, 1.41 to 1.70; incidence rate 15, 14 to 16) and heavy smokers (hazard ratio 2.11, 1.92 to 2.31; incidence rate 26, 24 to 27).

Conclusions Regardless of smoking status, overweight and obesity in late adolescence increases the risk of adult mortality. Obesity and overweight were as hazardous as heavy and light smoking, respectively, but there was no interaction between BMI and smoking status. The global obesity epidemic and smoking among adolescents remain important targets for intensified public health initiatives.

INTRODUCTION

In middle aged adults, obesity increases the risk of mortality twofold to threefold compared with people of normal weight.[1-4] Whether risk of mortality is also increased in overweight adults is debatable,[4-8] with reports of both lower[4 5] and higher mortality.[1 3 7 8] The conflicting views mainly concern handling of possible confounding because of smoking and reverse causation.[8] The common finding of excess mortality in underweight people might be an artefact caused by insufficient adjustment for smoking.[5 9 10] Available studies of younger people, however, are limited by coarse BMI modelling[11] and lack data on important covariates.[12] In adolescents as well as in adults, smoking and obesity are probably the two most important modifiable risk factors for mortality in the Western world.[13] Despite that, the combined effects on mortality associated with these two risk factors and their interaction in late adolescence are not known.

We hypothesised that overweight and smoking in late adolescence increase the risk of mortality and that their effects are synergistic. Our secondary hypothesis was that excess risk in underweight people is accounted for by smoking.

METHODS

The study was based on nationwide military conscription data from 49 321 Swedish men born 1949-51 who performed military conscription tests in 1969-70. Only 2-3% of Swedish men were exempt from conscription. The men we included accounted for 97.7% of all conscripts in 1969-70. We performed record linkage of the conscription registry and the cause of death registry. To be included in the study, men were required to have performed their induction tests between the ages of 16 and 20.

Baseline examinations—We used WHO defined categories of body mass index: underweight (<18.5), normal weight (18.5-24.9), overweight (25-29.9), and obese (≥30).[14] We categorised smoking status into three levels (non-smoker, 1-10 (light smoker), >10 cigarettes/day (heavy smoker)). Covariates considered were muscle strength (leg extension, arm flexion, and hand grip), household socioeconomic status, and age at testing. We retrieved parental socioeconomic status from the population and housing census in 1970.

Follow-up and outcomes—Mortality data were retrieved until 1 September 2007.

Statistical analysis—Unadjusted incidence rates (deaths/10 000 person years) and Kaplan-Meier failure functions were used to present the absolute risk of death. We fitted unadjusted Cox proportional hazards models for BMI, smoking, and both variables combined. The three models were thereafter adjusted for muscle strength, socioeconomic status, and age at testing. Multivariable adjusted BMI models were then repeated in four categories of smoking and smoking models were repeated in four categories of BMI. In our secondary analyses, we fitted an additional model with the underweight category split into moderate (BMI 17-18.4) and extreme underweight (BMI<17). We investigated interaction between BMI and smoking status by calculating the relative excess risk because of the interaction. We compared the hazard ratios for heavy smoking (*v* non-smoking) and obesity (*v* normal weight) and those for light smoking (*v* non-smoking) and overweight (*v* normal weight) in the fully adjusted model.

RESULTS

Of 50 398 participants in the database, 4611 were excluded because of missing or outlying data or they were aged >20 at the conscription test, leaving a final 45 920 participants for analysis.

Unadjusted survival analyses

During 1.7 million person years (median 38 years) of follow-up, 2897 men died and 1806 emigrated. The incidence of death was the lowest in normal weight men and highest in obese men. In unadjusted models with normal weight participants as reference, the risk of mortality was significantly higher for overweight (hazard ratio 1.35, 95% confidence interval 1.17 to 1.55, P<0.001) and obese (2.25, 1.70 to 2.98, P<0.001) men but not underweight men (1.04, 0.93 to 1.15, P=0.51). With non-smokers as the reference category, there was a gradually increasing risk from men who
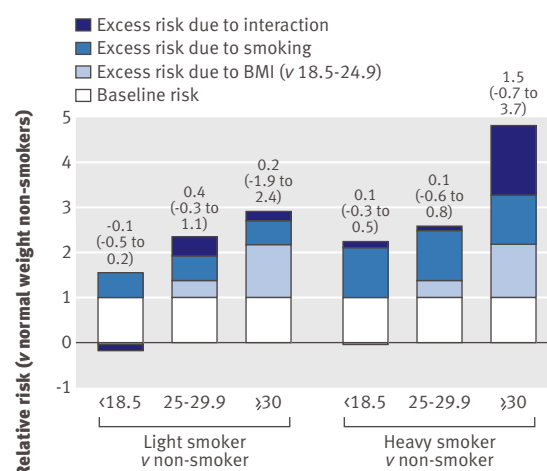

Relative risks of death with separate contributions from the exposure categories BMI status, smoking status, and their interaction, with point estimates and 95% confidence intervals for relative excess risk due to interaction (RERI) between BMI and smoking status. Models adjusted for muscle strength, socioeconomic status, and age

smoked 1-10 cigarettes/day (1.55, 1.41 to 1.70, P<0.001) to >10 cigarettes/day (2.18, 1.99 to 2.39, P<0.001) in unadjusted analyses. The absolute risks of death were 14.2 (13.3 to 15.1), 15.2 (14.2 to 16.2), and 25.5 (24.0 to 27.0) per 10 000 person years in non-smokers, light smokers, and heavy smokers, respectively.

Multivariable adjusted survival analyses

The significantly increased risks in overweight and obese men remained in our multivariable adjusted analyses of obesity status as a predictor for mortality, with adjustment for smoking, muscle strength, socioeconomic class, and age (table 1). The hazard ratios changed little when we included or excluded smoking as a covariate, or analysed smokers and non-smokers, and light and heavy smokers separately.

Similarly, the hazard ratios for smoking remained unchanged before and after adjustment for BMI status

Table 1 | Relative risks of premature death estimated by Cox regression analysis* (with 95% confidence intervals) according to categories of BMI† and smoking

	Total (n=45 884)		Smoking status			
BMI	Base model	Adjusted also for smoking	Non-smokers (n=18 990)	Smokers (n=26 894)	Light (1-10/day) (n=14 846)	Heavy (>10/day) (n=12 048)
Underweight	1.00 (0.89 to 1.12), P=0.99	0.97 (0.86 to 1.08), P=0.56	0.94 (0.75 to 1.18), P=0.62	0.97 (0.85 to 1.11), P=0.69	0.91 (0.75 to 1.10), P=0.32	1.05 (0.88 to 1.25), P=0.61
Normal weight	1	1	1	1	1	1
Overweight	1.34 (1.16 to 1.55), P<0.001	1.33 (1.15 to 1.53), P<0.001	1.37 (1.05 to 1.79), P=0.02	1.35 (1.14 to 1.60), P<0.001	1.44, (1.11 to 1.86), P=0.006	1.23 (0.98 to 1.54), P=0.08
Obesity	2.22 (1.66 to 2.95), P<0.001	2.14 (1.61 to 2.85), P<0.001	2.16 (1.24 to 3.76), P=0.007	2.23 (1.60 to 3.12), P<0.001	1.83 (0.98 to 3.42), P=0.06	2.27 (1.53 to 3.38), P<0.001

*All models adjusted for muscular strength, socioeconomic status, and age.
†Body mass index (kg/m²): underweight <18.5, normal weight 18.5-24.9, overweight 25-29.9, obese ≥30.

(table 2). Although the point estimates differed in magnitude across BMI categories, all were in the same direction and all but one were significant.

Subcategories of BMI and risk of mortality

Extremely underweight men (BMI <17) had a significantly increased risk of about the same magnitude (adjusted hazard ratio 1.33, 1.07 to 1.64, P=0.009; unadjusted 1.47, 1.20 to 1.80, P<0.001) as that in overweight men compared with the normal weight reference category.

Combined effects of smoking and BMI

The unadjusted mortality rate was similar for obese non-smokers and normal weight heavy smokers. After adjustment, the difference in hazard ratios between heavy smoking (v non-smoking) and obesity (v normal weight) was −0.02 (bootstrap obtained 95% confidence interval −0.69 to 0.64, P=0.96). Similarly, overweight and light smoking were associated with similar increases in risk of mortality with a difference in hazard ratios between light smoking (v non-smoking) and overweight (v normal weight) of 0.22 (−0.04 to 0.45, P=0.08).

Compared with normal weight men who did not smoke, the hazard ratios for groups defined by BMI and smoking status were large (1.31 to 4.74; see bmj.com) and highly significant (P<0.001 to P=0.02) for all but two groups: moderately underweight non-smokers (0.92, 0.72 to 1.17, P=0.48) and extremely underweight non-smokers (1.24, 0.81 to 1.91). Overweight and obese heavy smokers, respectively, had hazard ratios >2 (2.55, 2.03 to 3.20, P<0.001) and close to five times higher (4.74, 3.20 to 7.03, P<0.001) than normal weight non-smokers.

The figure shows the separate contributions to the relative risk of death from BMI and smoking status, as well as the interaction between the two. The relative excess risk due to interaction between smoking and BMI status did not reach significance in any category of BMI. Furthermore, the point estimates were generally small (see bmj.com). Though not significant, however, the combined effect of obesity and heavy smoking was large, with a relative excess risk due to interaction of 1.5.

DISCUSSION

In this follow-up study of men aged 16-19 we found excess risks of premature death, compared with men of normal weight, for overweight and obese men, irrespective of smoking status. Although the combination of heavy smoking and obesity was associated with a large increase in risk, we found no significant interaction between BMI and smoking status. The excess risk conferred by obesity in late adolescence was of similar magnitude as smoking >10 cigarettes/day, and the risk associated with overweight was similar to that of 1-10/day.

Absence of interaction between BMI and smoking

Most previous studies on the relation between BMI in late adolescence and mortality have not had access to data on smoking.[11][12][15] We explicitly investigated potential synergistic effects between smoking and categories of BMI and found no significant interaction. The combination of obesity and heavy smoking was associated with a large but non-significant relative excess risk because of interaction. Whether the combination of heavy smoking and obesity has synergistic effects requires further study.

Overweight and mortality

The finding of a significantly increased risk of death with obesity agrees with several previous studies in late adolescence.[10-12] Few previous studies have investigated overweight in late adolescence for men. Significantly increased risks of death for Norwegian men and women aged 14-19 with a BMI between the 85th and 94th centile have been reported, but no data were available on any potential confounders.[12] Our findings constitute an extension of these previous findings. These studies indicate adolescent overweight to be a serious health concern, in contrast with some reports from adult samples.[4-6]

Table 2 | Relative risks of premature death estimated by Cox regression analysis* (with 95% confidence intervals) according to categories of smoking and BMI†

Smoking	Total (n=45 884)		Obesity status			
	Base model	Adjusted also for BMI	Underweight (n=6320)	Normal weight (n=36 575)	Overweight (n=2622)	Obese (n=367)
Non-smokers	1	1	1	1	1	1
Light (1-10/day)	1.53 (1.40 to 1.68), P<0.001	1.54 (1.41 to 1.70), P<0.001	1.47 (1.13 to 1.91), P=0.004	1.56 (1.40 to 1.73), P<0.001	1.66 (1.17 to 2.35), P=0.005	1.36 (0.60 to 3.11), P=0.46
Heavy (>10/day)	2.11 (1.93 to 2.32), P<0.001	2.11 (1.92 to 2.31), P<0.001	2.36 (1.83 to 3.04), P<0.001	2.09 (1.89 to 2.32), P<0.001	1.85 (1.33 to 2.57), P<0.001	2.17 (1.11 to 4.23), P=0.02

*All models adjusted for muscular strength, socioeconomic status, and age.
†Body mass index (kg/m²): underweight <18.5, normal weight 18.5-24.9, overweight 25-29.9, obese ≥30.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Smoking and obesity are two of the most important behavioural risk factors for premature death in the West

Whether overweight (but not obesity) and underweight in late adolescence are associated with increased risk of premature death, and whether smoking and BMI status have synergistic effects on risk of mortality in men is not known

WHAT THIS STUDY ADDS

In late adolescence, overweight was as hazardous as smoking 1-10 cigarettes a day, while obesity was as hazardous as smoking >10 cigarettes a day

While the underweight group as a whole did not have any excess risk of premature death compared with normal weight men, having a BMI <17 was associated with a similar risk increase as overweight

No significant synergistic effects of smoking and BMI status on risk of premature death were detected, although the combination of heavy smoking and obesity was associated with a large excess risk

Underweight and mortality

Underweight has also been found to be significantly associated with small increases in relative risk of mortality in some[1 3 5] but not all previous studies.[9 10] We found no significant increase in risk in underweight men. A potential contributing factor might be that our study, based on 16-19 year old men, was less likely to be affected by reverse causality than studies on older adults. When we further stratified the underweight group, we found a significantly increased risk of death for men with a BMI <17. This indicates that there might be a relevant threshold somewhere within the underweight category.

Public health impact

Although there was little evidence of synergistic effects, compared with normal weight non-smokers the risk of mortality was more than doubled for overweight light smokers, tripled for obese light smokers, and close to quintupled for obese heavy smokers. In addition, extreme underweight conferred increased risk of mortality even after adjustment for smoking. This indicates that the relation between BMI and mortality is not linear, as has been suggested for adolescent women[10] and adults.[2 9]

Strengths and limitations

Our study was representative of adolescent men and had a long follow-up. We used objective measures of weight and height limiting risks of measurement error.

There were several limitations. Firstly, we had no data on women. US data on recalled BMI at age 18 in women, however, strongly suggest that the associations also hold for women.[10] Secondly, although BMI is a widely used proxy for fatness, it takes neither the muscle v fat mass relation nor the distribution of fatness into account. Finally, the risk of mortality might also be related to changes in weight and smoking during follow-up, for which we had no data.

Summary and conclusion

In summary, we found that overweight and obesity in late adolescence is associated with premature death, regardless of smoking status. Obesity and overweight were as hazardous as heavy and light smoking, respectively, and there was no interaction between smoking and obesity status. The findings indicate that overweight, obesity, and smoking among adolescents might be good targets for intensified public health initiatives.

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Combined effect of health behaviours and risk of first ever stroke in 20 040 men and women over 11 years' follow-up in Norfolk cohort of European Prospective Investigation of Cancer (EPIC Norfolk): prospective population study

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ABSTRACT

Objective To quantify the potential combined impact of four health behaviours on incidence of stroke in men and women living in the general community.

Design Population based prospective study (EPIC-Norfolk).

Setting Norfolk, United Kingdom.

Participants 20 040 men and women aged 40-79 with no known stroke or myocardial infarction at baseline survey in 1993-7, living in the general community, and followed up to 2007.

Main outcome measure Participants scored one point for each health behaviour: current non-smoking, physically not inactive, moderate alcohol intake (1-14 units a week), and plasma concentration of vitamin C ≥50 µmol/l, indicating fruit and vegetable intake of at least five servings a day, for a total score ranging from 0 to 4.

Results There were 599 incident strokes over 229 993 person years of follow-up; the average follow-up was 11.5 years. After adjustment for age, sex, body mass index (BMI), systolic blood pressure, cholesterol concentration, history of diabetes and aspirin use, and social class, compared with people with the four health behaviours the relative risks for stroke for men and women were 1.15 (95% confidence interval 0.89 to 1.49) for three health behaviours, 1.58 (1.22 to 2.05) for two, 2.18 (1.63 to 2.92) for one, and 2.31 (1.33 to 4.02) for none (P<0.001 for trend). The relations were consistent in subgroups stratified by sex, age, body mass index, and social class, and after exclusion of deaths within two years.

Conclusion Four health behaviours combined predict over a twofold difference in incidence of stroke in men and women.

INTRODUCTION

Lifestyle behaviours influence the risk of cardiovascular disease, including stroke. Previously we have looked at the combined impact of four health behaviours—smoking, physical activity, alcohol intake, and fruit and vegetable intake—on total and cause specific mortality in men and women living in the general community.[1] Here we examine the potential magnitude of their combined impact on the incidence of stroke in men and women aged 40-79.

METHODS

The participants were 20 040 men and women aged 40-79 at baseline, drawn from the Norfolk component of the European Prospective Investigation of Cancer (EPIC-Norfolk). This prospective population study first surveyed participants in 1993-7, 99.5% of whom were white. Participants were recruited from age-sex registers of general practices, and the Norfolk cohort was comparable with national population samples with respect to characteristics including anthropometry, blood pressure, and lipids, but with a lower prevalence of current smokers.[2]

At the 1993-7 baseline survey, participants were asked about medical history, smoking history, alcohol consumption, aspirin use and habitual physical activity. See bmj.com. For the purposes of the current study, we dichotomised the population into physically inactive (sedentary job and no recreational activity) and physically not inactive (any category with activity levels above the latter). We used the registrar general's

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Health behaviour score

Smoking habit
Non-smoker=1 point

Physical activity
Not inactive=1 point; person has a sedentary occupation, but at least half an hour of leisure time activity a day, such as cycling or swimming; or else a non-sedentary occupation with or without leisure time activity

Alcohol intake
One or more but <14 units/week=1 point; 1 unit=about 8 g alcohol—that is, one glass of wine, one small glass of sherry, one single shot of spirits, or one half pint (about 0.2 l) of beer

Fruit and vegetable intake
Five servings or more as indicated by blood concentration of vitamin C ≥50 µmol/l=1 point

Adapted from: Khaw et al, 2008[1]

occupation based social class classification scheme, and also re-categorised social class into manual (III manual, IV and V) and non-manual (I, II, and III non-manual) social classes. Unemployed men, and women without a partner, were coded as unclassified and excluded from the current study.

Nurses measured blood pressure, height and weight (to calculate body mass index (weight (kg)/(height (m)²)) and took non-fasting blood samples for serum concentrations of total cholesterol, high density lipoprotein cholesterol, and triglycerides. Six months after the start of the study we also collected samples to measure vitamin C concentration. We have previously reported that high plasma vitamin C concentration is inversely associated with mortality from all causes. Studies have reported that a blood value of 50 mmol/l or more of vitamin C indicates an intake of at least five servings of fruit and vegetables daily.[3 4] We therefore used plasma vitamin C concentrations as an objective biomarker of fruit and vegetable intake.

We constructed a simple pragmatic health behaviour score (box).[1] Participants could therefore have a total health behaviour score ranging from 0 to 4.

Case ascertainment

We ascertained incident cases of stroke using death certificate data (flagging participants for death at the UK Office for National Statistics (ONS)) and hospital record linkage (through routine annual record linkage to the NHS hospital information systems so that admission anywhere in the UK are notified to EPIC-Norfolk).

The current study is based on follow-up to the end of March 2007. A separate validation study showed this method for stroke ascertainment had a high positive predictive value of 94%. The follow-up period was defined as time interval between the date of the health examination at enrolment to the date of death for those who died, the date of first stroke for those who had a stroke, and the end of follow-up (31 March 2007) for the remaining participants.

Statistical analysis

We excluded participants with a history of stroke and myocardial infarction at baseline (n=913) and those who had any missing values for the variables included in the study (n=9492). We included only participants with all available data for all the covariates in the models.

We used Cox proportional hazards models to determine the associations between health behaviours, either individually or as their combined score, and the risk of incident stroke during the follow-up. Multivariate Cox regression models were constructed for health behaviour scores (0-4) with the highest score category (4) as the reference category.

We made multivariate adjustments to examine how far the effect of health behaviours might be explained by known cardiovascular risk factors. We adjusted for age (and sex in the combined model) in model A; age (sex), body mass index, systolic blood pressure, cholesterol concentration, aspirin use, and history of diabetes mellitus in model B; and as for model B with the addition of social class in model C.

To address the issue of reverse causality—that is, when people with subclinical chronic disease might be likely to change their lifestyle, such as reducing their physical activity—we excluded all those who had

Rates and relative risk of incident stroke by number of health behaviours, adjusted by age, sex, and BMI, systolic blood pressure, cholesterol, diabetes mellitus, social class category (manual and non-manual), and aspirin use stratified by sex, age, body mass index, and social class in men and women aged 40-79 without known stroke and myocardial infarction in EPIC-Norfolk 1993-2007, Cox regression model

Category	Events/No of participants	Health behaviour score					P value
		4	3	2	1	0	
By sex							
Male	289/8967	1.0	1.05 (0.71 to 1.54)	1.35 (0.92 to 1.98)	1.84 (1.20 to 2.82)	1.48 (0.62 to 3.53)	0.012
Female	310/11 073	1.0	1.21 (0.85 to 1.71)	1.82 (1.29 to 2.59)	2.58 (1.73 to 3.84)	3.49 (1.71 to 7.12)	<0.001
By age group							
<65 years	194/14 178	1.0	1.27 (0.83 to 1.93)	2.02 (1.32 to 3.08)	1.92 (1.10 to 3.37)	4.48 (2.06 to 9.76)	<0.001
≥65 years	405/5862	1.0	1.06 (0.77 to 1.48)	1.39 (1.01 to 1.93)	2.22 (1.56 to 3.15)	1.48 (0.67 to 3.27)	<0.001
By BMI (kg/m²)							
<25	222/8096	1.0	0.83 (0.57 to 1.22)	1.28 (0.87 to 1.88)	1.62 (1.04 to 2.54)	2.76 (1.34 to 5.69)	0.001
25-30	283/9091	1.0	1.41 (0.95 to 2.10)	1.85 (1.24 to 2.76)	2.65 (1.70 to 4.13)	1.29 (0.39 to 4.22)	<0.001
≥30	94/2853	1.0	2.17 (0.84 to 5.65)	2.67 (1.05 to 6.84)	4.12 (1.53 to 11.12)	4.59 (1.08 to 19.53)	0.036
By social class							
Non-manual	351/12 182	1.0	1.12 (0.81 to 1.55)	1.73 (1.25 to 2.39)	2.38 (1.63 to 3.47)	3.23 (1.59 to 6.55)	<0.001
Manual	248/7858	1.0	1.20 (0.78 to 1.84)	1.42 (0.93 to 2.18)	2.02 (1.27 to 3.22)	1.61 (0.66 to 3.89)	0.022

BMI= body mass index.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The relation between individual lifestyle behaviour such as smoking and health has been examined

Four health behaviours combined—smoking, physical activity, alcohol intake, and fruit and vegetable intake—have an impact on mortality

WHAT THIS STUDY ADDS

Relatively modest and achievable health behaviours in combination can produce a substantial reduction in risk of stroke

men and women who scored 0 for health behaviours had about 2.3 times the risk of stroke (relative risk 2.31, 95% confidence interval 1.33 to 4.02) compared with those who scored 4. The table shows stratified analyses with a model with all covariates (model C). The findings were consistent across the sample population regardless of sex, age, BMI, and social class. The absolute risks for incident stroke were 1.7% (84 events/5006), 2.4% (186/7822), 4.0% (206/5191), 6.1% (108/176), and 5.8% (15/259) for behaviour scores of 4, 3, 2, 1, and 0, respectively (P<0.001).

stroke within the first two years of follow-up and constructed model D controlling for all of the above mentioned variables. We also performed stratified analyses by sex, age category (<65 and ≥65), body mass index (<25, 25-30, ≥30), and social class (non-manual and manual).

RESULTS

There were a total of 599 strokes during the 229 992 person years of follow-up (average 11.5 years). Of these, 168 (28%) were fatal. Comparison between those included (20 040) and excluded (10 405) from the study with missing data showed no material difference in terms of their mean age (58.2 v 60.0), sex (44.7% v 45.5% male), BMI 26.5 v 26.9, systolic blood pressure 135 mm Hg v 137 mm Hg, and total cholesterol concentration 6.2 mmol/l v 6.3 mmol/l.

Baseline characteristics of the sample according to sex showed that men were older, had higher BMI and higher systolic blood pressure, were current or previous smokers, consumed ≥21 units of alcohol a week, and were physically active, and fewer consumed five or more portions of fruit and vegetables a day. See bmj.com. With large numbers, these and other characteristics showed significant differences between men and women. A significantly higher percentage of women scored 4 for combined health behaviours. Incidence of stroke was not significantly different between men and women.

The independent relative risks for the individual lifestyle behaviours and risk of stroke showed that people who smoked, were physically inactive, consumed no alcohol or more than 14 units/week, and ate fewer than five portions of fruit and vegetables a day, were at a significantly higher risk of stroke (see bmj.com).

With the combined health behaviour score and risk of stroke in different multivariate adjusted Cox regression models, the risk of stroke increased in linear fashion with every point decrease in combined health behaviour score. In the fully adjusted model (model C),

DISCUSSION

Modifiable lifestyle behaviours including not smoking, physically not inactive, moderate consumption of alcohol (1-14 units/week), and eating at least five portions of fruit and vegetables a day are associated with a substantially lower risk of subsequent stroke.

A large proportion of strokes occur in people who do not have known risk factors such as hypertension and atrial fibrillation. The large geographical variations and secular trends in incidence of and mortality from stroke suggest that environmental factors have an important role. Evidence indicates that lifestyle factors influence risk.[5] Other studies support the strong relation between lifestyle behaviours and cardiovascular disease.[6] The lifestyle behaviours examined in this study are potentially achievable in the general population, which means that our findings are of relevance to middle aged and older populations worldwide.

Our primary aim was to examine the relation between health behaviours and risk of stroke, irrespective of the probable biological mediating factors. Some of these health behaviours, such as high intake of fruit and vegetables or physical activity, might relate to lower levels of blood pressure, a major risk factor for stroke. Nevertheless, the relation of health behaviours with risk of stroke was independent of systolic blood pressure.

Study limitations

There are limitations in our study. Reverse causality is a potential major issue, which we addressed in our analysis. Secondly, residual confounding with known or unknown factors is always possible. Thirdly, there are potential measurement errors in the assessment of exposures; we used only one measure at one point in time to characterise individuals and did not take into account possible changes in lifestyles over follow-up. Nevertheless, random measurement error would probably attenuate any associations observed, so the estimated differences in risk are likely to be larger than those observed. Fourthly, the proportions of the

population with some or all positive health behaviours were relatively high as the definitions for health behaviours were not necessarily optimal (for example, for physical activity). Fifthly, we excluded about 9000 participants who consented to the study but were not able to attend the health check. Exclusion of these individuals is unlikely to influence the relation between health behaviours in stroke unless this association was in the opposite direction in those excluded, which seems implausible. The potential healthy responder bias resulting in truncation of sample distribution would probably only attenuate the findings and be unlikely to change the direction of the study results. We were unable to identify people with mild stroke who were not admitted to hospital, and some strokes might have been included in the "non-stroke" group. In a cohort of this size, however, the effect on estimates of risk would not be substantial. Misclassification of non-stroke cases as stroke cases would attenuate the association between health behaviours and stroke risk.

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CORRECTIONS AND CLARIFICATIONS

Modern approaches to teaching and learning anatomy
We illustrated the print version of this Analysis article by John P Collins (*BMJ* 2008;337:a1310, print publication 20 Sep, pp 665-7) with a painting by Johann Zoffany showing Dr William Hunter teaching anatomy at the Royal Academy. We forgot to acknowledge the copyright holder, the Royal College of Physicians.

The invisible epidemic
An error during page layout for publication led to the wrong information on competing interests being appended to the end of this article by Bob Roehr in the print version (*BMJ* 2008;337:a2566, print publication 29 Nov, pp 1262-4). In fact, Roehr has no competing interests. We also made some mistakes when redrawing the map from the International Lesbian and Gay Association. Contrary to what our map shows, homosexuality is punishable by death in northern Nigeria but not in Gambia, Guyana, Sierra Leone, or Niger. The correct information is available at www.ilga.org/map/LGBTI_rights.jpg.

Obituary: Barclay John Sherry
In this obituary of Barclay John Sherry by Mark Sherry (*BMJ* 2008;337:a2440, print publication 22 Nov, p 1238) the year of qualification of Dr Barclay John Sherry is 1951 (not 1950 as published).

Developing countries should have a greater say in local research agendas
We illustrated this News article by Robert Walgate with what we thought was a picture of Ok Pannenborg, senior health adviser for the World Bank's Africa region (*BMJ* 2008;337:a2713, print publication 29 Nov, p1259). However, the picture showed Kiyoshi Kurokawa, special adviser to the cabinet of the Japanese government.

Obituary: Ronald Mark Davis
In this obituary of Ronald Mark Davis by Douglas Kamerow (*BMJ* 2008;337:a2643, print publication 22 Nov, p 1237), we referred to the former United States Surgeon General Charles Koop. However, he was known as C Everett Koop.

Health promotion: from clinic to classroom
In this Filler article, we omitted the first author's name (*BMJ* 2008;336:210, print publication 26 Jan). The authors should have been given as Shree Datta and Janesh Kumar Gupta.

p i c o

Effect of tobacco smoking on survival of men and women by social position: a 28 year cohort study

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STUDY QUESTION How do smoking, sex, and social position affect the long term survival of middle aged men and women?

SUMMARY ANSWER Both male and female smokers in all social positions had poorer survival than those who had never smoked in even the lowest social positions. The differences in survival between smokers and never smokers were much greater than those between smokers in different social positions. Smoking nullified women's otherwise large survival advantage over men. Smoking itself was thus a greater source of health inequality than social position in this population. This suggests the scope for reducing health inequalities related to social position is probably limited, in this and similar populations, unless many smokers in lower social positions can be enabled to stop smoking.

Participants and setting

Men and women aged 45-64 years were recruited during 1972-6 in Renfrew and Paisley, two towns in west central Scotland.

Design, size, and duration

This was a prospective cohort observational study of 8353 women and 7049 men followed up for 28 years. Data obtained at recruitment included occupation, place of residence, and smoking status (current, former, or never smokers). The cohort was divided into 24 groups by sex, smoking status, and social class (classes I + II, III non-manual, III manual, and IV + V) or deprivation category of place of residence. The main outcome measure was death, reported as relative mortality (adjusted for age and other risk factors) and as Kaplan-Meier survival curves and survival at 28 years.

Main results and the role of chance

Of the 7988 women and 6967 men with complete data, 4387 women and 4891 men died over 28 years.

Compared with women in social classes I + II who had never smoked (the group with lowest mortality), the adjusted relative mortality of smoking groups ranged from 1.7 (95% confidence interval 1.3 to 2.3) to 4.2 (3.3 to 5.5). Former smokers' mortalities gradually fell towards those of never smokers. By social class (highest first), age adjusted survival after 28 years was 65%, 57%, 53%, and 56% for female never smokers; 41%, 42%, 33%, and 35% for female current smokers; 53%, 47%, 38%, and 36% for male never smokers; and 24%, 24%, 19%, and 18% for male current smokers (figure). Analysis by deprivation category gave similar results.

Bias, confounding, and other reasons for caution

With a participation rate of almost 80%, complete records of social class and death of over 97% and 99% respectively for the cohort, and adjustment for age and other factors, the scope for bias and confounding was low. Because smoking status was taken at recruitment and many, especially the more affluent, smokers would have subsequently stopped and improved their health, the full impact of lifelong smoking on survival may have been understated.
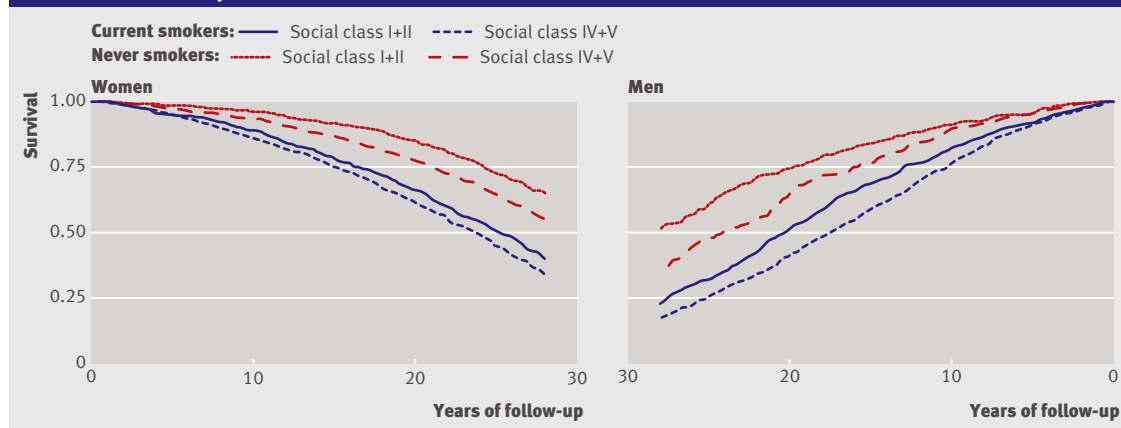
Generalisability to other populations

Comparisons with similar post-industrial populations in Europe suggest the findings could be expected wherever smoking has been prevalent for many decades.

Study funding/potential competing interests

AGE ADJUSTED SURVIVAL IN HIGHEST AND LOWEST SOCIAL CLASSES BY SMOKING STATUS

Current smokers: Social class I+II ── Social class IV+V ----
Never smokers: Social class I+II ········· Social class IV+V ──

p i c o

Low intensity pulsed ultrasonography for fractures: systematic review of randomised controlled trials

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STUDY QUESTION What is the efficacy of low intensity pulsed ultrasonography for fracture healing?

SUMMARY ANSWER Evidence for the effect of low intensity pulsed ultrasonography on healing of fractures is moderate to very low in quality and provides conflicting results. Although overall results are promising, establishing the role of low intensity pulsed ultrasonography in the management of fractures requires large, blinded trials directly addressing outcomes that are important to patients, such as return to function.

Selection criteria for studies

We identified clinical trials that randomly allocated patients with any form of bone fracture to low intensity pulsed ultrasonography or a control, by an electronic literature search without language restrictions of CINAHL, Embase, Medline, HealthSTAR, and the Cochrane Central Registry of Controlled Trials, from inception of the database to 10 September 2008. All outcomes were included.

Primary outcome(s)

We focused on patient important outcomes, in particular functional recovery.

Main results and role of chance

We included 13 randomised trials in the analysis, five of which assessed outcomes of importance to patients (table). Moderate quality evidence from one trial showed no effect of low intensity pulsed ultrasonography on functional recovery from conservatively managed fresh clavicle fractures; whereas low quality evidence from three trials suggested benefit in non-operatively managed fresh fractures (faster radiographic healing, mean reduction in healing time 36.9%, 95% confidence interval 25.6% to 46.0%). A single trial provided moderate quality evidence suggesting no effect on return to function among non-operatively treated stress fractures. Three trials provided very low quality evidence for accelerated functional improvement after distraction osteogenesis (results not shown). One trial provided low quality evidence for a benefit in accelerating healing of established non-unions managed with bone graft. Four trials provided low quality evidence for acceleration of healing of operatively managed fresh fractures.

Bias, confounding, and other reasons for caution

The trials in our analysis had methodological limitations including lack of blinding of all relevant parties and substantial loss to follow-up in some trials. Results were sometimes inconsistent across trials, and most studies used surrogate end points; larger effects were typically reported for surrogates compared with direct measures of function. Concerns about publication bias arose from the limited number of small trials, and the inconsistent reporting of outcomes across trials raises the possibility of selective reporting bias, although we did not rate down the evidence for publication bias or selective reporting bias. The strength of inference is therefore limited.

Study funding/potential competing interests

JWB, MB, and GHG are currently involved in a multicentre, randomised controlled trial that has received partial funding from Smith and Nephew, the company that manufactures the Exogen ultrasound device that was used in many of the studies. GHG and HJS are members of the GRADE working group.

EFFECTS OF ULTRASONOGRAPHY ON FRACTURE HEALING

No of studies, patients	Size of effect (95% CI)	Overall quality
Non-operatively managed fresh fractures		
1 trial, 101 patients	1.40 days (-0.56 to 3.36) faster return to function	⊕⊕⊕◯ Moderate
3 trials, 158 patients	36.9% (25.6% to 46.0%) reduction in healing time*	⊕⊕◯◯ Low
Non-operatively treated stress fractures		
1 trial, 26 patients	0.4 days (-13.1 to 13.9) faster return to active duty	⊕⊕⊕◯ Moderate
Operatively managed non-union		
1 trial, 21 patients	40.4% (30.8% to 48.7%) reduction in healing time*	⊕⊕◯◯ Low
Operatively managed fresh fractures		
2 trials, 61 patients	3.4 weeks (-2.1 to 8.9) faster return to full weight bearing	⊕⊕◯◯ Low
2 trials, 61 patients	16.6% (-76.8% to 60.7%) reduction in healing time*	⊕◯◯◯ Very low

*Evidence from surrogate measure only (radiographic healing)

BMJ pico: advice to authors

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