Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: a systematic review of the research evidence

John Wright, Rachel Johns, Ian Watt, Arabella Melville, Trevor Sheldon

Abstract

Objective: To examine the research evidence for the health consequences of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure.

Design: A systematic review of published research, studies being identified by searching Medline (1966-96), Embase (1974-96), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1982-95); scanning citations; and consulting experts. Studies in all languages were considered which either investigated the association between obstructive sleep apnoea in adults and key health outcomes or evaluated the effectiveness of treatment of obstructive sleep apnoea with continuous positive airways pressure in adults.

Main outcome measures: Mortality, systematic hypertension, cardiac arrhythmias, ischaemic heart disease, left ventricular hypertrophy, pulmonary hypertension, stroke, vehicle accidents, measures of daytime sleepiness, and quality of life.

Results: 54 epidemiological studies examined the association between sleep apnoea and health related outcomes. Most were poorly designed and only weak or contradictory evidence was found of an association with cardiac arrhythmias, ischaemic heart disease, cardiac failure, systemic or pulmonary hypertension, and stroke. Evidence of a link with sleepiness and road traffic accidents was stronger but inconclusive. Only one small randomised controlled trial evaluated continuous positive airways pressure. Five non-randomised controlled trials and 38 uncontrolled trials were identified. Small changes in objectively measured daytime sleepiness were consistently found, but improvements in morbidity, mortality, and quality of life indicators were not adequately assessed.

Conclusions: The relevance of sleep apnoea to public health has been exaggerated. The effectiveness of continuous positive airways pressure in improving health outcomes has been poorly evaluated. There is enough evidence suggesting benefit in reducing daytime sleepiness in some patients to warrant large randomised placebo controlled trials of continuous positive airways pressure versus an effective weight reduction programme and other interventions.

Introduction

Obstructive sleep apnoea is the periodic reduction (hypopnoea) or cessation (apnoea) of breathing due to narrowing of the upper airways during sleep. The main symptom is daytime sleepiness, and it is thought to be a cause of premature death, hypertension, ischaemic heart disease, stroke, and road traffic accidents.[1 2] Prevalence surveys estimate that 4% of middle aged men and 2% of middle aged women are affected by sleep apnoea.[3 4] The high prevalence of the syndrome and the morbidity and mortality thought to be associated with it have led to the view that sleep apnoea may be as big a public health hazard as smoking.[5] The recommended initial treatment of choice is nasal continuous positive airways pressure,[6] and purchasers are increasingly being urged to fund sleep services.[2 7]

Most discussion on the topic is based on selective and at times uncritical examination of the available research. We conducted a systematic review to examine (*a*) the evidence of a causal association between sleep apnoea and morbidity and mortality and (*b*) evidence for the effectiveness of continuous positive airways pressure.

Methods

We conducted the review using national structured guidelines.[8] A computerised search of Medline (1966 to January 1996), Embase (1974-96), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1982 to December 1995) was undertaken (see appendix). Existing reviews were sought, reference lists of identified papers scanned, and experts in the United Kingdom approached. All studies in any language that included adults were considered for review. Epidemiological studies of any design examining the association between sleep apnoea and mortality, hypertension, pulmonary hypertension, cardiovascular disease, and accidents were identified. They were classified as prospective cohort (A1), retrospective cohort (A2), case-control (B), or cross sectional (C).[9] Additional grading was based on the adequacy of case ascertainment, adjustment for confounding variables, and validity of the measurement of disease possibly caused by sleep apnoea. All experimental studies were classified according to an internationally established hierarchy

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Bradford Royal Infirmary, Bradford, West Yorkshire BD9 6RJ
John Wright, *consultant in epidemiology and public health medicine*
North Yorkshire Health Authority, York YO3 4XF
Rachel Johns, *research development manager*
NHS Centre for Reviews and Dissemination, University of York, York YOU DD
Ian Watt, *consultant in public health medicine*
Arabella Melville, *research fellow*
Trevor Sheldon, *director*
Correspondence to: Dr Wright (j.wright@leeds.ac.uk).

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Table 1 Epidemiological studies examining association between sleep apnoea and mortality

Study	Design†	Sample‡	Results	Comments
Bliwise *et al* (1988), United States[11]	Prospective cohort A1 (1,1,1)	General population recruited by advertisement,1974-83. Elderly: 69 men, 129 women Apnoea-hypopnoea index <10 Age 67 Body mass index ?34	Follow up not recorded ?up to 12 years; 20 deaths, 8 vascular Mortality risk ratio for apnoea-hypopnoea index >10 was 2.7 (95% confidence interval –0.95 to 7.5) Survival analysis showed no significant association with apnoea-hypopnoea index	Good follow up Validation by death certification White middle class population Age had clearest association with mortality
Ancoli-Israel *et al* (1989), United States[12]	Prospective cohort A1 (0,0,1)	233 nursing home residents: 151 women, 82 men Apnoea-hypopnoea index 19 Body mass index 31 Age: men 80, women 84 74% had pre-existing cardiovascular disease 51% had neurological disease	Median follow up 626 days for survivors; 116 (50%) dead at follow up Men had significantly higher total mortality (P<0.001). No association of apnoea-hypopnoea index and death in men but significant association in women (P=0.015). Odds ratio for survival for women with apnoea-hypopnoea index >50=0.18 (n=8) and for apnoea-hypopnoea index 30-50=0.74 (n=23) Mortality also significantly associated with pre-existing pulmonary, renal, and gastrointestinal disease and body mass index. No association with age. No adjustment for effects of existing disease, body mass index, and other potential confounding variables	Not obstructive sleep apnoea patients: asymptomatic Elderly population Uncertain validity of apnoea-hypopnoea index groupings Validation by death certification High levels of pre-existing morbidity, especially cardiovascular, neurological, respiratory Possibility that subjects had Cheyne-Stokes respiration rather than obstructive sleep apnoea
Mant *et al* (1995), Australia[13]	Prospective cohort A1 (1,1,1)	Two random samples (163) of non-demented retirement village residents Sample 1, age 83.5 Sample 2, age 78.5 Those with respiratory disturbance index ⩾15 classified as having sleep disordered breathing	After adjustment for age there was no relation between respiratory disturbance index and survival: odds ratio 0.99 (95% confidence interval 0.94 to 1.04). Comorbidity predicted survival	Small sample Low prevalence of sleep disturbed breathing in this sample Results may not be generalisable to younger populations
Lavie *et al* (1995), Israel[14]	Prospective cohort A1 (1,1,1)	1620 patients referred to Technion sleep laboratory for sleep apnoea and found to have sleep apnoea on basis of characteristic symptoms and an apnoea index >10 over period 1976-88 90% male; age 48 Compared with 1986 national mortality data	With Cox proportional hazards model age, body mass index, hypertension, and apnoea index were statistically significant predictors of deaths. Apnoea index had least effect: odds ratio 1.012 (95% confidence interval 1.0008 to 1.024) Only age and body mass index were predictors of death from heart and lung causes and (along with hypertension) predictors of myocardial infarction	Because sleep laboratory evaluation is covered by all medical insurance groups in Israel the cohort was not likely to be biased by social class Apnoea index ignores hypopnoeas which are included in the apnoea-hypopnoea index and so severity may be underestimated in some cases Study lacked proper control group
Gonzalez-Rothi *et al* (1988), United States[15]	Retrospective cohort A2 (1,0,1)	126 adult referrals from 1978 to 1986 35 controls: apnoea-hypopnoea index 3; age 56 67 treated, 2 with continuous positive airways pressure: apnoea-hypopnoea index 39; age 46 24 not treated: apnoea-hypopnoea index 45; age 51	Duration of follow up (months): control 30, treated 37, not treated 29 No significant differences in all cause mortality: relative risk 1.35 (95% confidence interval –1.0 to 3.7) Cause of death closely related to antecedent medical conditions	Higher proportion of women in control group, so lower mean weight Small sample Validation by death certification Good follow up No adjustment for possible confounding
He *et al* (1988), United States[16]	Retrospective cohort A2 (0,0,0)	706 male obstructive sleep apnoea patients, apnoea index >5 385 (55%) response Apnoea index 35 Body mass index 34 Age 52 118 treated, 25 with continuous positive airways pressure	Duration of follow up not recorded 22 deaths/385 subjects Apnoea index >20 associated with shorter survival than apnoea index <20 (relative risk 1.5; P<0.05) especially when patient <50 years and untreated. This group also had significantly higher body mass index (P<0.05)	Poor response. All men Low apnoea index for case definition Self reported data on deaths and no causes recorded Unknown pre-existing morbidity No validation of deaths No adjustment for effects of body mass index and other potential confounders

†Study designs were A1 (prospective cohort), A2 (retrospective cohort), B (case-control), and C (cross sectional). In addition, three aspects of quality—namely, adequacy of case ascertainment (that is, sleep apnoea), adjustment for confounding variables (for example, obesity, smoking, age), and validity of measurement of disease outcome—were coded 1 for adequate and 0 for inadequate. ‡Values are means.

of design, in which randomised controlled trials are regarded as the least susceptible to bias.[10] All case definitions used in studies were considered.

Abstracts and letters were included if they contained enough methodological information and results. We excluded case reports, studies with no clinical outcome measures, studies which examined only acute or physiological changes during sleep, and studies on sleep apnoea in children. Each paper was evaluated independently by two assessors using a series of predetermined validity criteria on a data extraction form. Disagreements were resolved by a third assessor. Summary tables of each epidemiological study were drawn up by using the grading described above. Summaries of intervention studies with continuous positive airways pressure were included in a table only if they contained some form of control group.

Results

We found 54 epidemiological studies of the association of obstructive sleep apnoea with mortality (n=6),[11-16] hypertension (n=18),[17-34] cardiac arrhythmias (n=8),[35-42] coronary heart disease and left ventricular failure (n=6),[43-49] pulmonary hypertension (n=6),[49-54] stroke (n=3),[55-57] and road traffic accidents (n=7).[14 58-65] Disagreements over study design classifications arose in eight papers and were satisfactorily resolved after discussion. Most epidemiological studies were limited in their ability to establish a causal association because of failure to take sufficient account of the potential effects of confounding by such variables as measures of obesity and smoking (which are correlated with both sleep apnoea and poor health) or because they failed to establish a causal time sequence, sleep apnoea being

established after the poor health outcome had been diagnosed.[9]

Mortality

Two prospective cohort studies examined the association between apnoea-hypopnoea scores and mortality in the general population (table 1). One found no significant association[11] and the other found a significant association in women.[12] A four year follow up of non-demented retired older people found that the respiratory disturbance index was not a predictor of mortality.[13] One prospective study followed up patients with diagnosed sleep apnoea syndrome and examined the death rate relative to that expected for such age and sex groups.[14] Multivariate analysis showed that age, hypertension, and body mass index (weight (kg)/height $(m)^2$) had the largest and most significant effects on excess mortality. Apnoea index (but not apnoea duration) was also a predictor of excess mortality but not of excess deaths due to heart or lung causes.

Systemic hypertension

A previous review of daytime blood pressure and obstructive sleep apnoea based on seven observational studies concluded that the evidence of a causal association was still lacking and the confounding influence of body weight had not been assessed adequately.[66] Eighteen additional cross sectional studies were identified and are listed in table A (tables A-C are available from JW and on the *BMJ*'s home page www.bmj.com). Six of these studies found no association of sleep apnoea with raised blood pressure.[20 21 27 28 31 33] Four found statistically significant associations with early morning blood pressure,[18 19 22 26] but this may be a marker of nocturnal blood pressure.[29 67] Eight studies found a significant positive correlation of sleep apnoea with daytime blood pressure but none adjusted for the effects of smoking, alcohol, or antihypertensive drugs.[17-25 29 30 32] One of these studies, in truck drivers, found that obstructive sleep apnoea was associated with blood pressure over and above body mass index only in obese drivers.[17]

Arrhythmias, ischaemic heart disease, and left ventricular hypertrophy

Eight studies investigated the prevalence of nocturnal arrhythmias in patients with sleep apnoea.[35-42] Two were prospective studies which followed up consecutive referrals and included a control group.[35 41] The

Table 2 Epidemiological studies examining association between sleep apnoea and pulmonary hypertension

Study	Design†	Sample‡	Results	Comments
Krieger *et al* (1989), France[49]	Cross sectional C (1,0,1)	114 consecutive patients with obstructive sleep apnoea, apnoea index >5 Apnoea-hypopnoea index 79 Body mass index 32 Age 53 Patients with pre-existing lung disease excluded Measured pulmonary artery pressure	100 patients had right heart catherisation; 19 had pulmonary hypertension Multiple regression: pulmonary artery pressure significantly correlated with forced expiratory volume in one second (r=–2.41) and pressure of arterial oxygen (r=–0.11) and pressure of arterial carbon dioxide (r=0.22). No contribution from nocturnal hypoxia or apnoea-hypopnoea index	Smokers included but confounding influence not analysed
Weitzenblum *et al* (1988), France[50]	Cross sectional C (1,0,1)	46 consecutive patients with obstructive sleep apnoea Apnoea index >5 Apnoea-hypopnoea index 89 Weight 145% of ideal Age 52 Patients with pre-existing lung disease excluded	Linear regression found significant correlations between pulmonary artery pressure and forced expiratory volume in one second (r=–0.52; P<0.001), ratio of forced expiratory volume in one second to forced vital capacity (r=–0.40; P<0.01), pressure of arterial oxygen (r=–0.61; P<0.001), and pressure of arterial carbon dioxide (r=0.55; P<0.001) but not apnoea-hypopnoea index (r=0.2; P>0.05)	Smokers included but confounding influence not analysed
Sajkov *et al* (1994), Australia[51]	Cross sectional C (0,1,1)	27 patients with obstructive sleep apnoea, apnoea-hypopnoea index >10, and normal lung function values Apnoea-hypopnoea index 55 Body mass index 30 Age 49	11 patients diagnosed as having pulmonary hypertension on basis of echocardiography. These had significantly lower pressure of arterial oxygen than non-pulmonary hypertension patients (difference in mean 5.4 mm Hg (0.72 kPa)); 95% confidence interval 1.3 to 9.5 (0.2 to 1.3 kPa)) but no significant difference in apnoea-hypopnoea index (difference in mean 5; 8.7 to 18.7). No significant difference in smoking, body mass index, or lung function values	Echocardiogram surrogate marker for catheter pulmonary artery pressure; uncertain validity for borderline pulmonary hypertension Uncertain selection of cases Small sample
Laks *et al* (1995), Australia[53]	Cross sectional C (1,1,1)	100 patients with obstructive sleep apnoea, apnoea-hypopnoea index >20 Apnoea-hypopnoea index 64 Age 52 Body mass index 37	42 patients had pulmonary hypertension on basis of catheter studies Multiple regression: pulmonary artery pressure significantly correlated with forced expiratory volume in one second (r^2=0.071; P<0.001) and pressure of arterial oxygen (r^2=0.064; P=0.01) but not with apnoea-hypopnoea index or body mass index	Smokers and patients with pre-existing lung disease included Attempt at consecutive recruitment but unable to assess fully from information included
Bradley *et al* (1985), Canada[52]	Cross sectional C (1,0,1)	50 consecutive obstructive sleep apnoea patients, apnoea-hypopnoea index >10 Apnoea-hypopnoea index 49 Weight 154% of ideal Age 49	6 patients had clinical diagnosis of right heart failure (peripheral oedema+one other sign). This group had significantly higher weight (P<0.05) and pressure of arterial carbon dioxide (P<0.001) and significantly lower pressure of arterial oxygen (P<0.001), forced vital capacity (P<0.001), forced expiratory volume in one second (P<0.001), and ratio of forced expiratory volume in one second to forced vital capacity (P<0.001) but no difference in apnoea-hypopnoea index (difference in mean 3; 95% confidence interval –2 to 8). All 6 patients were smokers	Non-blinded clinical assessment of right heart failure; uncertain validity No regression or correlation analysis
Shinozaki *et al* (1995), Japan[54]	Cross sectional C (1,0,1)	25 patients with diagnosed obstructive sleep apnoea; 8 had pulmonary hypertension (≥20 mm Hg) 11 male, 6 female Age range 22-69 Weight 154% of ideal Apnoea index 54	Mean pulmonary artery pressure was not significantly correlated with apnoea index (r=0.06; P<0.05) or oxygen desaturation. Instead, it was related to daytime hypoxaemia, obesity, and other respiratory impairments	Small sample

†Study designs were A1 (prospective cohort), A2 (retrospective cohort), B (case-control), and C (cross sectional). In addition, three aspects of quality—namely, adequacy of case ascertainment (that is, sleep apnoea), adjustment for confounding variables (for example, obesity, smoking, age), and validity of measurement of disease outcome—were coded 1 for adequate and 0 for inadequate.‡Values are means.

Table 3 Epidemiological studies examining association between sleep apnoea and stroke

Study	Design†	Sample‡	Results	Comments
Palomaki (1991), Finland[55]	Case-control study B (0,1,1)	177 consecutive male patients aged 16-60 admitted for brain infarction. 177 age matched male controls admitted to same hospital for acute reasons other than brain infarction and no history of cerebrovascular disease. History of snoring and sleep disturbance by self report (83%) or cohabitee (17%) Age 49 167 age matched case-control pairs	Stepwise multiple logistic regression analysis adjusting for confounders identified heavy drinking (odds ratio 6.8; 95% confidence interval 1.9 to 25.0), coronary heart disease (odds ratio 2.9; 1.5 to 5.7), hypertension (odds ratio 2.9; 1.6 to 5.3), and habitual snoring (odds ratio 2.1; 1.3 to 3.5) as main independent risk factors. If history of sleep apnoea, excessive daytime sleepiness, and obesity was present the association with snoring (McNemar's tests) increased (odds ratio 8.0; 1.1 to 356.0). Obesity contributed more to risk of stroke than apnoea	Body mass index included only as binary variable (>27). Possible susceptibility to recall bias and inaccurate history of sleep. Results remained unchanged when patients with prior stroke history were excluded
Dyken *et al* (1996), United States[56]	Cross sectional C (1,1,1)	24 patients with recent stroke: 13 men, 11 women Age 65 27 healthy volunteers without stroke: 13 men, 14 women Age 62 All had complete overnight polysomnography	Significant difference in apnoea-hypopnoea index between men with and without stroke (difference in mean 16.7; 95% confidence interval 10.8 to 22.6)	Not clear if controls were representative, as they were volunteer respondents to advertisement Comorbidities (for example, hypertension) could be confounders Causal direction not clear, as stroke can cause sleep apnoea

†Study designs were A1 (prospective cohort), A2 (retrospective cohort), B (case-control), and C (cross sectional). In addition, three aspects of quality—namely, adequacy of case ascertainment (that is, sleep apnoea), adjustment for confounding variables (for example, obesity, smoking, age), and validity of measurement of disease outcome—were coded 1 for adequate and 0 for inadequate. ‡Ages are means.

study with the most valid measurement and classification of arrhythmias found no difference between the groups.[35] The prevalence of arrhythmias in both prospective studies was similar to that observed in healthy adults (table B). Three studies, two using a case-control and one a cross sectional design, found an association between the apnoea index and coronary heart disease.[43-45] Two did not adjust for the effects of all important confounding factors.[43 44] In all studies the diagnosis of sleep apnoea was made after the diagnosis of coronary artery disease. Two of the three cross sectional studies which examined the relation with left ventricular hypertrophy[46-48] found no association.[46 47]

Pulmonary hypertension and right heart failure

Six cross sectional studies reported a high prevalence of pulmonary hypertension in patients with obstructive sleep apnoea (table 2).[49-54] Only one used multiple regression to adjust for confounding,[49] and only one took smoking into account. All associations could be explained by pre-existing obstructive airways disease, smoking, and obesity.

Stroke

One case-control study found a relation between both self reported history of snoring and apnoea-like symptoms and the risk of stroke (table 3).[55] In addition to the possibility of recall bias in the diagnosis of apnoea, body mass index was poorly adjusted for, being included as a binary variable (body mass index >27.0) rather than as a continuous or more finely graded variable. One cross sectional study also reported that the prevalence of obstructive sleep apnoea was higher in people with recent stroke than in controls.[50] However, the sleep apnoea was diagnosed after the stroke, and a recent study has shown that stroke can cause sleep apnoea.[57]

Road traffic accidents

Six cross sectional studies examined the association between obstructive sleep apnoea and reported car accidents (table C).[14-63] None made adequate adjustment for potential confounding variables such as age, sex, drinking, obesity, annual milage, shiftwork, and social activities. Of the two studies looking at driving records, one (using state driving records) found an association in patients with severe sleep apnoea[58 59] whereas the other (using the records of a cohort of general truck drivers) did not.[60] Two of the three studies which relied on self reports of accidents[14 61 62] found a higher rate of accidents in people with sleep apnoea.[14 61] Three studies using film or computer driving simulators found that sleep apnoea patients made significantly more errors than controls.[63-65] An association between simulator performance and accident history has been shown in some studies,[63] though others have reported that performance is related to age, education, and cognitive function rather than to markers of sleep apnoea.[68 69]

Evaluation of continuous positive airways pressure

Forty five evaluations of continuous positive airways pressure were identified, of which one was a truly randomised controlled trial[70] and five non-randomised controlled trials (table 4).[71-75] Thirty eight were simple before and after studies without any control group.[47 65 76-113] Because of not being able to attribute moderate effects to interventions without a proper comparison group the uncontrolled studies are highly unreliable.[9] Clinical outcomes used in the seven controlled studies identified were principally sleepiness, mood, psychometric performance, blood pressure, and general health.

The randomised controlled crossover trial of Engleman *et al* followed up 32 patients and was the only one to compare continuous positive airways pressure directly with a placebo.[70] The researchers found a significant improvement in the multiple sleep latency time, vigilance, and Nottingham health profile part 2 scores but no significant difference in patient preference after one month of follow up. Improved performance on a computer driving simulator after treatment was also reported. That study, however, had important weaknesses. A pill was used as the placebo, so it was impossible completely to attribute the reported difference to positive pressure ventilation. Because there was no washout between the periods there was an increased probability of carryover, so underestimating the effect. Significant differential carryover was reported for one psychological outcome. The test for differential carryover has low power, so lower than conventional significance levels should be used. No information, however, was provided about

Table 4 Controlled trials evaluating effectiveness of continuous positive airway pressure

Study	Objective and design	Sample	Outcome measures	Results	Comments
Engleman *et al* (1994), United Kingdom[70]	To evaluate effect of continuous positive airways pressure on cognitive performance, sleepiness, and mood Randomised placebo controlled crossover trial	35 consecutive obstructive sleep apnoea patients. 32 followed up Apnoea-hypopnoea index 28 Body mass index 33 Age 49	Multiple sleep latency test Symptoms Cognitive performance and memory Vigilance General health questionnaire/Nottingham health profile/hospital anxiety and depression score Verbal fluency	Mean one month of continuous positive airways pressure: Symptoms lower on continuous positive airways pressure than placebo (2.1 (SE 0.2) *v* 4.3 (0.3); P<0.001) Longer multiple sleep latency test time—7.2 (SE 0.7) *v* 6.1 (0.7) minutes for placebo (P=0.03) Improved vigilance (76 (SE 5) obstacles hit *v* 81 (6); P=0.01) Improved mean hospital anxiety and depression score but all scores within normal limits (<8). No significant difference in number of "cases" detected in each group Improved Nottingham health profile scores (4.9 (SE 0.9) *v* 7.9 (0.9); P=0.002) Patient preference difference not significant (37% *v* 63%)	Compliance average 3.4 hours/night No washout between treatment periods Results of tests for differential carryover not reported except for one variable where significant Significant learning effect on outcome tests, especially cognitive tests showing significant improvements. Other cognitive test results not stated No baseline multiple sleep latency test. Uncertain clinical significance of small difference for this and changes in Nottingham health profile and general health questionnaire scores. Nottingham health profile scores in normal range for both continuous positive airways pressure and placebo. Unclear why Nottingham health profile part 2 scores used rather than main scores
Phillips *et al* (1990), United States[71]	To compare benefits of nasal continuous positive airways pressure, nasal oxygen, and an air placebo Randomised placebo controlled crossover trial and controlled before after. Patients randomised to receive oxygen or air (placebo) in first period. Change to other gas in second period, then all received continuous positive airways pressure in third period. Measurements were made at baseline and after each period	8 men with mild obstructive sleep apnoea Apnoea index 20.5 Weight 141% of ideal Age 57 Multiple sleep latency test time (minutes) 11.9 Excluded if apnoea-hypopnoea index ⩾40	Apnoeas, hypopneas, apnoea-hypopnoea index, mean high and low arterial oxygen saturation, multiple sleep latency test, sleep "architecture," blood pressure, neuropsychological test performance	Significant reduction in apnoea-hypopnoea index with continuous positive airways pressure compared with air (19.1; 95% confidence interval 7.8 to 30.4) or baseline (17.5; 7.9 to 27.0). No significant change in mean high arterial oxygen saturation from baseline (2.0 mm Hg (0.3 kPa); 1.9 to 6.9 (0.3 to 0.9)). Little change in sleep architecture as measured, for example, by sleep efficiency (difference –0.2%; –6.3% to 5.8%). Non-significant improvement in daytime sleepiness compared with air (multiple sleep latency test difference 3.1 minutes; –2.6 to 8.8) No significant change with continuous positive airways pressure in diastolic (2 mm Hg; –6.2 to 10.0) and systolic blood pressures (8.1 mm Hg; –4.0 to 20.0) from baseline. Significant improvement in several neuropsychological variables such as attention and recall in both continuous positive airways pressure and oxygen groups	Patients and outcome assessors blind to allocation in periods 1 and 2 but not to continuous positive airways pressure in third period Repeated measures analysis used Small numbers, no washout period, no tests performed for differential carryover
Engleman *et al* (1993), United Kingdom[72]	To evaluate effect of continuous positive airways pressure on cognitive performance and sleepiness Non-randomised controlled study	21 obstructive sleep apnoea patients: Apnoea-hypopnoea index 57 Body mass index 34 Age 53 16 controls: Apnoea-hypopnoea index 49 Body mass index 32 Age 53 Multiple sleep latency test time longer in controls	Multiple sleep latency test Psychometric tests Hospital anxiety and depression score	Mean 6 months of continuous positive airways pressure (compliance average 5.9 hours/night): Both control and continuous positive airways pressure groups had significant improvement in all psychometric values with no significant difference between groups 2.1 minute increase in multiple sleep latency test time from baseline in continuous positive airways pressure group and 1.2 minute decrease in controls (P<0.02)	Both groups gained weight Baseline multiple sleep latency test result significantly different between continuous positive airways pressure and control groups (P=0.01)
Deriderian *et al* (1988), United States[73]	To assess mood changes in obstructive sleep apnoea patients after continuous positive airways pressure Non-randomised controlled trial	7 men with obstructive sleep apnoea: Apnoea index 41 Weight 120% of ideal Age 59 Controls—7 men: "Similar" apnoea index scores No alcohol, drugs, or tobacco during study	Profile of mood states	"At least 2 months' treatment" Significant improvement with continuous positive airways pressure in depression (-1.9; 95% confidence interval –2.7 to –1.1) and fatigue (–4.0; –7.8 to –0.2) scores but not in controls. No significant difference in 4 other scores: tension/anxiety (–1.1; –2.9 to 0.7), anger/hostility (–1.6; –4.0 to 0.75), vigour/activity (0.3; –2.1 to 2.7), confusion (–0.4; –1.4 to 0.6)	Compliance not measured Small sample; military hospital Baseline differences between control and intervention groups Change in 4/6 scores not reported for control group Uncertain validity of profile of mood status
Rauscher *et al* (1993), Austria[74]	To compare effect of continuous positive airways pressure and weight loss on blood pressure in hypertensive patients with obstructive sleep apnoea Non-randomised controlled trial	73 consecutive obstructive sleep apnoea patients on antihypertensive treatment: Apnoea-hypopnoea index 43 Body mass index 33 Age 54 39 continuous positive airways pressure; 34 weight loss; analysis for 33 continuous positive airways pressure, 27 weight loss Non-random allocation	Blood pressure or surrogate marker for change, reduction, or omission of antihypertensive treatment Weight	Mean 512 days of continuous positive airways pressure (compliance taken as 4 or more hours/night). 4 patients excluded as poor compliers Multivariate analysis showed hypertension dependent only on body mass index for study group as whole and for both treatment groups (P<0.005)	9 patients excluded because of change in blood pressure treatment during study period, so 13 patients excluded from analysis (6 continuous positive airways pressure, 7 weight loss)

(continued on p 856)

Table 4 Controlled trials evaluating effectiveness of continuous positive airway pressure *(continued from p 855)*

Study	Objective and design	Sample	Outcome measures	Results	Comments
Smith and Shneerson (1995), United Kingdom[75]	To assess sensitivity of the SF-36 to sleep disruption Quasiexperimental study (non-randomised control)	223 subjects investigated for snoring or daytime somnolence, or both 139 simple snorers: Age 49.7; M:F 4:1 Desaturation index 1.4 Epworth sleepiness score 9.0 25 mild obstructive sleep apnoea patients (desaturation index 5-20): Age 53.5; M:F 4.1 Desaturation index 38 Epworth sleepiness score 8.8 43 obstructive sleep apnoea patients requiring treatment (desaturation index ⩾20): Age 55.6; M:F 6:1 Desaturation index 19 Epworth sleepiness score 15 16 known obstructive sleep apnoea patients having received continuous positive airways pressure for at least 6 months: Age 53.1; M:F 15:1 Desaturation index 1.8 Epworth sleepiness score 8.0	SF-36 Epworth sleepiness score at baseline and 6 month follow up	Baseline SF-36 scores significantly different from population norms for those requiring treatment, those with mild obstructive sleep apnoea, and even those with simple snoring Patients previously started on continuous positive airways pressure not significantly different from general population At six months scores of groups with simple snorers and mild obstructive sleep apnoea not significantly different from baseline Subjects with obstructive sleep apnoea newly on continuous positive airways pressure scored significantly higher on all SF-36 dimensions at 6 months, and vitality not significantly different from population norms. Subjects used continuous positive airways pressure for average of 5.3 hours/night Epworth sleepiness score also significantly improved No change in weight, employment status, or symptoms	No details in other confounders such as smoking Controls not equivalent at baseline

the critical significance values used in the tests of differential carryover for the other variables. Differential carryover can bias the results, and in the one variable for which it was reported an analysis of the first period as a parallel trial showed no significant difference between the groups. Another randomised crossover trial was found, but only an oxygen intervention was directly compared with a placebo (air).[71] In the third period of the study all patients received continuous positive airways pressure. We therefore categorised it as a non-randomised controlled trial.

All trials which reported changes in sleepiness found that the multiple sleep latency time[114] increased in the treated group compared with controls[70-72 74] by around one minute in the randomised controlled trial, to up to seven minutes.[74] Other measures of daytime sleepiness also improved in the treated arm.[71 75] Some studies also found improvement in psychological outcomes such as the hospital anxiety and depression scale,[70] attention and recall,[71] and general health as measured by the Nottingham health profile part 2[70] or SF-36 score.[75] Only one study found no difference in psychometric performance between the continuous positive airways pressure and comparison groups.[72] The two studies which examined blood pressure found no effect of continuous positive airways pressure compared with either a weight loss[74] or oxygen control group.[71] Though these studies were often poorly designed and the continuous positive airways pressure and control groups often not comparable at baseline, they strongly suggest that continuous positive airways pressure may be effective in reducing sleepiness. This is supported by "switch back" studies, which show a resumption of symptoms on removing continuous positive airways pressure.[104 111]

Compliance has been studied extensively.[105-128] Between 50% and 81% of patients accepted continuous positive airways pressure machines, which were switched on for 3.7-6.0 of the 24 hours[115-129] and used at a "therapeutic pressure" for between 3.4 and 4.5 hours a night.[121 123 124]

Discussion

This systematic review indicates that the evidence for a causal association between sleep apnoea and a range of poor health outcomes is generally weak, with the exception of daytime sleepiness and possibly vehicle accidents, for which the evidence is more convincing. Obstructive sleep apnoea is closely associated with obesity[130 131] and aging.[132] This raises the question of the extent to which sleep apnoea is a separate disease entity or a marker or a symptom of obesity and aging. A major difficulty in investigating the independent health effects of sleep apnoea is in adjusting out the effect of confounding factors. Many epidemiological studies found no association between sleep apnoea and cardiovascular morbidity after adjustment for age and obesity.

Prospective cohort studies which adequately adjust for the effects of confounding factors are the most reliable design for investigating these links.[9] The association between sleep apnoea and morbidity found in some retrospective studies may be an artefact of other, coexisting medical conditions or may be explained by sleep apnoea resulting from rather than causing the disease under study. Similar conclusions were arrived at in a review of the relation between snoring and vascular disease.[133] Uncontrolled studies of continuous positive airways pressure are also unreliable.[9] For example, some patients with sleep apnoea reported improved subjective assessments and increased multiple sleep latency times without any intervention[134] and others showed reduced blood pressure with placebo.[135] Weight loss has also been shown

to lead to significant improvements in symptoms.[136] Only comparison with an appropriate (preferably randomised) control group can eliminate these sources of bias.

The quality of the controlled trials was poor. In particular, we cannot be confident that the control groups were sufficiently comparable to eliminate bias, and none included an adequate placebo. A reliable estimate of the true size of any treatment effect of continuous positive airways pressure is likely to be obtained only if the control group receives a placebo which adequately controls for any effect on sleep or breathing patterns, or both, which can occur when appliances are used during sleep.[71 137] The feasibility of using continuous positive airways pressure machines set at a low, non-therapeutic pressure as a comparable placebo has been shown.[138] The results from these experimental studies do not therefore provide sufficiently robust evidence for the effectiveness of continuous positive airways pressure. The poor standard of evaluative research in sleep apnoea has also been commented on in other reviews, which have examined orthodontic[139] and surgical[140] interventions.

Daytime tiredness and reduced attention

Anecdotal evidence from clinicians suggests that some patients obtain dramatic benefit from treatment. There are several examples in the history of medicine, however, in which health care interventions, when rigorously evaluated in randomised controlled trials, have been shown to be less effective than anticipated.[141 142]

The evidence from epidemiological studies suggests that possibly the only significant adverse effect of obstructive sleep apnoea is daytime tiredness and a reduction in attention. Almost all the intervention studies showed some improvement in measures of sleepiness, though the multiple sleep latency test measures the tendency to fall asleep rather than the ability to stay awake, and other measures may be more appropriate.[143] Probably the large benefits claimed by some observers are confined to the minority of patients with very severe sleep apnoea who also display obvious symptoms of profound daytime sleepiness. However, these benefits are unlikely to be generalisable to those with less severe sleep apnoea.

High quality research on sleep apnoea in general and continuous positive airways pressure in particular is needed, not in order to deny the validity of clinically apparent benefits in profoundly apnoeic patients but in order to determine which subgroups of patients may derive benefit, how much benefit, at what cost, and how these patients can be identified simply. The results are sufficiently suggestive, however, to justify conducting well designed, large scale, randomised controlled trials to assess objectively the effectiveness and cost effectiveness of treatment with continuous positive airways pressure relative to a suitable placebo. Because obesity is a cause of sleep apnoea and an important determinant of several purported negative effects of sleep apnoea, greater emphasis should be placed on evaluating the impact of effective programmes of weight loss instead of or as adjuncts to more invasive approaches discussed above. It is also important that other treatments for sleep apnoea (such as surgery[140] and dental orthoses[144]) which are rapidly diffusing are evaluated as part of the same research programme so that unified multidisciplinary guidelines can be established. Patients' needs can then be assessed accurately and managed scientifically rather than according to the vagaries of the referral system and the particular enthusiasms of the clinician the patients consult. Calls for widespread investment in health service provision in this topic may be premature until this research has been carried out.

Key messages

- Obstructive sleep apnoea is claimed to be an important cause of premature death and disability
- There is increasing pressure to provide sleep services for the treatment of patients with sleep apnoea
- Epidemiological evidence suggests that sleep apnoea causes daytime sleepiness and possibly vehicle accidents
- Evidence for a causal association between sleep apnoea and other adverse health outcomes is weak
- There is a paucity of robust evidence for the clinical and cost effectiveness of continuous positive airways pressure in the treatment of most patients with sleep apnoea

Tables A-C may be obtained by writing direct to JW and are also available on the *BMJ*'s home page (www.bmj.com). We thank the four anonymous referees for helpful comments, Diedre Fullerton for help in data abstraction, Olwen Jones for support in literature searching and document acquisition, and Paula Press and Sally Baker for secretarial work.

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Appendix

Search terms

In the Medline search the following terms were used to retrieve items on (*a*) sleep apnoea and continuous positive airways pressure and (*b*) sleep apnoea and its health effects and epidemiology.

Thesaurus terms (medical subject headings; MeSH)
Sleep apnoea syndromes (exploded)
Positive-pressure respiration (exploded)
Mortality
Morbidity (exploded)
Hypertension (exploded)
Cerebrovascular disorders (exploded)
Accidents, traffic (exploded)
Automobile driving
Myocardial infarction (exploded)
Arrhythmia (exploded)
Heart failure, congestive (exploded)
Coronary disease (exploded)
Myocardial ischemia
Anoxemia

Text words
Apn?ea
Obstructive sleep apn?ea
Hypopn?ea
SAHS [sleep apnoea hypopnoea syndrome]
OSA [obstructive sleep apnoea]
Continuous positive airways pressure
CPAP [continuous positive airways pressure]

High blood pressure
Stroke
Coronary thrombosis
Coronary artery disease
Isch?emic heart disease
Daytime sleepiness
Hypersomnolence
Hypox?emia
Heart attack
Falling asleep at the wheel

The Medline thesaurus terms were translated across into the equivalent Embase thesaurus terms for searching on Embase.

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Snoring and breathing pauses during sleep: telephone interview survey of a United Kingdom population sample

Maurice M Ohayon, Christian Guilleminault, Robert G Priest, Malijai Caulet

See editorial by Fleetham and p 851

Centre de Recherche Philippe Pinel de Montreal, Montreal, Quebec H1C 1H1, Canada
Maurice M Ohayon, *director*
Malijai Caulet, *scientist*
Stanford University School of Medicine, Sleep Disorders Clinic and Research Centre, Stanford, California, USA
Christian Guilleminault, *professor*
University of London, Imperial College School of Medicine at St Mary's, Paterson Centre, London W2 1PD
Robert G Priest, *head, academic department of psychiatry*
Correspondence and reprint requests to: Dr Ohayon.

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Abstract

Objectives: To determine the prevalence of snoring, breathing pauses during sleep, and obstructive sleep apnoea syndrome and determine the relation between these events and sociodemographic variables, other health problems, driving accidents, and consumption of healthcare resources.
Design: Telephone interview survey directed by a previously validated computerised system (Sleep-Eval).
Setting: United Kingdom.
Subjects: 2894 women and 2078 men aged 15-100 years who formed a representative sample of the non-institutionalised population.
Main outcome measures: Interview responses.
Results: Forty per cent of the population reported snoring regularly and 3.8% reported breathing pauses during sleep. Regular snoring was significantly associated with male sex, age 25 or more, obesity, daytime sleepiness or naps, night time awakenings, consuming large amounts of caffeine, and smoking. Breathing pauses during sleep were significantly associated with obstructive airways or thyroid disease, male sex, age 35-44 years, consumption of anxiety reducing drugs, complaints of non-restorative sleep, and consultation with a doctor in the past year. The two breathing symptoms were also significantly associated with drowsiness while driving. Based on minimal criteria of the International Classification of Sleep Disorders (1990), 1.9% of the sample had obstructive sleep apnoea syndrome. In the 35-64 year age group 1.5% of women (95% confidence interval 0.8% to 2.2%) and 3.5% of men (2.4% to 4.6%) had obstructive sleep apnoea syndrome.
Conclusions: Disordered breathing during sleep is widely underdiagnosed in the United Kingdom. The condition is linked to increased use of medical resources and a greater risk of daytime sleepiness, which augments the risk of accidents. Doctors should ask patients and bed partners regularly about snoring and breathing pauses during sleep.

Introduction

There have been several epidemiological studies of snoring but none has been conducted on a large representative sample of a major European population. Such investigations are of interest, as regular, heavy snoring is the most noticeable feature associated with disordered breathing during sleep and there is a known association with hypertension, cerebrovascular accidents, and coronary artery disease.[1-6] We report a telephone questionnaire survey in 1994 to determine the prevalence of snoring and breathing pauses during sleep in a representative sample of the United Kingdom population.

Subjects and methods

The target population was all non-institutionalised residents of the United Kingdom aged 15 or over (roughly 45 709 600 people). A representative sample was obtained by a stratified probabilistic approach using 1991 census data to determine distribution among the 11 areas of the United Kingdom and the Kish selection method[7] used to elect the person to be interviewed within each targeted household. One of eight different selection tables was randomly assigned to a household before the number was called. Based on the number of people in the household and their sex and age, the table indicated which member should be interviewed. Subjects who did not speak English, who had impaired hearing or a speech impediment, or who were too ill to be interviewed were excluded. Interviews were completed with 4972 subjects (79.6% of those

Table 1 Prevalence of snoring and breathing pauses by sex and age group. Figures are weighted percentages of subjects (95% confidence interval)

	Age group (years)						
	15-24 (n=859)	25-34 (n=935)	35-44 (n=855)	45-54 (n=711)	55-64 (n=631)	≥65 (n=980)	Total (n=4972)
Snoring:							
Total	23.1 (20.3 to 25.9)	38.1 (35.0 to 41.2)	45.8 (42.5 to 49.1)	53.5 (49.8 to 57.2)	49.3 (45.4 to 53.2)	37.3 (34.3 to 40.3)	40.3 (38.1 to 41.7)
Men	26.1 (22.0 to 30.2)*	44.9 (40.4 to 49.4)**	55.0 (50.3 to 59.7)***	62.0 (57.0 to 67.0)***	56.5 (51.0 to 62.0)**	46.8 (41.9 to 51.7)***	47.7 (45.7 to 49.7***
Women	20.2 (16.4 to 24.0)	31.5 (27.3 to 35.7)	36.8 (32.2 to 41.4)	45.1 (39.9 to 50.3)	42.4 (37.0 to 47.8)	30.9 (27.2 to 34.6)	33.6 (31.8 to 35.4)
Breathing pauses:							
Total	2.5 (1.5 to 3.5)	2.7 (1.7 to 3.7)	4.8 (3.4 to 6.2)	4.6 (3.1 to 6.1)	5.1 (3.4 to 6.8)	3.9 (2.7 to 5.1)	3.8 (3.3 to 4.3)
Men	1.9 (0.6 to 3.2)	5.1 (3.1 to 7.1)***	6.8 (4.4 to 9.2)**	6.1 (3.6 to 8.6)*	7.1 (4.2 to 10.0)*	6.1 (3.7 to 8.5)**	5.4 (4.5 to 6.3)***
Women	3.1 (1.5 to 4.7)	0.4 (0.0 to 1.0)	2.8 (1.2 to 4.4)	3 (1.2 to 4.8)	3.3 (1.4 to 5.2)	2.3 (1.1 to 3.5)	2.4 (1.8 to 3.0)

*P<0.05. **P<0.01. ***P<0.001.

approached). The highest rate of completed interviews was in Northern Ireland (86.8%) and the lowest rate in East Midlands (78.2%; $\chi^2 = 4.019$, $P < 0.05$).

Interviews were conducted by BPS Teleperformance, Birmingham, which specialises in large telephone surveys. Interviews were directed by the Sleep-Eval knowledge based system,[8 9] a computer program designed to provide homogeneous and standardised evaluations. The system is a previously validated, non-monotonic level 2 expert system with a causal reasoning mode.[10 11] The program selects the questions and displays them on a monitor. The interviewer reads each question to the subject, then enters his or her response. Expected responses vary with the questions, from a simple "yes" or "no" or "present," "absent," or "unknown" to answers on a five point scale or requiring use of the keyboard by the interviewer—for example, to record name and duration of illness.

The system is based on a logical reasoning module that poses questions in a manner adapted to the specific individual. Sleep-Eval pre-emptively eliminates irrelevant questions based on prior responses. For example, a subject who is completely satisfied with his or her quality of sleep will not be asked about the impact of sleep related problems.

Statistical analysis

Data from the 1991 census pertaining to the non-institutionalised population aged 15 or over were used as the standard population. The weighting procedure was adjusted for sample design and took into account the geographic distribution of the sample. The unweighted sample comprised 2894 women and 2078 men ranging from 15 to 100 years of age. After weighting, the sample consisted of 52.3% women and 47.7% men.

These calculations were performed for all variables and the results presented as weighted percentages. 95% Confidence intervals were also calculated. Univariate analyses (by χ^2 tests) and multivariate analyses were performed with SPSS statistical software. Colinearity problems between variables (that is, information redundancy) were checked. The method of INDICATOR contrasts[12] was used to determine which categories of the independent variables were significantly associated with the presence of snoring and breathing pauses during sleep. Odds ratios were calculated according to the different categories with the cut off point for significance set at 5%.

The International Classification of Sleep Disorders (1990)[13] provided the criteria for identifying sleep disorders.

Results

A total of 40.3% of the population (2004 subjects) reported snoring regularly, men more often than women, the prevalence of snoring increasing with age up to 55. Breathing pauses during sleep were reported by 3.8% of the sample (190 subjects) and also increased with age (table 1). The association of both snoring and breathing pauses was reported by 2.5% of the sample (124 subjects). A total of 7.8% of the population (386 subjects) did not know whether they snored or had breathing pauses during sleep.

Regression analysis (table 2) indicated that snoring was significantly associated with being an obese (body mass index (kg/m^2) ≥30) married man aged 25 or more. Snoring was also significantly associated with daytime sleepiness, napping, night time awakenings, high caffeine intake (≥6 cups of tea or coffee daily), and smoking.

Breathing pauses were significantly associated with being a 35-44 year old man taking anxiolytics, who had been diagnosed with obstructive airways or thyroid disease, and who had consulted a doctor at least once during the past year. Table 3 gives the odds ratios. When snoring and breathing pauses during sleep were reported together there was a significant association with being an obese (body mass index ≥30; odds ratio 2.9 (95% confidence interval 2.3 to 3.5)) man (odds ratio 4.4 (3.9 to 4.8)) with leg pain (3.1 (2.5 to 3.8)), difficulty maintaining sleep (2.9 (2.4 to 3.4)), and usually not sleeping fully supine (4.4 (3.1 to 5.6)). The model also identified as significant variables urinary problems (3.9 (2.9 to 4.8)), high blood pressure (2.5 (1.8 to 3.1)), daytime sleepiness (2.3 (1.9 to 2.7)), and daily intake of more than six cups of caffeinated beverages (1.8 (1.2 to 2.4)).

A nationwide survey with such a large sample is based on interview responses. To evaluate further the responses to the questions we used the criteria (A + B + C) outlined in the International Classification of Sleep Disorders to define diagnoses of obstructive sleep apnoea syndrome and investigate the independent variables associated with this diagnosis. As above, the logistic regression model indicated a significant association with being an obese (body mass index ≥30; odds ratio 2.0 (95% confidence interval 1.4 to 2.5)) man (3.8 (3.3 to 4.2)) with difficulty maintaining sleep (4.0 (3.5 to 4.5)), daytime sleepiness (3.8 (3.3 to 4.2)), high blood pressure (2.8 (2.2 to 3.5)), presence of leg pain (2.7 (2.1 to 3.3)), and non-restorative sleep (1.9 (1.4 to 2.3)). Despite the frequency of sleep related complaints among subjects with snoring and breathing

Table 2 Factors associated with snoring—logistic regression models

Variable	Regression coefficient	Wald	Correlation coefficient	Odds ratio (95% confidence interval)	P value
Men	0.639	93.615	0.120	1.9 (1.8 to 2.0)	0.0000
Age (years):					
25-34	0.360	6.957	0.028	1.4 (1.2 to 1.7)	0.0083
35-44	0.579	15.900	0.047	1.8 (1.5 to 2.1)	0.0001
45-54	0.842	31.915	0.069	2.3 (2.0 to 2.6)	0.0000
55-64	0.764	24.752	0.060	2.1 (1.8 to 2.4)	0.0000
≥65	0.393	6.567	0.027	1.5 (1.2 to 1.8)	0.0104
Medical consultations	0.254	11.230	0.038	1.3 (1.1 to 1.4)	0.0008
Body mass index (kg/m^2) ≥30	0.664	34.106	0.071	1.9 (1.7 to 2.2)	0.0000
Marital status:					
Married	0.654	53.636	0.090	1.9 (1.7 to 2.1)	0.0000
Separated or divorced	0.233	2.870	0.012	1.3 (1.0 to 1.5)	0.0902
Widowed	0.140	1.116	0.000	1.1 (0.9 to 1.4)	0.2907
Sleep duration:					
Too short	0.433	4.598	0.020	1.5 (1.1 to 1.9)	0.0320
Appropriate	0.451	5.438	0.023	1.6 (1.2 to 1.9)	0.0197
Daytime sleepiness	0.171	4.276	0.019	1.2 (1.0 to 1.3)	0.0387
Napping:					
Sometimes	0.226	5.106	0.022	1.3 (1.1 to 1.5)	0.0238
At least twice a week	0.160	2.712	0.011	1.2 (1.0 to 1.4)	0.0996
Nightmares:					
One a month	0.051	0.393	0.000	1.1 (0.9 to 1.2)	0.5305
More than one a month	0.317	5.854	0.025	1.4 (1.1 to 1.6)	0.0155
Daily coffee consumption:					
1 or 2 cups	0.100	1.444	0.000	1.1 (0.9 to 1.3)	0.2295
3 to 5 cups	0.144	2.929	0.012	1.2 (1.0 to 1.3)	0.0870
≥6 cups	0.333	9.607	0.035	1.4 (1.2 to 1.6)	0.0019
Daily cigarette consumption:					
≤20	0.289	12.968	0.042	1.3 (1.2 to 1.5)	0.0003
21 to 35	0.522	5.953	0.025	1.7 (1.3 to 2.1)	0.0147
>35	0.316	0.599	0.000	1.4 (0.6 to 2.2)	0.4391
Frequency of night time awakenings:					
Once a week	0.110	1.154	0.000	1.1 (0.9 to 1.3)	0.2828
More than once a week	0.282	12.844	0.041	1.3 (1.2 to 1.5)	0.0003

Reference categories: Female; age 15-24 years; no medical consultation; body mass index ≤30; single; too long sleep duration; no daytime sleepiness; no napping; never nightmares; no coffee; no smoking; night time awakenings never or less than once a week.

Table 3 Factors associated with breathing pauses—logistic regression models

Variable	Regression coefficient	Wald	Correlation coefficient	Odds ratio (95% confidence interval)	P value
Men	1.062	15.272	0.147	2.9 (2.4 to 3.4)	0.0001
Age (years):					
25-34	–0.502	0.656	0.000	0.6 (–0.6 to 1.8)	0.4180
35-44	1.042	4.293	0.061	2.8 (1.8 to 3.8)	0.0383
45-54	0.196	0.110	0.000	1.2 (0.1 to 2.4)	0.7403
55-64	0.461	0.661	0.000	1.6 (0.5 to 2.7)	0.4163
≥65	0.494	0.834	0.000	1.6 (0.6 to 2.7)	0.3611
Obstructive airways diseases	2.509	40.901	0.252	12.3 (11.5 to 13.1)	0.0000
Medical consultations	0.774	5.082	0.071	2.2 (1.5 to 2.8)	0.0242
Anxiety reducing drugs	1.124	3.097	0.042	3.1 (1.8 to 4.3)	0.0785
Thyroid disease	2.074	6.583	0.087	8.0 (6.4 to 9.5)	0.0103
Non-restorative sleep	1.033	11.103	0.122	2.8 (2.2 to 3.4)	0.0009

Reference categories: Female; age 15-24 years; no obstructive airways disease; no medical consultation; no anxiety reducing drugs; no thyroid disease; restorative sleep.

pauses only 18.2% (n = 31) of the subjects with breathing pauses and 9.2% of the snorers (n = 185) believed they had a sleep problem.

Our survey allowed us to evaluate the association between reports of snoring and breathing pauses and three different major healthcare related problems.

Driving accidents—In our representative sample 5.3% of drivers had an accident during the preceding year. However, there was no significant difference between snorers (4.6%), subjects with breathing pauses (6.1%), and other subjects (5.9%). Reports of falling asleep at the wheel, however, were significantly more frequent in subjects who reported breathing pauses (6.2%) and regular snoring (4.3%) than in other subjects (2.4%; $\chi^2 = 8.593$, $P < 0.05$).

Healthcare resource consumption—The percentage of snorers who had consulted a doctor at least once in the past 12 months did not differ significantly from that of non-snorers (62.2% *v* 60.2%). However, there was a significant difference between subjects with breathing pauses and those without (81.0% *v* 60.8%; $\chi^2 = 12.385$, $P < 0.001$). Also health resource consumption was significantly higher in subjects reporting breathing pauses during sleep. Thirty one per cent of subjects reporting breathing pauses had sought medical help six times or more in the past 12 months compared with only 12.0% of regular snorers and 11.9% of non-snorers ($\chi^2 = 27.013$; $P < 0.001$). Numbers of admissions to hospital reported by 11.0% of the sample disclosed a trend only in respect of the small number of subjects with breathing pauses during sleep. Admissions were reported by 11.4% of snorers and 18.8% of subjects with breathing pauses during sleep.

Treatment for physical illness not linked by doctor to sleep related problem—At the time of interview 15.5% of subjects were being treated for a physical illness. The rate was significantly higher in subjects reporting breathing pauses during sleep (39.8%) than in snorers (16.9%) and other subjects (14.0%; $\chi^2 = 30.384$, $P < 0.001$). Treated or untreated hypertension was also significantly more frequently reported by subjects with breathing pauses during sleep (13.8%) than by snorers (8.6%) and other subjects (5.6%; $\chi^2 = 21.504$, $P < 0.005$).

Prevalence of obstructive sleep apnoea syndrome

Based on International Classification of Sleep Disorders criteria, which included daytime sleepiness, the prevalence of obstructive sleep apnoea syndrome in the sample (criteria A + B + C) was 1.9%. The prevalence of obstructive sleep apnoea syndrome in subjects aged 35-64 years was 1.5% in women (95% confidence interval 0.8% to 2.2%) and 3.5% in men (2.4% to 4.6%).

Discussion

Though there have been other studies of snoring and sleep apnoea syndrome in the United Kingdom,[14-16] so far as we know this is the first study with such a large representative sample of the general population. Some findings were expected, based on our knowledge of the pathophysiology of obstructive sleep apnoea—for example, the association between obesity or thyroid disease and breathing pauses during sleep. That obesity is a significant risk factor is not surprising given the extensive published data, and there is enough evidence to show that disordered breathing during sleep is an independent risk factor for hypertension.[17] This survey re-emphasises the common association between disordered breathing during sleep and reports of disrupted nocturnal sleep, non-restorative sleep, daytime sleepiness, greater intake of caffeinated beverages, and drowsiness while driving.

A surprising finding was that the sleep disorder was as often labelled "daytime sleepiness" as "insomnia." A diagnosis of insomnia may preclude recognition of the

sleep related breathing problem and explain our finding that breathing pauses during sleep were significantly associated with anxiolytic drugs, which would be contraindicated for patients with breathing problems during sleep. The association between sleep bruxism and disordered breathing during sleep included in the logistic regression is supported by clinical observation and seems to be related to the disproportionate maxillomandibular anatomy presented by obstructive sleep apnoea patients, particularly those with family histories.[18] The prevalence of obstructive sleep apnoea syndrome in our sample was much higher than the prevalence (0.3%; 95% confidence interval 0.07% to 0.9%) reported in men aged 35-65 from a survey in 1990 in Wheatley, near Oxford.[19] This can be explained by the criteria used at that time, which probably identified only a severely affected population. Our results are very similar to those of Young *et al* in the United States (who found a prevalence of 2% in women and 4% in men)[20] and Gislason *et al* in Iceland.[21] Our study indicates that obstructive sleep apnoea syndrome is still widely unrecognised in the British Isles. It also suggests that consumption of healthcare resources may be higher in this specific population, raising the question of the cause of this higher consumption.

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Conflict of interest: None.

Key messages

- Disordered breathing during sleep is related to several health problems and may have important daytime repercussions
- The prevalence of disordered breathing during sleep has not been well known in the United Kingdom until now
- Middle aged men are at higher risk of reporting snoring, breathing pauses during sleep, or obstructive apnoea syndrome
- Daytime sleepiness, poor sleep, obesity, and the use of healthcare resources are highly correlated with disordered breathing during sleep
- Obstructive sleep apnoea syndrome is widely unrecognised, and consumption of healthcare resources is higher in this specific population, raising the question of the cause of this higher consumption

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ANY QUESTIONS

What is the maximum frequency of blood donation and how has it been decided on? Is there any scientific evidence behind prohibiting activities such as swimming in the day or two following blood donation? On a recent visit to the local blood donor centre I was told not to take off the plaster occluding my venepuncture site for 24 hours "to prevent infection." Is there any evidence for this?

The UK *Guidelines for the Blood Transfusion Service* state that an absolute minimum interval of 12 weeks should be left between donations of whole blood, while also stating that "usually" only two donations should be given in a 12 month period. The risk to the donor of frequent donation is that of iron deficiency, and clearly it is impossible to define a minimum interval that will be equally appropriate to all donors (some other countries bleed donors as frequently as every eight weeks, sometimes with the help of iron supplements). It is also important to take into account the level of haemoglobins considered necessary for blood donation (currently 135 g/l for men and 125 g/l for women) are recommended in the United Kingdom. The arguments have been well rehearsed, and the current United Kingdom recommendations are produced for the United Kingdom transfusion services by the standing advisory committee on donor medical care and selection policies.

Blood donors are usually advised not to undertake in the 24 hours or so after donation any activity which might put them at risk if they should faint.[1] Such so called delayed faints are relatively uncommon, but are quite unpredictable and occur even in experienced regular donors. A full whole blood donation amounts to 10-13% of total blood volume, depending on body weight, a volume loss which should not be regarded as trivial.

My understanding of the use of a plaster to cover the site of venepuncture is that it might help prevent bleeding. I am not aware of any evidence that it could also prevent infection, but full marks to the donor attendant for coming up with an explanation that was at least plausible.

J Gillon, *consultant physician, Edinburgh and South East Scotland Blood Transfusion Service*

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Effectiveness of the public health policy for breast cancer screening in Finland: population based cohort study

Matti Hakama, Eero Pukkala, Minna Heikkilä, Mervi Kallio

University of Tampere, School of Public Health, Box 607, FIN-33101 Tampere, Finland
Matti Hakama, *professor of epidemiology*
Finnish Cancer Registry, Liisankatu 21B, FIN-00170 Helsinki
Eero Pukkala, *research scientist*
Minna Heikkilä, *research assistant*
Mervi Kallio *research scientist*
Correspondence to: Dr Hakama.

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Abstract

Objective: To evaluate the effectiveness of screening for breast cancer as a public health policy.
Design: Follow up in 1987-92 of Finnish women invited to join the screening programme in 1987-9 and of the control women (balanced by age and matched by municipality of residence), who were not invited to the service screening.
Setting: Finland.
Subjects: Of the Finnish women born in 1927-39, 89 893 women invited for screening and 68 862 controls were followed; 1584 breast cancers were diagnosed.
Main outcome measures: Rate ratio of deaths from breast cancer among the women invited for screening to deaths among those not invited.
Results: There were 385 deaths from breast cancer, of which 127 were among the 1584 incident cases in 1987-92. The rate ratio of death was 0.76 (95% confidence interval 0.53 to 1.09). The effect was larger and significant (0.56; 0.33 to 0.95) among women aged under 56 years at entry. 20 cancers were prevented (one death prevented per 10 000 screens).
Conclusions: A breast screening programme can achieve a similar effect on mortality as achieved by the trials for breast cancer screening. However, it may be difficult to justify a screening programme as a public health policy on the basis of the mortality reduction only. Whether to run a screening programme as a public health policy also depends on its effects on the quality of life of the target population and what the resources would be used for if screening was not done. Given all the different dimensions in the effect, mammography based breast screening is probably justifiable as a public health policy.

Introduction

The first randomised, population based trial on breast cancer screening based on mammography was in the 1960s.[1] This study showed that about one in three deaths from breast cancer can be prevented if women are screened. Later, similar results from Sweden[2 3] and the Netherlands[4 5] were published. Mammography based screening became widespread, and in several countries it has been part of a public health policy or organised screening programme. Nowhere has a screening programme been reported to result in reduction of breast cancer mortality—a reduction in mortality is the goal of any cancer screening programme. Finland was the first country with a nationwide screening programme. We report here its effectiveness.

Subjects and methods

In Finland, nationwide population based breast cancer screening was introduced in 1987. Women in birth cohorts recommended by the National Board of Health are individually identified and invited for screening. The programme covers women aged 50-59 years and can be continued up to age 64. Women are screened every two years.

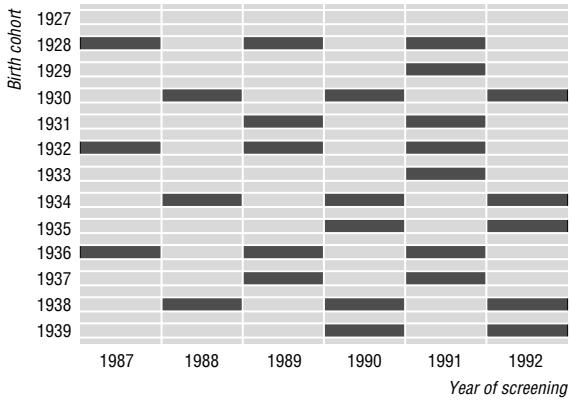

Fig 1 Finnish National Board of Health's recommendation for screening rounds in organised screening programme for breast cancer, by birth cohort and calendar year

The Cancer Society of Finland (and its regional member societies) established 11 mammography screening centres. Local municipalities (which in Finland are responsible for the public health services) were entitled to make an agreement with one of these screening centres. The programme organised by the cancer society covered two thirds of the 460 Finnish municipalities during the first years of the nationwide screening programme. In 1987, 84% of the municipalities with agreements with the cancer society followed the guidelines of the National Board of Health. The programme was introduced gradually with cohorts born in even years; the women born in odd years were controls during the first years of the programme (fig 1).

Each woman in the cohorts selected by the municipal council receives a letter with a personal appointment as well as details of the screening procedure. Every participant receives a letter notifying her whether the screen was positive or negative. The women with a positive result are given an appointment time for confirmation of the diagnosis. No reminders are sent to women who do not attend for screening. Two view mammography is used. Two radiologists interpret the mammograms, of whom one carries out further examinations in women with positive screen results.

A centralised mass screening registry for identification, invitation, and follow up of the women is part of the Finnish Cancer Registry, which operates nationwide and is population based. The National Population Registry, national registration of deaths, and cancer registrations are linked with the screening results by the mass screening registry.

Table 1 Numbers of women by screening status and year of birth during breast cancer screening programme in Finland, 1987-9

	Women invited for screening		
Year of birth*	Screened	Not screened	Controls
1927	1 341	250	12 812
1928	12 770	2 442	0
1929	3 029	524	13 332
1930	11 370	1 607	0
1932	10 536	1 805	0
1933	2 444	415	11 297
1934	9 837	1 176	0
1935	5 306	1 034	13 011
1938	13 924	2 017	0
1939	5 796	2 234	18 410
Total	76 389	13 504	68 862

*Women born in 1931 and 1937 were excluded from the analysis (see methods).

We studied women born in 1927-39 living in the municipalities who were screened by the Cancer Society of Finland. We classified women invited in 1987-9 as either "screened" or "not screened" (those who did not attend for screening). The controls were women in the same municipalities as those screened, born in 1927, 1929, 1933, 1935, or 1939 (fig 1). The women born in 1931 and 1937 were recommended to be screened for the first time in 1989. As they potentially provided few person years and with short follow up, we excluded them from the present analyses. We also excluded women born in 1936 to achieve a balance in age between cases and controls. We identified, by linkage to the Finnish Cancer Registry, breast cancer cases diagnosed at screening, interval cancers, cancers diagnosed among the women invited but not screened, cancers diagnosed in the control cohorts, and deaths from breast cancer. The follow up was extended to the end of 1992.

We evaluated the effect of screening in terms of standardised mortality ratios among the women invited for screening compared with those in the controls, and we called the ratio of these two ratios the rate ratio. The comparison rates for the standardised mortality ratios were those for the whole of Finland during the total period of follow up. The mortality due to breast cancer was estimated by including and by excluding the cases of breast cancer diagnosed before the first screening round ("total" mortality and "refined" mortality respectively). The person years were estimated from the month of screening for those screened. For the controls and for women invited but not screened, the start of follow up was defined as the mean date of screening in the municipality in that year. The end of follow up was 31 December 1992, date of death, or date of migration to a foreign country, whichever occurred first. If a control was invited in 1987-9 to be screened she was moved from the control group to the group of invited women, and the woman years were distributed to the control group or the "invited" group according to the time of screening. Such invitations took place only if the woman's municipality of residence did not comply with the general recommendations.

Table 2 Numbers (percentages) of new cases of and deaths from breast cancer in 1987-92

	Women invited for screening			
	Screened	Not screened	Controls	Total
Women	76 389 (48)	13 504 (9)	68 862 (43)	158 755 (100)
Woman years	349 679 (50)	51 125 (7)	299 228 (43)	700 032 (100)
New cases of breast cancer	774 (49)	133 (8)	677 (43)	1 584 (100)
Deaths from breast cancer:				
Total	114 (30)	96 (25)	175 (45)	385 (100)
Refined	49 (39)	15 (12)	63 (50)	127 (100)

Results

Table 1 shows the numbers of women invited and screened and the controls by year of birth. Table 2 shows the numbers of new cases of breast cancer and deaths from breast cancer during 1987-92. Table 3 shows the standardised mortality ratios.

There were 64 deaths among the women invited for screening and 63 deaths among the controls from breast cancers diagnosed after the start of follow up (table 2). The standardised mortality ratio of refined mortality was higher among the women invited but not screened than among the controls (rate ratio = 1.42). For the women screened the rate ratio was 0.67. This resulted in a total rate ratio of 0.76 (95% confidence interval 0.53 to 1.09) for the women invited for screening, which showed a 24% protective effect due to screening, which was not significant. The protective effect varied by the year of follow up; the effect emerged only during the three to four years of follow up (rate ratio = 0.69) and was significant (0.35 to 0.99). Because this effect occurred relatively early, it was seen only for deaths that occurred before the age of 60 years. Therefore, the protective effect also differed by age at entry to the study. Among those born in 1927-30—that is, women mainly aged over 57 years at the time of the first screen—the effect was negligible. Those born in 1932 and later (mainly aged under 56 at entry) had a rate ratio for death from breast cancer of 0.56, which was significant (0.33 to 0.95) (table 4[4]).

Had the refined standardised mortality ratio among women invited for screening been the same as in the control population, there would have been 84 deaths from breast cancer (64/0.76) among the invited women. As there were only 64 deaths, the number of deaths prevented because of the screening can be estimated to be 20.

Discussion

Randomised trials show that screening with mammography reduces mortality from breast cancer, with an

Table 3 Standardised mortality ratios (numbers of deaths) for breast cancer in 1987-92 by age

	Women invited for screening			
Age (years) at death	Women screened	Women not screened	Total	Controls
45-49	0	8.29 (2)	1.09 (2)	1.17 (8)
50-54	0.55 (25)	3.99 (34)	1.09 (59)	1.29 (45)
55-59	0.6 (42)	4.22 (38)	1.01 (80)	0.95 (47)
60-64	0.70 (47)	2.65 (22)	0.96 (69)	1.20 (72)
65-69	0	0	0	0.67 (3)
Total	0.63 (114)	3.67 (96)	1.01 (210)	1.12 (175)

Table 4 Rate ratios of refined* standardised mortality ratios for death from breast cancer in 1987-92 for women invited for screening and women screened to those for controls by year of follow up, age at death, and year of birth. Values are rate ratios; 95% confidence intervals (numbers of women who died)

	Women invited for screening			No of deaths among controls
	Screened	Not screened	Total	
Year of follow up:				
1-2	0.73 (7)	3.14 (5)	1.08; 0.41 to 3.03 (12)	8
3-4	0.58 (25)	0.69 (4)	0.59; 0.35 to 0.99 (29)	35
5-6	0.87 (17)	2.83 (6)	1.06; 0.56 to 2.03 (23)	20
Age (years) at death:				
<60	0.48 (23)	1.25 (9)	0.58; 0.35 to 0.96 (32)	37
⩾60	1.00 (26)	1.78 (6)	1.09; 0.63 to 1.90 (32)	26
Year of birth†:				
1927-30	0.91 (27)	2.03 (8)	0.94; 0.56 to 1.61 (35)	28
1932-9	0.49 (22)	1.05 (7)	0.56; 0.33 to 0.95 (29)	35
Total	0.67 (49)	1.42 (15)	0.76; 0.53 to 1.09 (64)	63

*Only cancers diagnosed after the start of screening were included.
†Women born in 1931, 1936, and 1937 were excluded from the analysis (see methods).

average reduction of about 30%.[6-8] On the basis of such results, screening was introduced as a national public health policy or with an organised programme in several countries, including the United Kingdom,[9 10] Sweden,[11] the Netherlands,[12] and Finland.[13] Spontaneous or opportunistic screening is a widespread practice in several other countries. The effectiveness of such a public health policy in terms of a reduction in mortality was evaluated in the United Kingdom on the basis of the national rates before and after the introduction of screening.[10] The evaluation found a decrease in mortality, which was, however, unlikely to be due to screening. Such a design may not be able to disclose the potential effect of screening because of small and gradual effect.[14]

Finland was the first country to introduce nationwide breast cancer screening as a public health policy. The participation rate in the first year, 1987, was 88%,[13] which is among the highest rates reported anywhere, and the programme was successfully carried out. The programme first covered women born in even-year birth cohorts. The availability as controls of women born in odd years adjacent to the screened cohorts decreased during the four year implementation period as the programme expanded. In Finland the general health services are funded by the municipalities, who receive state subsidies for such purposes. Success of the design depended on the motivation of the municipalities to comply with the National Board of Health's guidelines on screening.

Eliminating bias

The potential bias due to self selection of municipalities was eliminated by having the controls from the same municipality as the women invited for screening. The analysis was based on 10 birth cohorts of women born 1927-39. All the control women belonged to five birth cohorts, two of which (1935, 1939) were recommended to be screened for the first time in 1990, two (1929, 1933) in 1991, and one (1927) not at all. It was assumed that this late screening would not substantially affect the deaths from breast cancer by the end of 1992. The controls were unbiased for age, because the trend in mortality from breast cancer is linear over the ages 50 years to 65 years, and the one year differences in women invited for screening and the controls were balanced.

Some of the municipalities began to organise screening for women born in these five control cohorts; the women who were invited for screening were removed from the group of controls at the time of first screening and were further classified according to their actual participation to prevent any effect due to dilution. Such changes were relatively few for women born in 1927, 1929, and 1933, but more than 30% of the women in cohorts born in 1935 and 1939 had to be removed from the control group.

We eliminated the obvious bias due to self selection (women attending for screening and women not attending) by comparing the mortality among all the women who were invited for screening (regardless of whether they attended) to that of the controls. We evaluated the basic risk of death by comparing the numbers of deaths from breast cancer among the women invited for screening and among the controls to that expected for the overall mortality for Finland. The total standardised mortality ratio for women invited but not screened was high, because breast cancer reduces the feasibility of attending the programme. The women invited for screening had a mortality from breast cancer equal to that expected on the basis of the total Finnish rates (standardised mortality ratio = 1.0). This would point to ineffectiveness of the screening programme. However, the controls had a higher risk of death than expected (1.1), which indicates that municipalities in which women had a high risk of breast cancer were more likely to be included in our material. Because risk of breast cancer is high among more wealthy women, the more wealthy municipalities were more ready to start screening with the Cancer Society of Finland and its regional member societies.

Disappearing effect

There was only a narrow window by year of follow up to evaluate the Finnish programme. The effect of screening on mortality did not appear until the third and fourth year of follow up and then was lost because the controls were also gradually being screened. The difference in calendar years between the women screened first and those screened last was only four years, in line with the national recommendation. Therefore, because of dilution of screening in the controls, we could evaluate only the early effect. Several trials examining the effect of screening on mortality have shown a significant difference in cumulative deaths from breast cancer only a few years after the first round. However, the point estimates have been consistent, with a constant proportion of deaths prevented almost immediately after the first round of screening among women aged 50-65 years at entry.[3 7 15] The delayed effect was a consistent finding only among those aged under 50 years at entry.[3 7 15] In our study the effect in mortality rapidly disappeared as controls merged into the national programme. The disappearance of the effect is different from the experience in several randomised trials,[1 3 7] where the difference of cumulative rates increased for many years after the programme ended or after the control arm was merged into a programme identical to that offered for the screening arm. For evaluation a period of implementation of the public health policy in Finland

Key messages

- Several countries have a breast cancer screening programme, but none has yet reported this as resulting in a reduction of breast cancer mortality
- This study shows that a breast cancer screening programme can achieve similar reduction in mortality to that seen in randomised trials
- Effects on quality of life, cost of breast cancer screening, and the alternative use of resources should affect the decision whether to introduce a screening programme

longer than four years would have been feasible. However, Finland had the resources to expand the programme relatively rapidly, and it was not justifiable to withhold the public health policy from more women than necessary.

An effective policy

During the follow up of 700 000 person years, 1600 breast cancers were diagnosed and 400 deaths from breast cancer occurred. Our final estimate of effect—a 24% reduction in mortality from breast cancer—was based on 127 refined deaths from breast cancer only. The reduction is not significant, but it is consistent with the results from randomised trials.[2 3 8] It was larger (42%) and significant in women aged under 56 years at entry. Was the effect large enough to justify the time and resources spent on this public health policy? The small effect of breast cancer screening had already been pointed out 10 years previously,[16] and scepticism is getting more common.[17] In our study about 200 000 screening tests prevented 20 deaths. This result is similar to that found by Wright and Mueller.[17]

The screening programme also has effects other than reduction in deaths from breast cancer—namely, longer survival. Most women in Finland attend cancer screening programmes for reassurance that they do not have preclinical cancer.[18 19] The quality of life of the patient is likely to improve—for example, through breast conserving surgery. If no screening programme operates the resources will go elsewhere. Breast cancer screening is cost effective compared with many other healthcare services.[20] Much of the health service resources are spent with poor control of effectiveness.

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ONE HUNDRED YEARS AGO

Battle of the clubs

Female membership of Friendly Societies

The *Western Gazette* of August 21st reports that a deadlock has ensued in connection with the Trowbridge Medical Institute on account of the medical staff objecting to a rule which states "that a female on marriage should not be re-examined by the surgeon." This in effect would mean, "Once a member, always a member," and the medical officers generally object to it as being unfair. The matter has been referred for further consideration, but it is by no means clear what it is the local profession specially object to. We have always strongly dissented from accepting women as members of friendly societies, at least at anything like the same rate as that paid by men, and in the case of married women the rate ought to be proportionately higher. But where the surgeon has examined a female member and passed her, it is not easy to see any valid reason why he should re-examine her on marriage, except for reasons which the public would never consent to. Doubtless the risks of married life would be greater in the case of some women than in others, but these must be estimated by the medical examiner at the time of the first examination, if at all, although it might be reasonably demanded that female members on marriage should pay an increased premium. (*BMJ* 1897;ii:675.)

Timing of paediatric deaths after trauma

JP Wyatt, L McLeod, D Beard, A Busuttil, TF Beattie, CE Robertson.

Department of Accident and Emergency Medicine, Royal Hospital for Sick Children, Edinburgh EH9 1LF
Jonathan Wyatt, *senior registrar*
Lorna McLeod, *senior house officer*
Thomas Beattie, *consultant*

Scottish Trauma Audit Group, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW
Diana Beard, *national co-ordinator*

Forensic Medicine Unit, Medical School, University of Edinburgh, Edinburgh EH8 9AG
Anthony Busuttil, *regius professor of forensic medicine*

Department of Accident and Emergency, Royal Infirmary, Edinburgh EH3 9YW
Colin Robertson, *consultant*

Correspondence to: Mr Wyatt.

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Trauma is the leading cause of death in children aged over 1 year.[1 2] The government has identified this problem as worthy of special attention. *The Health of the Nation* sets a target of reducing the death rate for accidents in children by at least 33% by the year 2005, to no more than 4.5 per 100 000.[2] The principal methods of reducing the death rate are either to improve treatment for those injured or to prevent the injuries. We examined the timing of death after injury for insight into the potential of each stratagem.

Subjects, methods, and results

The deaths of all children after injury in south east Scotland are investigated by the police and by postmortem examination under the direction of the procurator fiscal. We identified deaths following trauma in children aged less than 15 years in Lothian and Borders regions of south east Scotland during the 11 years 1985-95 from forensic medicine records and the records of the procurator fiscal. A cross check was performed against data from the registrar for deaths to confirm that the dataset was complete. The mechanism of injury and times of trauma and death were obtained from forensic medicine and the procurator fiscal's records and from police, ambulance, and hospital records. Injury severity scores were calculated for each child, using the 1990 revision of the abbreviated injury scale.[3]

A total of 138 children (84 boys, 54 girls) died after injury during the 11 years. The 1991 census showed 146 826 children aged less than 15 years for the region; hence the overall death rate was 8.5 per 100 000 children per year. The rate varied from year to year (9.5 (14 deaths) in 1985; 8.9 (13) in 1986; 6.1 (9) in 1987; 10.9 (16) in 1988; 7.5 (11) in 1989; 4.8 (7) in 1990; 18.4 (27) in 1991; 4.1 (6) in 1992; 7.5 (11) in 1993; 8.2 (12) in both 1994 and 1995), with no discernible trend.

The mechanisms of injury responsible, and time of death, are shown in table 1. Fifty seven of the 138 deaths (41%) occurred in preschool children (aged less than 5 years). Twenty of these had been left unsupervised in the presence of an obvious danger (access to matches, deep water, an open road, or an unguarded drop). Ninety nine children (72%) died within one hour of injury or were dead when found; 92 of these children showed no signs of life when the ambulance crew arrived at the scene. These included 40 children who had injuries considered to be unsurvivable (injury severity score = 75) and 36 other children who were found dead after an unwitnessed incident.

Table 1 Mechanism, age, and time of death after injury in children in south east Scotland, 1985-95

	Mean age (years)	Time of death after injury (hours)			No of deaths
		< 1	1-4	> 4	
Road traffic accidents:					
Pedestrian	8.6	16	0	16	32
Car passenger	5.5	22	2	2	26
Pedal cyclist	11.7	6	0	3	9
Fall from a height	4.8	6	1	4	11
Hanging	11.5	10	0	1	11
Drowning	5.4	13	0	2	15
Fire	4.5	20	1	1	22
Other	3.6	6	1	5	12
Total	6.7	99	5	34	138

Comment

Children continue to die after accidents with relatively predictable causes.[2] In south east Scotland the death rate after trauma in children fluctuates somewhat from year to year, but the overall rate remains unacceptably high. To achieve the government target for 2005, the death rate in the region needs to be reduced by 47%.

Improving hospital treatment offers only limited potential for preventing some deaths of children in hospital after injury.[4] Most children in this study, however, were either dead when found or died at the scene of the accident before receiving medical attention. The potential for improving survival by providing seriously injured children with earlier medical attention at the scene is difficult to quantify but seems to be limited, as most children either had unsurvivable injuries or were found dead after an unwitnessed incident. These results are in keeping with those relating to adults.[5]

As with adults, the greatest potential for reducing the number of children dying after trauma lies with introducing and implementing effective accident prevention measures. The high proportion of deaths related to road traffic accidents shows the need to concentrate efforts in this area. Research designed to identify appropriate accident prevention measures should be strongly encouraged and supported. The number of deaths from injury in children will not be reduced unless this is borne in mind and resources allocated appropriately.

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Drug points

Quinolones may induce hepatitis

S E Jones, R H Smith, North Tees General Hospital, Stockton on Tees, Cleveland TS19 8PE

A 21 year old man with Wegener's granulomatosis had been treated with cyclophosphamide 50 mg three times a day, prednisolone 5 mg daily, and ranitidine and domperidone for 18 months. He developed jaundice after a five day course of ofloxacin (Tarivid) and two doses of ciprofloxacin prescribed for a productive cough. He was heterosexual and teetotal, with no history of foreign travel, intravenous drug misuse, or contact with jaundice.

Abdominal examination showed a tender liver palpable 3 cm from the edge but no splenomegaly or ascites. Initial investigation were as follows: bilirubin 92 µmol/l (normal up to 17), aspartate transaminase 348 U/l (up to 40), alkaline phosphatase 321 U/l (normal range 20-90), albumin 50 g/l. His haemoglobin was 165 g/l, white cell count 2.3×10^9/l, and platelet count 103×10^9/l. Abdominal ultrasonography yielded normal results and a serological test for viral hepatitis gave negative results. The patient declined a liver biopsy.

Table 1 Liver function tests from onset of jaundice

Days from onset	Bilirubin (µmol/l)	Aspartase transaminase (U/l)	Alkaline phosphate (U/l)
4	92	348	321
7	50	286	299
8	69	501	410
9	71	460	461
11	140	557	530
15	44	130	413
39	24	33	151

Cyclophosphamide and all other drugs apart from prednisolone, which was increased to 20 mg daily, were discontinued. The liver function tests showed that values were slow to return to normal (table 1).

On recovery cyclophosphamide was reintroduced and his prednisolone reduced to the maintenance dose without any problem; markers for activity of Wegener's granulomatosis remained low throughout this episode. The only change in this patient's drug treatment was the introduction of ofloxacin followed by ciprofloxacin—the proposed aetiological agent for hepatitis in this case.

Fluoroquinolones such as ofloxacin should be used as a first line treatment only for subjects with cystic fibrosis or bronchiectasis[1]; they lack a broad Gram positive spectrum of activity and so should not be used as monotherapy in neutropenic patients. Sequential use of different fluoroquinolones does not make sense.

Quinolones may induce transient abnormal results in liver function tests, and they have been used successfully in existing hepatic impairment. Prolonged hepatitis is rare, and the Committee on Safety of Medicines received 18 reports of liver disorder from a total of 640 reports of adverse reactions to ofloxacin (Regional Drugs and Therapeutics Committee, personal communication). There have only been a few case reports of hepatitis induced by quinolones,[2 3] with only one implicating ofloxacin.[4]

1 Hodson ME, Roberts CM, Butland RJ, Smith MJ, Batten JC. Oral ciprofloxacin compared with conventional intravenous treatment for Pseudomonas aeuruginosa infection in adults with cystic fibrosis. *Lancet* 1987;i:235-7.
2 Fuchs S, Simon Z, Brezis M. Fatal hepatic failure associated with ciprofloxacin. *Lancet* 1994;343:738-9.
3 Davoren P, Mainstone K. Norfloxacin induced hepatitis. *Med J Aust* 1993;159:423.
4 Blum A. Ofloxacin induced acute severe hepatitis. *South Med J* 1991;84:1158.

Hypoglycaemia associated with formestane treatment

E Brankin, A Gallagher, M Soukop, Glasgow Royal Infirmary, Glasgow G4 0SF

We report a case of recurrent hypoglycaemia in a 64 year old woman with non-insulin dependent diabetes mellitus receiving formestane for metastatic breast carcinoma. She had previously been treated with surgery and local radiotherapy, followed by hormone manipulation with tamoxifen, medroxyprogesterone acetate, and then aminoglutethimide. All of these drugs had been poorly tolerated. She showed no signs of adrenal dysfunction when receiving aminoglutethimide, or subsequently. She had also received chemotherapy for relapse (variously cyclophosphamide, methotrexate, fluorouracil, epirubicin, mitomycin). She had been diabetic for about 10 years, and her glycaemic control had been excellent as a result of careful diet and oral treatment with gliclazide 40 mg twice a day (recent haemoglobin A_{1c} concentration 5.5% (normal laboratory range 4.9-7.6%)).When formestane treatment was started she was also taking captopril 25 mg three times a day and ranitidine 150 mg twice a day, and her condition had been stable with this treatment for over four months. One week after taking formestane she had recurrent dizzy episodes, which were diagnosed as hypoglycaemic attacks on the basis of low blood glucose concentrations during monitoring both at home and in the clinic. Consequently, the gliclazide dose was halved and finally withdrawn. No other cause for this transient period of recurrent hypoglycaemic attacks could be found.

Formestane (4-hydroxyandrostenedione) is a new mechanism based aromatase inhibitor which irreversibly inactivates the enzyme, preventing the conversion of androstenedione to oestradiol and oestrone; its antitumour effect is mediated by a reduction in oestrogen synthesis. So far as we are aware there have been no other reported cases of hypoglycaemia associated with formestane treatment (Committee on Safety of Medicines, Medicines Control Agency; adverse drug reactions online information tracking), although no studies have been performed in diabetic patients (datasheet, Ciba Pharmaceuticals). It is therefore recommended that blood glucose concentration should be monitored as a precautionary measure.

Although ours is an isolated case, formestane might induce hypoglycaemia in patients with non-insulin dependent diabetes mellitus. Why episodic hypoglycaemia continued after the gliclazide was stopped is unclear, but this suggests that the effect is not merely an interaction between the sulphonylurea and formestane. New reports of similar findings and the possible mechanism are currently being investigated by the manufacturers. Formal studies will be required to establish a causal relation more fully, but it would seem prudent to advocate careful monitoring of blood glucose concentration at home, with reduction in oral hypoglycaemic dose if necessary, in diabetic patients receiving formestane for postmenopausal breast carcinoma.