RESEARCH REPORT

Sleep disturbance, stroke, and heart disease events: evidence from the Caerphilly cohort

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Objective: To test the hypothesis that sleep disorders are relevant to the risk of ischaemic stroke and ischaemic heart disease events in older men.
Design: A cohort study.
Setting: The Caerphilly cohort, a representative population sample of older men in South Wales, UK.
Participants: 1986 men aged 55–69 years completed a questionnaire on sleep patterns with help from their partners. This asked about symptoms of disturbed sleep: insomnia, snoring, restless legs, obstructive sleep apnoea, and about daytime sleepiness. During the following 10 years 107 men experienced an ischaemic stroke and 213 had an ischaemic heart disease event.
Main results: Up to one third of the men reported at least one symptom suggestive of sleep disturbance, and one third reported daytime sleepiness. Compared with men who reported no such symptoms, the adjusted relative odds of an ischaemic stroke were significantly increased in men with any sleep disturbance, the strongest association being with sleep apnoea (relative odds 1.97; 1.26 to 3.09). The association with daytime sleepiness was not significant for stroke. Relations with ischaemic heart disease events were all raised in men with symptoms of sleep disturbance, but none was significant, other than daytime sleepiness (relative odds: 1.41; 1.04 to 1.92). There were no significant relations with blood pressure.
Conclusion: The risk of an ischaemic stroke is increased in men whose sleep is frequently disturbed, and daytime sleepiness is associated with a significant increase in ischaemic heart disease events.

Adequate undisturbed sleep is an essential component in a healthy lifestyle, and contributes to optimal daytime function and wellbeing.[1–3] There is little certainty as to the frequency of disturbed sleep, a consequence in part from the use of selected subjects in many studies, and also because of the wide range of definitions that have been used, from snoring and restless legs to apnoea with cessation of breathing and oxygen desaturation.

There is further uncertainty as to the degree of sleep disturbance that is of clinical importance. Cross sectional and retrospective studies suggest that disturbed sleep, and sleep apnoea in particular, is associated with an increase in prevalent vascular disease.[4–9] More certain evidence of a relation comes from prospective studies but very few such studies have been reported. In the large national health and nutrition survey in the USA (NHANES 1) cohort the risk of stroke was found to be significantly increased in subjects with daytime somnolence relative to that of subjects without this symptom.[10] A recently reported study of men with severe untreated obstructive sleep apnoea-hyponea has shown significantly increased risk of fatal and non-fatal cardiovascular disease events, compared with healthy controls.[11]

Some have judged that the health consequences of sleep disturbances have been exaggerated.[12] If, however, sleep disturbances are prevalent, and if they are associated with vascular disease, it is important to establish, in representative population samples, the symptoms that are relevant and the strength of the relation with vascular disease so that appropriate public health initiatives can be taken and adequate treatments tested.

This study looks at the prediction of incident vascular disease events by symptoms of sleep disturbance and daytime sleepiness in the Caerphilly cohort, a large population cohort of older men in South Wales.[13]

METHOD

The Caerphilly cohort study is based on a representative population sample of older men, born between 1920 and 1935 resident in a typical small town in South Wales.[13] The initial response rate was 89% of the total men eligible for the study. The primary aims of the study were to evaluate lifestyle, dietary, haemostatic, lipid, and other factors predictive of vascular disease.[14–16]

In the second follow up examination, when the men were aged 55-69 years, they were asked to complete the Wisconsin sleep questionnaire,[17] with help from their partners. This asks about the severity and frequency of symptoms of insomnia, restless legs, snoring, episodes of apnoea, and daytime sleepiness and definitions are shown in footnotes to table 1. The questionnaire does allow for the grading of symptoms into ''mild'' and ''severe'', based largely on the frequency of occurrence. Because the questionnaire was self administered and gave opportunity for trivial symptoms to be reported, we decided to ignore the ''mild'' or ''infrequent'' symptoms throughout.

Data were also collected at this time on a range of factors relevant to vascular disease, including social class (based on the man's most recent occupation) smoking (grouped as non-smoker, former smoker, and current smoker), weekly alcohol consumption (expressed as average cc/day) and height and weight. Blood pressure was measured with a random zero syphmomanometer.

At five-year intervals throughout the study, the men were questioned about symptoms suggestive of vascular disease, repeat ECGs were recorded and hospital and general practitioner notes inspected to identify all possible incident vascular events. Standard diagnostic criteria were applied to identify new ischaemic heart disease (IHD) events (deaths attributed to IHD plus non-fatal myocardial infarction: ICD

Table 1 Prevalence of sleep disorders in 1986 men aged 55–69 years in the Caerphilly cohort. (Men who had had a stroke or a myocardial infarct omitted)

Symptom	Numbers* of men without the symptom, or the symptom only occasionally	Numbers* of men (%) with the symptom
Insomnia: difficulty in getting to sleep and waking repeatedly once or twice a week, or more often.	1654	219 (12)
Restless legs: experiencing ''restless legs or bothersome twitches'' once or twice a week or more.	1444	427 (23)
Snoring: having been told, and being aware oneself of snoring on a few nights per month or more	1190	665 (36)
Sleep apnoea: having been told of gasping, choking or snorting on one night each week or more, and/or stopping breathing or breathing abnormally a few nights each month or more; and/or waking suddenly with a feeling of gasping or choking on a few nights each month or more	1499	352 (19)
Daytime sleepiness†: feeling today a little foggy, or slowed down, or loosing the struggle; and/or, at least once a week not feeling rested and/or feeling excessive sleepiness and/or a need for coffee or other stimulant	1287	587 (31)

*Numbers for the different symptoms differ slightly because some men did not answer all the questions. †Daytime sleepiness is shown separately as it is a consequence of any of the above.

121–5 10th revision) and ischaemic strokes (ICD 163–4).[18 19] Men with a prior IHD or stroke event have been omitted throughout.

Logistic regression analyses were used to estimate the risk of an ischaemic stroke (fatal or non-fatal), an IHD event (myocardial infarction or IHD death). Risks are expressed as odds for a disease event in the men with a sleep disturbance relative to the risk in the men with no disturbance, the latter being set at unity. All probability values are two sided and exact values are stated. Significance is judged as $p = 0.05$ or less.

Adjustments were made for possible confounding. Two groups of factors that might confound the relation were included. Firstly, adjustments were made for age, and alcohol consumption. Adjustments were also made for two further factors that are believed to be causal of sleep disturbances, namely, body mass index (BMI; kg/m^2), and maximum neck circumference.

RESULTS

Completed questionnaires were returned by 1986 men, but 79 men who had had a previous myocardial infarction and 33 who had had a prior stroke were omitted from the appropriate analyses. There were 1874 men with complete data. Altogether 106 men reported the regular use of sleeping tablets, but as no meaningful relations were detected with vascular disease outcomes, tablet taking has been ignored in what follows.

The cohort has been described in detail elsewhere.[13 15] In summary: 65% of the men were manual workers, 34% were current smokers, the mean BMI was 26.8 SD 3.7 cm, and the mean neck circumference 39.0 SD 2.6 cm.

Table 1 shows the prevalence of symptoms of sleep disturbance. Between 12% and 36% gave evidence of sleep disturbance, the most common symptom being frequent snoring (36%). All the symptoms were significantly related to daytime sleepiness, this being reported by 13% of men who snored, 10% who reported apnoea, 9% of those who reported insomnia, and 14% who reported restless legs. The overall prevalence of daytime sleepiness was 31%.

Table 2 shows relations with possible confounding factors. Social class and smoking are clearly relevant. Weekly alcohol intake however shows no significant relations. The men with disturbed sleep had higher BMIs and larger neck circumferences. The absolute differences between men with and without evidence of sleep disturbance are however comparatively small.

Table 2 Relations between sleep disorders and possible confounding factors, and with possible explanatory factors

	Possible confounding factors				Possible explanatory factors	
Symptom	Mean age (y)	Social class (% manual)	Smoking (% current)	Mean alcohol intake (cc/week)	Mean BMI (kg/m^2)	Mean neck circumference (cm)
Insomnia						
No	61.9	64	33	142	26.7	38.9
Yes	61.3	76	37	133	27.2	39.3
	p=0.072	p<0.001	p=0.256	p=0.514	p=0.063	p=0.075
Restless legs						
No	61.8	62	33	140	26.6	38.8
Yes	61.6	77	37	142	27.5	39.5
	p=0.154	p<0.001	p=0.097	p=0.840	p<0.001	p<0.001
Snoring						
No	62.0	65	33	141	26.4	38.7
Yes	61.3	65	35	137	27.5	39.4
	p<0.001	p=0.986	p=0.570	p=0.646	p<0.001	p<0.001
Sleep apnoea						
No	61.9	63	33	141	26.6	38.8
Yes	61.4	72	39	139	27.4	39.4
	p=0.072	p=0.002	p=0.028	p=0.862	p<0.001	p<0.001
Daytime sleepiness						
No	61.8	61	32	147	26.6	38.8
Yes	61.7	73	38	127	27.1	39.2
	p=0.437	p<0.001	p=0.004	p=0.026	p=0.003	p=0.002

Table 3 Relations between sleep disturbances and incident vascular events. (Men with prior myocardial infarct and/or stroke have been omitted)

		Number of events		Adjusted* relative odds (95% CI)	
	Number of men	Ischaemic strokes	IHD event	Stroke	IHD event
Insomnia					
None	1654	88	178	1.00	1.00
Frequent	219	19	35	1.75 (1.02 to 3.01)	1.47 (0.98 to 2.21)
Probability				0.042	0.065
Restless legs					
No	1444	74	155	1.00	1.00
Yes	427	33	58	1.67 (1.07 to 2.60)	1.24 (0.89 to 1.74)
Probability				0.024	0.206
Snoring					
None	1190	59	130	1.00	1.00
Frequent	665	47	81	1.53 (1.01 to 2.23)	1.13 (0.84 to 1.54)
Probability				0.044	0.418
Sleep apnoea					
None	1499	75	159	1.00	1.00
Frequent	352	32	46	1.97 (1.26 to 3.09)	1.21 (0.84 to 1.74)
Probability				0.003	0.299
Daytime sleepiness					
None	1287	71	130	1.00	1.00
Frequent	587	36	83	1.20 (0.78 to 1.84)	1.41 (1.04 to 1.92)
Probability				0.396	0.026

*Adjusted for possible confounding by age, social class, smoking, alcohol consumption, BMI, and neck circumference. Numbers for the different symptoms differ slightly because some men did not answer all the questions.

Nevertheless, in what follows, relations with disease incidence have been adjusted for all the factors shown in table 2. Although BMI and neck circumferences are described in the literature as being possible causes of sleep disturbances, we found that adjustments for them made very little difference to relations and so they are not considered separately in what follows.

Men with a prior vascular event were omitted throughout, and over the period of follow up 107 men had an incident ischaemic stroke, 213 had an incident IHD event, and 17 men experienced both events. Table 3 shows relations with the symptoms of sleep disturbance. All the disturbances show a significant relation with stroke incidence, the relative odds for an event being highest in the men who had reported sleep apnoea (1.97; 1.26 to 3.09). On the other hand, there is only a weak and non-significant relation between stroke and daytime sleepiness.

Table 3 also shows incident IHD events. None of the relations with the sleep disturbances is significant, but there is evidence suggestive of an increased risk in the men who experienced daytime sleepiness (1.41; 1.04 to 1.92).

A small number of men (33) complained of all the symptoms of sleep disturbance and in these, the adjusted odds of a stroke, relative to the odds in men with some, or none of the symptoms, is 3.63(1.34 to 9.84). The adjusted relative odds for an IHD event in these same men is only 1.36 (0.51 to 3.59).

Relations with blood pressure were examined. The results are not shown, but for men with each of the sleep disturbances, the differences in systolic and in diastolic pressures were small and non-significant. In fact, the mean blood pressures of the 33 men who had complained of all the symptoms of disturbed did not differ from the mean in the other men (both 144.5 mm Hg).

What this paper adds

Evidence on the nature and strength of relations between sleep disturbances, stroke, and heart disease from a large representative population sample of men. Almost all the published evidence so far has come from selected samples of patients, or has been based on laboratory work.

DISCUSSION

The study we present has a number of strengths. It is based upon a large representative population sample of older men and all members of the cohort were carefully and repeatedly followed up to identify vascular disease events as completely as possible. Detailed information on confounding factors of possible relevance was collected from every subject and this has been used to adjust the incident rates presented.

The study has however certain weaknesses. Some men in the cohort were omitted from the study because of delays in the preparation of the questionnaire. We doubt that this introduced any serious selection bias as the men were seen in no special order. The study is however dependent upon answers to a rather simple questionnaire. The validity of the questionnaire had been tested against overnight polysomnography[17] but no attempt was made to further test its validity in older Welshmen. However a high degree of agreement has been shown between self, and partner reports of snoring and other symptoms.[20]

Stradling and Davies[21] have pointed out that estimates from studies using different diagnostic criteria yield prevalence rates that range so widely that firm estimates of prevalence cannot be made. In their review they point out that while the frequency of men who present to a sleep clinic in the UK is perhaps only 0.5%, yet more inclusive diagnostic criteria used in screening surveys lead to estimates of 24% and higher.

Policy implications

Sleep disturbances have a comparatively high prevalence in older men and carry an increased risk for stroke, and possible heart disease. Further work is required to evaluate the effects of treatment of the disturbances, but the available evidence does suggest that treatment, and in particular continuous positive airways pressure, may reduce the vascular consequences.

There seems however to be agreement among most authors that the prevalence of sleep disorders is high, particularly among men.[2 17] In this cohort, around 20% of the men reported frequent apnoea, about one third of the men (or their partners) reported frequent snoring, and about the same proportion reported frequent daytime sleepiness. In a review of 154 published investigations, Shamsuzzman *et al*[22] judged that 20% of adults have at least ''mild'' sleep apnoea. Prevalences of sleep disordered breathing of 24% in men and 9% in women were estimated in the sleep heart health study,[16] and 30% and 20% for daytime sleepiness.[2] In a study based on obese subjects, 25% reported frequent daytime sleepiness.[9]

Studies in a sleep laboratory have shown that mild disturbances of sleep, which do not lead to arousal, still lead to detectable effects on mood and cognitive function.[1] This suggests that disturbances that are detected by a simple questionnaire, like the one used in this study, are probably of clinical importance.

A systematic review of the literature, published in 1993, led to the conclusion that ''the evidence for a causal association between sleep apnoea and a range of poor health outcomes is generally weak''.[12] Since then, however, evidence from a number of reports has suggested a link between sleep patterns and stroke.[6 9] In a further study almost 8000 subjects in NHANES I in the USA were followed up and an increased adjusted incidence of stroke was found in those who had reported daytime somnolence (1.4; 1.1 to 1.8).[10] The authors of this report comment that a similar excess risk was found for coronary heart disease, although statistical significance was not achieved. In a recent study of men attending a sleep clinic, and matched population selected control subjects, adjusted risk ratios of 2.87 (1.17 to 7.51) for fatal and 3.17 (1.12 to 7.51) for non-fatal vascular events were found in men with untreated, severe obstructive sleep apnoea-hypnoea.[11]

The relations we find suggest that if there is an increased risk of a heart disease event, it is small, other than for daytime sleepiness (1.41; 1.04 to 1.92). On the other hand, there is clearly an increased risk of an ischaemic stroke. Overall, the risk of ischaemic stroke was increased about 50%, but in those men who reported more than one sleep symptom the relative risk of a stroke was higher, rising to a greater than threefold risk in the men who reported all the symptoms (3.63; 1.34 to 9.84).

A number of population studies have reported a positive effect of sleep disturbance on blood pressure,[23 24] even with snoring.[25] Other studies have shown a reduction in blood pressure from the treatment of obstructive sleep apnoea with nasal continuous positive airway pressure.[26] Our failure to find a relation with blood pressure is therefore surprising, and we have no explanation, although there is a suggestion in the published data that this association weakens with advancing age.[25]

The involvement of many mechanisms other than hypertension have however been suggested to explain the increased vascular risk associated with sleep disturbance. Thus there are reports of increased carotid atherosclerosis,[27] increased platelet activity,[28 29] changes in fibrinogen and the fibrinolytic system,[29 30] and changes in other haemostatic factors.[31] A raised C reactive protein has also been reported, suggestive of an inflammatory process.[32]

CONCLUSION

Sleep disorders including obstructive sleep apnoea, insomnia, and daytime sleepiness are common. They are readily identifiable and they are predictive of ischaemic cerebrovascular disease, and possibly ischaemic cardiac events. We therefore find ourselves in agreement with Silverberg *et al*, that sleep disturbance is ''a neglected, under-diagnosed and under-treated condition''.[33]

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CONTRIBUTIONS OF THE AUTHORS

P C Elwood, directed the Caerphilly study and had overall responsibility for the paper. Melissa Hack gave clinical advice and direction regarding the analysis of the data. Janet Pickering analysed the data and contributed to the writing of the paper. Janie Hughes was chief field worker throughout the Caerphilly study, interviewed the subjects, responsible for the collection of the data, searched the literature, and contributed to the writing of the paper. J E J Gallacher was involved in all aspects of the work of the Caerphilly cohort study and now directs the work in Caerphilly.

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