Excessive Daytime Sleepiness Is an Independent Risk Indicator for Cardiovascular Mortality in Community-Dwelling Elderly

The Three City Study

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Background and Purpose—Excessive daytime sleepiness, one of the most frequent sleep complaints in the elderly, may affect survival, but inconsistent results have been observed in that population so far. We therefore estimated the risk of mortality for excessive daytime sleepiness (EDS) in community-dwelling elderly participating in the Three City Study.

Methods—The Three City Study is a French population-based multicenter prospective study including 9294 subjects (60% women) aged ≥65 years at recruitment between 1999 to 2001. At baseline, 8269 subjects rated EDS and nocturnal sleep complaints as never, rare, regular, and frequent in response to an administered questionnaire and provided information on medication use for sleep or anxiety. Hazard ratios (HR) of EDS (regular or frequent) for mortality over 6 years were estimated by a Cox proportional hazard model.

Results—At baseline, 18.7% of the study participants had regular or frequent EDS. After 6 years of follow-up, 762 subjects had died including 260 from cancer and 196 from cardiovascular disease. EDS was associated with a significant 33% increased risk of mortality (95% CI: 1.13 to 1.61) after adjustment for age, gender, study center, body mass index, previous cardiovascular disease, Mini Mental State Examination score, and cardiovascular risk factors. Further adjustment for current use of medication for sleep and for depressive symptoms slightly diminished the HRs. EDS was equally predictive of mortality in those who snored loudly and in those who did not. EDS was related to cardiovascular mortality but not to mortality attributable to cancer.

Conclusion—EDS might be independently associated with total and cardiovascular mortality in community-dwelling elderly. (Stroke. 2009;40:1219-1224.)

Key Words: epidemiology • elderly • sleep complaints • mortality

Sleep disturbances are frequent in the general population, increase with age, and have a deleterious impact on health. Whereas the prognosis of severe sleep disturbances, such as sleep disorder breathing syndrome, have been studied extensively, that of sleep complaints have received less attention, especially in the elderly. Excessive daytime sleepiness (EDS) is one of the most frequent sleep complaints in the population and affects 10 to 30% of older adults aged 65 years and more. EDS has been consistently associated with an adverse risk profile, and hence may be associated with an increased risk of mortality. However, prospective studies evaluating the association of EDS with mortality have been lacking and have reported mixed results. Discrepancies between studies may be attributable to insufficient statistical power and inadequate controlling for confounding factors. In addition, factors potentially mediating the association of EDS with mortality, such as the atherosclerotic burden, have not been considered. Given the frequency of EDS in the elderly population, the demonstration of an association between EDS and mortality may have substantial implications in terms of primary prevention.

The aim of the present study was therefore to estimate the risk of mortality associated with EDS in community-dwelling elderly participating in a large French prospective cohort the Three City Study.
Methods

Study Population
The Three City Study is a large French population-based multicenter prospective community study investigating new determinants of incident coronary heart disease, dementia and stroke in older adults. The study protocol has been described previously.14–15 Briefly, between March 1999 and March 2001, subjects aged 65 years and older were selected from the electoral rolls of 3 cities, Bordeaux in the South-West, Dijon in the North-East, and Montpellier in the South-East, and then invited to participate in the study. The acceptance rate was 37%, yielding a study sample size of 9294 subjects (3469 men and 5645 women), respectively 2104 in Bordeaux, 4931 in Dijon, and 2259 in Montpellier. The study protocol was approved by the Ethical Committee of the University hospital of Kremlin-Bicêtre, and each participant signed an informed consent.

Baseline Data Collection
Data were collected during a face-to-face interview using a standardized questionnaire administered by nurses. A wide range of information was collected including demographic characteristics, educational level, occupation, daily life habits such as smoking and alcohol consumption, and ability to perform everyday activities. Depressive symptoms were evaluated with the CES-D questionnaire, using a total score ≥23 in women and ≥17 in men as the cut-off value. Cognitive testing and screening for prevalent dementia were also performed by trained psychologists. History of cardiovascular disease was obtained through self-reporting of hospitalized myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, or hospitalized stroke. Participants were also invited to bring to the study center all medications they had regularly used in the past month.

Sleep Complaints Assessment
Sleep complaints were assessed at baseline by a face-to-face questionnaire. The participants self-rated as never, rarely, regularly, or frequently the frequency of (1) being excessively sleepy during the day, (2) having trouble falling asleep, (3) having several awakenings during night, (4) having early awakening in the morning without being able to go back to sleep, (5) having nightmares, (6) having restless sleep, and (7) snoring loudly. We defined EDS a priori as the self-report of a regular or frequent feeling of being excessively sleepy during the day. We also defined insomnia as a self-report of having regular or frequent trouble falling asleep, several awakenings during the night, or early awakening in the morning without being able to go back to sleep. Participants also rated the quality of their sleep as good/bad/poor, and reported whether they were currently using medication for sleep, anxiety, or stress.

Of the 9294 subjects included at baseline, 8425 had complete data on EDS. The 869 subjects with missing data were older, more often women, and had a worse profile than the remaining subjects. The 156 subjects with dementia at baseline were excluded from the study population to obtain more reliable self-reported information, leaving 8269 subjects for the present analysis.

Physical Examination
Participants underwent a standardized physical examination performed by technicians. Blood pressure was measured twice with a digital electronic tensiometer (sitting and lying), and the average of the two measurements was used in the statistical analyses. Height, weight, and waist were estimated in a subject in a light dressing. A 12-lead ECG was recorded and resting pulse rate was measured. Blood samples were collected and centralized measurements of fasting total cholesterol, HDL-cholesterol, triglycerides, and glucose levels were carried out. LDL-cholesterol was calculated according to the Friedewald formula only for triglycerides values ≤4.5 g/L.

An ultrasound examination of the carotid arteries was performed in participants aged less than 85 years who were able to come to the examination center (6150 study participants with complete EDS data). The protocol has been described in detail elsewhere.16–18 Briefly, the same B-mode system (Ultramark 9 High Definition Imaging) with a 5- to 10-MHz sounding was used in each center and a centralized reading was performed by one trained reader at the Reference Reading Center (Hôpital Broussais, Paris) according to a standardized protocol. The examinations involved scanning of the common carotid arteries (CCA), the carotid bifurcations, and the origins of the internal carotid arteries. The near and far walls of these arterial segments were scanned longitudinally and transversally to assess the presence of plaques, which was defined as localized echo structures encroaching into the vessel lumen for which the distance between the media-adventitia interface and the internal side of the lesion was ≥1 mm.18 When several plaques were present on the same arterial segment, the number of plaques was recorded, and examination was centered on the segment showing the greatest encroachment into the lumen. For intima media thickness (IMT), far and near walls of the right and left CCAs 2 to 3 cm proximal to the bifurcation were imaged and frozen in end-diastole. The IMT was measured at site free of any discrete plaque along a 10-mm-long segment of the far wall of the CCA and defined as the distance between the lumen-intima interface and the media-adventitia interface. The mean of 75 measurements was automatically performed on each image and on each side.

Follow-Up
Vital status was followed over 6 years until March 31, 2007. Of the 8269 study participants, vital status was unknown for only 10 subjects. The vital status of each participant was checked annually via the participant’s family or physician. The circumstances of death were obtained not only from death certificates but also from the participant’s family or physician or from hospital records. A validation committee used all information to classify the cause of death using ICD10 classification algorithms. ICD codes C00 to C97 defined cancer causes, whereas ICD codes from I00 to I19 and from R960 to R961 defined cardiovascular causes, respectively. To minimize classification bias on the cause of death, only the first cause of death reported on the death certificate was considered.

Statistical Analysis
The baseline characteristics of the study participants were compared according to the presence of EDS using logistic regression and analysis of variance adjusted for age, gender, and study center for categorical and continuous variables, respectively. The survival rates of those with and without EDS were described using univariate Kaplan–Meier survival curves and compared using a Log-rank test. The hazard ratios (HRs) and 95% confidence intervals (CIs) of EDS for mortality were estimated by a Cox proportional hazard model. Systematic adjustment was made for age, sex, and study center. Subsequent adjustment was made on potential confounding factors including current smoking status, weekly daily alcohol consumption (abstainers, 1 to 3 glasses and more than 3 glasses), body mass index, diabetes, systolic blood pressure, MMSE score, HDL, and total cholesterol, lipids lowering and antihypertensive medications, and prior cardiovascular disease. In a third model, depressive symptoms and current use of sleep medication were successively added. Intima media thickness and the presence of carotid plaques measured during carotid ultrasound examination were explored as possible mediators and were included in the Cox regression model. The association of EDS with mortality was finally explored in subgroups defined by age (using the median value of 78 years as cut-off), gender, prior cardiovascular disease, body mass index (<25, 25 to 30, ≥30 kg/m²), depressive symptoms, medications for sleep, insomnia, and snoring. Product interaction terms of EDS with each of these factors was included in separate multivariable Cox models. To minimize the possible confounding effect of prevalent chronic conditions, Cox analysis was repeated after excluding deaths that occurred in the first 2 years of follow-up. There was no deviation from the proportionality assumption of the Cox model for EDS and each covariate, which was checked graphically (−log(−log survival)). All analyses were 2-sided, and a probability value <0.05 was judged as statistically significant. SAS software, 9.1 version (SAS Institute Inc) was used for the statistical analyses.
Results

General Characteristics
The study sample consisted of 8269 nondemented subjects with complete data on EDS at baseline. The mean age (SD) was 74 years (5.47), and there were 4992 women (60.3%). Overall, 18.7% had EDS (14% and 4.7% had regular and frequent EDS, respectively), 10.1% and 18.0% currently used medications for stress/anxiety and for sleep, respectively.

The baseline characteristics of the cohort according to the presence of EDS are compared in Table 1. Subjects with EDS were older, more often men, tended to be less educated, but had higher incomes. They were more often depressed and diabetic, had higher BMI, lower HDL cholesterol, lower systolic and diastolic blood pressure, and used more antihypertensive treatment. In contrast, EDS was not related to prior cardiovascular disease, lipid lowering medication, carotid plaques, or intima-media thickness. Moreover, those with EDS had poorer sleep quality, snored more frequently, had more insomnia and more frequently used medication for sleep or anxiety.

Follow-Up and Mortality Data
After 6 years follow-up, 762 subjects had died (9.2%). Of these, 260 were attributable to cancer (34.1%) and 196 to cardiovascular causes (25.7%), including 15.3% from cerebrovascular disease, 16.3% from myocardial infarction, and 20% from heart failure; 207 were attributable to other causes (27.2%), among which only 8 were attributable to trauma including traffic accident and 2 to falls. As shown in the Figure, those with EDS at baseline had a significantly worse survival rate over 6 years than those without. Consistent findings were observed for cardiovascular mortality but not for mortality attributable to cancer (not shown).

Hazard Ratio of Mortality
The hazard ratios of mortality for EDS are reported in Table 2. Subjects with EDS had a significant 42% increased risk of mortality (95% CI: 1.21 to 1.68) compared to those without EDS after adjustment for age, gender, and study center. After additional adjustment for BMI, systolic blood pressure, personal history of cardiovascular disease, diabetes, current smoking status, daily alcohol consumption, total and HDL cholesterol, antihypertensive and lipids lowering medications, and MMSE score, there remained a significant 33% increased risk of mortality (95% CI: 1.13 to 1.61). Successive adjustment for baseline depressive symptoms and current use of medication for sleep changed minimally the hazard ratios. As shown in Table 2, consistent and even stronger associations were observed with cardiovascular mortality, but not with mortality attributable to cancer.

Subgroups Analysis
The associations of EDS with total mortality in prespecified subgroups defined by gender, age, prior CVD, BMI, depressive symptoms, medications for sleep, loud snoring, and insomnia are reported in Table 3. Significant associations were found in all subgroups except in women, in overweight study participants, and in those with depressive symptoms. None of the interactions explored were, however, statistically significant.

Additional Analysis
When we excluded the 187 subjects who died during the first two years of follow-up, consistent results were found: EDS remained associated with total mortality (adjusted HR = 1.43; 95% CI: 1.17 to 1.74) and with cardiovascular mortality (65

Table 1. Baseline Characteristics of Study Participants With and Without Excessive Daytime Sleepiness: The Three City Study

<table>
<thead>
<tr>
<th></th>
<th>No EDS</th>
<th>EDS</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>73.8 (5.4)</td>
<td>75.1 (5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men†</td>
<td>77.3</td>
<td>22.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women†</td>
<td>83.9</td>
<td>16.1</td>
<td>0.009</td>
</tr>
<tr>
<td>Leaving alone</td>
<td>18.3</td>
<td>19.7</td>
<td>0.009</td>
</tr>
<tr>
<td>University level</td>
<td>37.7</td>
<td>36.5</td>
<td>0.032</td>
</tr>
<tr>
<td>Income</td>
<td>33.5</td>
<td>39.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.5 (3.9)</td>
<td>26.5 (5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>146.7 (21.6)</td>
<td>145.9 (21.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>82.5 (11.2)</td>
<td>81.3 (11.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Abstainers</td>
<td>20.3</td>
<td>21.9</td>
<td>0.011</td>
</tr>
<tr>
<td>1–3 glasses of alcohol daily</td>
<td>65.5</td>
<td>60.7</td>
<td>0.011</td>
</tr>
<tr>
<td>&gt;3 glasses of alcohol daily</td>
<td>14.3</td>
<td>17.4</td>
<td>0.011</td>
</tr>
<tr>
<td>MMSE score</td>
<td>27.4 (1.9)</td>
<td>27.2 (2.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.8 (0.98)</td>
<td>5.7 (0.98)</td>
<td>0.007</td>
</tr>
<tr>
<td>HDL-chol, mmol/l</td>
<td>1.63 (0.40)</td>
<td>1.53 (0.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td>48.5</td>
<td>58.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid lowering medications</td>
<td>30.1</td>
<td>30.8</td>
<td>0.39</td>
</tr>
<tr>
<td>Poor sleep quality</td>
<td>11.8</td>
<td>20.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heavy snoring (regular-frequent)</td>
<td>31.4</td>
<td>51.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insomnia‡</td>
<td>70.5</td>
<td>89.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current medication for sleep</td>
<td>17.2</td>
<td>21.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current medication for stress/anxiety</td>
<td>9.2</td>
<td>14.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid plaques§</td>
<td>44.5</td>
<td>52.4</td>
<td>&lt;0.186</td>
</tr>
<tr>
<td>Intima media thickness, mm</td>
<td>0.71 (0.12)</td>
<td>0.73 (0.12)</td>
<td>0.175</td>
</tr>
</tbody>
</table>

EDS refers to excessive daytime sleepiness. Data are % and mean (SD) for categorical and continuous variables respectively. *Logistic regression and linear regression analysis adjusted for age, gender, and the study centre for categorical and continuous variables respectively; †Rates by gender; ‡having trouble falling asleep or several awakenings during night or early awakening in the morning without being able to go back to sleep; §carotid Doppler ultrasound examination performed in participants aged <85 years (n = 6150).
deaths excluded; adjusted HR = 1.63; 95% CI: 1.09 to 2.43), but not with mortality attributable to cancer (56 deaths excluded; adjusted HR = 1.23; 95% CI: 0.87 to 1.73) in fully-adjusted models (not shown).

Discussion

The present large prospective study suggests that in nondemented community-dwelling elderly, EDS is associated with a 33% increased risk of mortality independently of confounding risk factors over 6 years. This is observed for cardiovascular mortality but not for mortality attributable to cancer.

The prospective association between EDS and mortality in community-dwelling elderly has been investigated in only a few previous studies. All were conducted in North America with relatively small sample sizes, contrary to the present study which includes nearly 9000 European participants with lower cardiovascular risk profiles. In the Duke EPSE study, EDS was defined as the necessity to nap during the day, which may not capture the same group of individuals with EDS as defined in the present study. In the remaining two earlier studies, the Cardiovascular Health Study and the Canadian Study of Health and Aging, EDS was assessed through a simple yes/no question whereas in the Three City Study, the frequency of EDS was considered on an ordinal scale, which is potentially more sensitive. In previous studies, the association of EDS with mortality was not consistently observed. An independent association was found in the Duke EPSE study and in the Cardiovascular Health Study, whereas in the Canadian study, the association was no longer significant after adjustment for classical cardiovascular risk factors. In addition, interactions reported in some earlier studies were not found in the Three City Study. In the Cardiovascular Health Study, women were at higher risk than men, whereas the opposite was found in the present analysis (although the interaction was not significant). Also, in the Duke EPSE study, frequent nappers who were cognitively impaired were at significant increased risk of mortality over 4 years, whereas frequent nappers without cognitive dysfunction had a significantly reduced risk of mortality, compared with cognitively nonimpaired non-nappers subjects. In the Three City, no significant interaction was found between baseline-MMSE, EDS, and mortality. Persons diagnosed with dementia at baseline were, however, excluded in our study.

Table 2. Hazard Ratios and 95% CI of 6-Year Mortality for Excessive Daytime Sleepiness: The Three City Study

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Total Mortality n=762</th>
<th>Cancer Mortality n=260</th>
<th>CV Mortality n=196</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>Events, n (%)</td>
<td>Model 1 HR and 95% CI</td>
<td>Model 2 HR and 95% CI</td>
</tr>
<tr>
<td>No EDS</td>
<td>546 (8, 1)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>EDS</td>
<td>216 (14.0)</td>
<td>1.42 (1.21–1.68)</td>
<td>1.33 (1.13–1.61)</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>Events, n (%)</td>
<td>Model 1 HR and 95% CI</td>
<td>Model 2 HR and 95% CI</td>
</tr>
<tr>
<td>No EDS</td>
<td>200 (3.0)</td>
<td>1.09 (0.80–1.47)</td>
<td>1.12 (0.81–1.54)</td>
</tr>
<tr>
<td>EDS</td>
<td>60 (3.9)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CV mortality</td>
<td>Events, n (%)</td>
<td>Model 1 HR and 95% CI</td>
<td>Model 2 HR and 95% CI</td>
</tr>
<tr>
<td>No EDS</td>
<td>132 (2.0)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>EDS</td>
<td>64 (4.2)</td>
<td>1.76 (1.28–2.41)</td>
<td>1.49 (1.05–2.10)</td>
</tr>
</tbody>
</table>

Hazard ratios (HR) and their 95% CI were derived from Cox proportional hazard regression analysis. Model 1 was adjusted for age, gender, and the study-centre; Model 2 was adjusted for risk factors included in model 1 and prior CVD, BMI, daily alcohol consumption, current smoking status, diabetes, MMSE, systolic blood pressure, total and HDL cholesterol, antihypertensive and lipids lowering medications; Model 3 was adjusted for risk factors included in model 2 and medications for sleep and depressive symptoms.
We extended previous studies of EDS with mortality by exploring several confounding factors. For instance, the association of EDS with mortality might be secondary to nocturnal sleep complaints including insomnia, but we observed consistent associations in subjects with and without insomnia. Similarly, results were unchanged when the impact of medications for sleep was controlled for. Association might also be attributable to chronic illness condition but excluding death that occurred in the first two years of follow-up did not materially change the results. Lastly, we explored the possible confounding effect of depressive symptoms and found that association of EDS with mortality was particularly observed in nondepressive participants. Nevertheless, residual confounding by unmeasured risk factors cannot be excluded. Although EDS remained associated with mortality after adjustment for obesity and loud snoring in the present study, the confounding effect of an underlying sleep apnea syndrome (SAS) may not be excluded because obesity and snoring have shown to be less powerful predictors of SAS in the elderly than in middle-aged populations. Tiredness may represent an additional confounder, but in the Canadian study, there was a moderate correlation between tiredness and EDS. Lastly, short and long duration of sleep has been related to mortality and may contribute to the association of EDS with mortality.

The mechanisms by which EDS itself might increase the risk of mortality remain poorly understood. Subjects with EDS may be sleep deprived, and experimental studies conducted with volunteers indicate that sleep deprivation is associated with sympathetic tone activation and elevated levels of circulating catecholamines, which may affect survival. In the present study, however, resting heart rate, a simple marker of autonomous imbalance, was not different in subjects with and without EDS. Modest sleep deprivation in normal volunteers has also been associated with increased levels of circulating inflammatory and hemostatic factors, which in turn might increase the risk of mortality. We explored the possibility that atherosclerosis mediated the association between EDS and mortality. In the present study, however, atherosclerotic burden, as measured by the presence of carotid plaques and IMT, was not different in subjects with and without EDS, and the association of EDS with mortality (including cardiovascular mortality) remained independent after adjustment for the presence of plaques and IMT. This suggests that atherosclerosis may not mediate the association between EDS and mortality. However, echographic criteria and the state of stability of the examined carotid plaques may give more sensitive information but these data were not available in the current study.

These data may have clinical implications adding to the body evidence that EDS is not a benign but rather an important risk marker for mid term mortality in community-dwelling elderly. Thus its assessment using a simple questionnaire should be part of routine examinations in the elderly. Screened subjects may thereafter be suggested to undertake polysomnographic recordings to detect a possible underlying sleep disorder.

In our study, EDS was self-reported using a short questionnaire rather than the more appropriate ESS. The ESS
has been used in one study-center (Montpellier) where the median ESS score was observed to increase gradually among the 4 frequency categories of EDS (never, rare, regular, frequent). However, only 12.6% of individuals who reported having regular or frequent EDS scored more than 10 on the EPPS, the cut-off used to define a high probability of daytime sleepiness. It is therefore highly likely that the current reported association between EDS and mortality is underestimated.

The present study has some limitations. Objective measures of sleep quality and daytime sleepiness by polysomnographic and multiple sleep latency tests recordings were not available for this study, but these are difficult to implement in a large multicentric cohort with multiple aims like the Three City Study. Sleep complaints were assessed only once at the baseline examination. As volunteers, the present study participants may not be representative of the French elderly population. The low participation rate of the study participants may not be representative of the French elderly population. The 3C Study is also supported by the Caisse Nationale des Maladies des Travailleurs Salaris, Direction Generale de la Santé et de la Recherche Medicales (INSERM), the Victor Segalen–Bordeaux II University, and Sanofi-Aventis.

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Disclosures
None.

References
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