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## RESEARCH ARTICLE



# The role of cardiovascular health and vascular events in the relationship between excessive daytime sleepiness and dementia risk

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## Summary

Many studies suggest a relationship between excessive daytime sleepiness (EDS) and dementia incidence, but the underlying mechanisms remain uncertain. The study aimed to investigate the role of cardiovascular burden in the relationship between EDS and dementia incidence over a 12-year follow-up in community-dwelling older adults. We performed analyses on 6171 subjects (aged  $\geq 65$  years) free of dementia and vascular disease at baseline. Participants self-reported EDS at baseline and an expert committee validated both prevalent and incident dementia. We defined cardiovascular burden by a low Cardiovascular Health score, constructed using the American Heart Association metrics, and incident vascular events. To explore the potential role of the cardiovascular burden in the relationship between EDS and dementia, we conducted mediation analyses with inverse odds ratio-weighted estimation, using multivariable-adjusted proportional hazard Cox and logistic regression models. Subjects with EDS had a higher risk of all-cause dementia (hazard ratio [HR] 1.39, 95% confidence interval [CI] 1.13–1.69) and dementia with vascular component (DVC) (HR 2.14, 95% CI 1.30–3.51), but not Alzheimer's disease (HR 1.18, 95% CI 0.93–1.51). Cardiovascular burden explained 5% (95% CI 4.1–5.2) and 11% (95% CI 9.7–11.3) of the relationship between EDS and all-cause dementia and DVC, respectively. These findings confirm that EDS may be implicated in the development of dementia and indicate a weaker than expected role of cardiovascular burden in the relationship between EDS and DVC.

## KEYWORDS

cardiovascular disease, dementia, excessive daytime sleepiness, mediation analysis, older people

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## 1 | INTRODUCTION

Research in the field of dementia has largely focused on the potential contribution of lifestyle behaviours and health factors (Livingston et al., 2020). Recently, sleep has received attention for its role in the development of cognitive impairment and the pathological processes of dementia (Shi et al., 2018; Xu et al., 2020), but the underlying mechanisms remain unclear. Particularly, excessive daytime sleepiness (EDS) has been shown to be associated with a higher risk of all-cause dementia and even more with dementia with vascular component (DVC) (Cavallès et al., 2022; Elwood et al., 2011; Foley et al., 2001; Merlino et al., 2010; Tsapanou et al., 2015). Most of these results suggest the potential role of cardiovascular burden in this association. Evidence from the literature has indicated that EDS was associated with metabolic diseases including obesity, diabetes mellitus, and hypertension (Akbaraly et al., 2015; Lindberg et al., 2007; Maugeri et al., 2018), and is a risk factor for cardiovascular morbidity and mortality (Bock et al., 2022; Ng et al., 2018). Given the well-documented association between cardiovascular burden and dementia (Deckers et al., 2017; Kivipelto et al., 2005; Kuźma et al., 2018; Livingston et al., 2020; Wagner et al., 2018), it may be hypothesised that a poor cardiovascular health characterised by risky behaviours (smoking, physical inactivity, dietary unbalance), unhealthy biological risk factors (high blood lipids, high blood pressure, obesity, diabetes mellitus) and/or clinical vascular events might play a role in the association between EDS and dementia. Quantifying mediating pathways can improve our understanding of the underlying mechanisms through which EDS may influence risk of dementia. In this context, causal mediation analyses can be used to investigate this complex relationship and to describe how EDS impacts the risk of dementia. This approach allows to decompose the total effect of EDS on incident dementia into its direct effect and its indirect effect via cardiovascular burden, and to quantify the importance of each pathway. We hypothesised that poor cardiovascular health and vascular events may mediate the association between EDS and incident dementia, and more strongly for DVC. The aim of this study was to investigate this hypothesis over a 12-year follow-up in the same cohort with longitudinal assessments of vascular events and dementia (including all-cause dementia and DVC).

## 2 | METHODS

### 2.1 | Study design and participants

Data were issued from the Three-City study, a prospective cohort involving three French cities: Bordeaux ( $n = 2104$ ), Dijon ( $n = 4931$ ) and Montpellier ( $n = 2259$ ) (Three-City Study Group, 2003). Its main objective was to assess the risk of dementia and cognitive impairment related to vascular factors. Overall, 9294 participants aged  $\geq 65$  years were recruited from the electoral rolls between 1999 and 2001. The participants were interviewed and underwent clinical examinations at baseline and every 2–3 years during 12 years. After excluding participants with a diagnosis of dementia or a history of vascular events,

those with missing data on EDS and covariates, and those without follow-up visits (Figure 1), the final study sample consisted of 6171 subjects. The ethics committees of the Hospital of Kremlin-Bicêtre and Sud-Méditerranée III (France) approved the study protocol, and written informed consent was obtained from each participant.

### 2.2 | Dementia diagnosis

In the three centres, the same standardised clinical protocol was used to establish the diagnosis of both prevalent and incident cases of dementia according to the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition. First, a neurologist made the diagnosis by considering neuropsychological tests, clinical data, the severity of cognitive disorders assessed by the Clinical Dementia Rating Scale, and when available, hospitalisation records, outpatient reports, as well as magnetic resonance imaging or computed tomography scans. Second, an independent committee of neurologists validated the diagnosis and determined the subtypes of dementia (such as probable or possible Alzheimer's disease [AD], mixed dementia, vascular dementia, and other types) based on clinical judgement (e.g., clinical Hachinski criteria and neuropsychological deficits) and neuroimaging data when available, in accordance with the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for AD (McKhann et al., 1984), and the National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria for vascular dementia (Román et al., 1993). Mixed dementia was defined as diagnosis of AD with either cerebrovascular lesions on brain imaging or a history of stroke and the presence of significant executive function deficits. Due to a small number of cases, mixed dementia and pure vascular dementia were pooled in a single category, DVC. The onset of dementia was estimated at the midpoint between diagnosis and the prior examination without dementia. Participants who did not develop dementia were censored at the date of last follow-up visit.

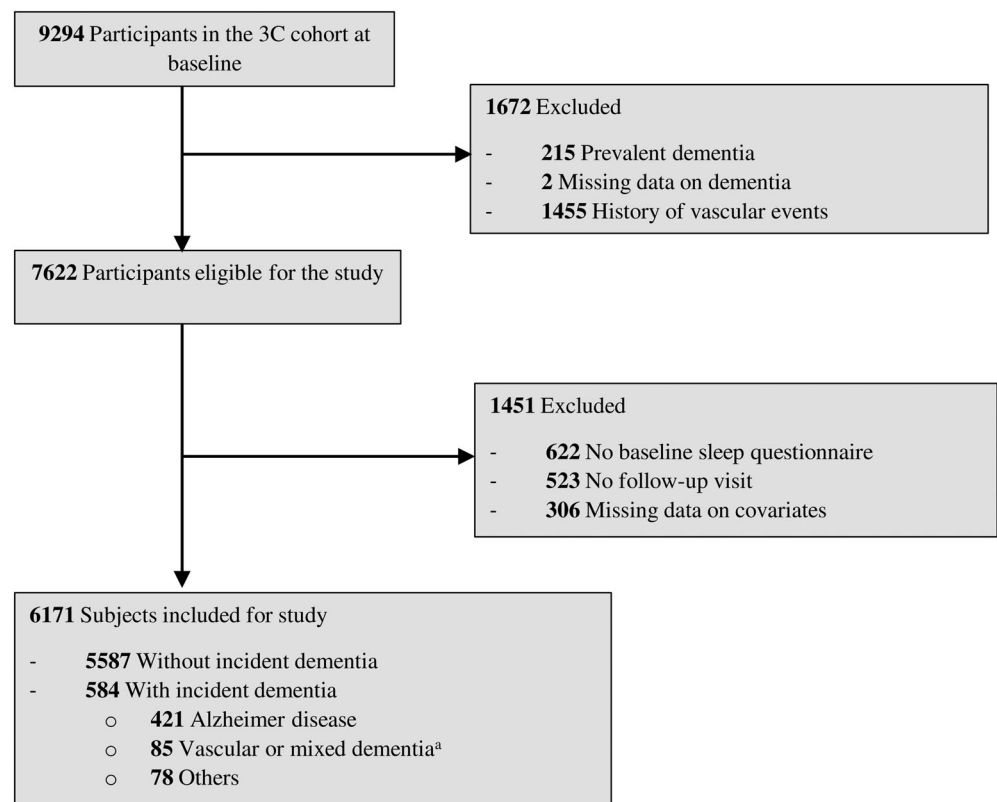
### 2.3 | Excessive daytime sleepiness

At baseline, EDS was assessed using a self-administrated sleep questionnaire about the condition at time of study that included the following question: 'Do you feel very sleepy during the day?' (Cavallès et al., 2022). Participants were invited to answer on a 4-point Likert scale (0 = never, 1 = rarely, 2 = frequently, 3 = often). The presence of EDS was defined by being 'frequently' or 'often' very sleepy.

### 2.4 | Cardiovascular burden: poor cardiovascular health and vascular events

We summarised the level of cardiovascular health at baseline by using a Cardiovascular Health score (CVH score). Briefly, the CVH score was constructed using the American Heart Association metrics for ascertainment

**FIGURE 1** Flow chart.  
<sup>a</sup>54 mixed dementia; 31 vascular dementia. 3C, Three-City.



of cardiovascular health status: smoking, physical activity, diet, body mass index, total cholesterol, blood pressure, and fasting plasma glucose (Lloyd-Jones et al., 2010). It was adapted in the Three-City study (Samieri et al., 2018) and calculated by assigning 0 points for each metric at poor level, 1 point for each metric at intermediate level, and 2 points for each metric at the recommended optimal level (total score range, 0–14). We classified participants in the lowest tertile of the CVH score (i.e., score <7) as having a poor cardiovascular health, while the remaining two tertiles were categorised as having a good cardiovascular health (i.e., score  $\geq 7$ ).

At each follow-up visit, participants were asked to report any new severe medical events or hospitalisations related to vascular events since the last interview, with help of general practitioners, specialists, and hospital records when possible. Two independent experts reviewed and validated these vascular events (Study Group, 2003). Coronary heart disease (CHD) events included hospitalised angina or myocardial infarction, coronary balloon dilatation, and arterial bypass. Stroke was defined, according to the criteria of the World Health Organization, as a new focal neurological deficit of sudden or rapid onset and of presumed vascular origin, lasting  $\geq 24$  h. In the case of multiple events during the follow-up, the first event was considered.

A poor CVH score, and the incidence of vascular events constituted the two mediators of interest.

## 2.5 | Baseline covariates

Sociodemographic variables consisted of gender, age, study centre (Bordeaux; Dijon; Montpellier), educational level (<6; 6–12;  $\geq 12$  years).

Alcohol consumption (<12; 12–36;  $\geq 36$  g of ethanol/day) was recorded. Health status variables included impaired mobility (none; confined to bed, seat, home, or neighbourhood) and depressive symptoms, defined as a score above the 16-point cutoff on the Center for Epidemiologic Studies-Depression Scale (CES-D), or current antidepressant treatment. Data on cardiac diseases (i.e., heart rhythm disorders, heart failure) and respiratory disorders (i.e., chronic bronchitis, asthma attacks) were collected. Apolipoprotein E (APOE)- $\epsilon 4$  was genotyped at baseline as described (Dufouil et al., 2005). Loud snoring and insomnia complaints, including difficulties in initiating sleep, difficulties in maintaining sleep, and early morning awakenings (around 4 a.m.), were assessed using binary questions (frequently/often versus never/rarely). The severity of insomnia was determined by the presence of one or more of these complaints.

The interviewer checked the use of prescribed drugs during the preceding month and coded them using the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system. The use of sleep prescribed medication was defined as taking at least one benzodiazepine (BZD) or BZD-like compounds (zolpidem and zopiclone), or miscellaneous medications (including barbiturates, anti-histamines, and other pharmacological categories such as neuroleptics and sedative antidepressants [e.g., doxepin, mirtazapine, trazodone]) during the preceding month.

## 2.6 | Statistical analyses

We performed multivariable-adjusted proportional hazard Cox models with delay entry, using age as the time scale, to estimate the hazard

ratios (HRs) and their 95% confidence intervals (CIs) for the association between EDS at baseline and the incidence of dementia (Commenges et al., 1998). All the models were minimally adjusted for study centre, gender, educational level, APOE-ε4, impaired mobility, and alcohol consumption, and further adjusted for sleep medication use, depressive symptoms, number of insomnia complaints, or loud snoring (selection based a priori from the literature [Livingston et al., 2020]).

### 2.6.1 | Mediation analyses

First, we explored the effect of the two mediators (i.e., baseline poor CVH score and incident vascular events) considered together and then, separately. Three hypothetical causal frameworks modelling the relationship between EDS and incident dementia according to the choice of mediator have been implemented (Figure 2). For each causal framework, a mediation analysis was conducted using the inverse odds ratio-weighted (IORW) method (Tchetgen, 2013). This approach is a flexible method for estimating mediation effects that can handle multiple mediators that may be related to each other (Nguyen et al., 2015). This method aims at decomposing the total effect (TE) of EDS on incident dementia into its natural direct effect (NDE; i.e., estimated association of EDS with dementia incidence not mediated by the potential mediators) and its natural indirect effect (NIE; i.e., estimated associations between EDS and dementia incidence mediated by the potential mediators). For each mediation analysis, implementation of the different effects was done in several steps. First, IORW weights were calculated from a multiple logistic regression model for exposure (i.e., EDS), given mediator of interest and covariates. The linearity hypothesis for quantitative variables (i.e., age) was verified using fractional polynomials. Then, NDE was estimated using Cox regression model of the outcome (i.e., dementia incidence) on the exposure (i.e., EDS) and covariates, weighted by the load calculated previously. These models were adjusted for age, study centre, gender, educational level, APOE-ε4, impaired mobility, and alcohol consumption. TE was further estimated via the same Cox regression model but without considering the IORW weight; and NIE was calculated as the difference between TE and NDE. Interaction terms were tested between: (i) study centre, (ii) gender, (iii) APOE-ε4, (iv) sleep medication use, (v) depressive symptoms, (vi) insomnia complaints, (vii) loud snoring, and (viii) each mediator and EDS for the risk of dementia. Finally, bootstrapping based on 1000 replications was computed to derive 95% CIs for TE, NDE and NIE parameters. The estimates were presented as HRs with their 95% CIs. Moreover, the estimated proportion of the TE of EDS on dementia mediated through each mediator was calculated (proportion mediated (PM) =  $(HR^{NDE}(HR^{NIE} - 1))/(HR^{NDE}HR^{NIE} - 1)$ ).

Four sensitivity analyses were performed. First, to examine the potential differential effects of vascular events, we performed mediation analyses by separating stroke and CHD. Second, to take into account attrition in the mediation models (including death, withdrawal and lost to follow-up), we estimated inverse probability of censoring weights (IPCW; Cerdá & Keyes, 2017). We included study centre, age

at baseline, gender, educational level, APOE-ε4, alcohol consumption, smoking habits, diabetes mellitus, other cardiac diseases, and respiratory disorders as predictors of attrition to build IPCWs. Third, as sleep medication use may bias the assessment of EDS, we performed additional analyses excluding participants taking a sleep medication at baseline. Fourth, to study the reliability of the results in a higher-risk population, we added participants with vascular events at baseline in the analysis.

As a supplementary analysis, we evaluated another hypothesis, where a poor CVH score would cause EDS (Figure S1) (Bixler et al., 2005; Yusuf et al., 2022). Indeed, a poor CVH score could represent a confounding factor in the relationship between EDS and dementia rather than a mediating factor. To evaluate this alternative causality scenario, we performed a mediation analysis using incident vascular events as the only mediator, while adjusting for poor CVH score in the models.

Statistical analyses were performed using the Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA) and R 3.6.3 statistical software (R Foundation for Statistical Computing, Vienna, Austria).

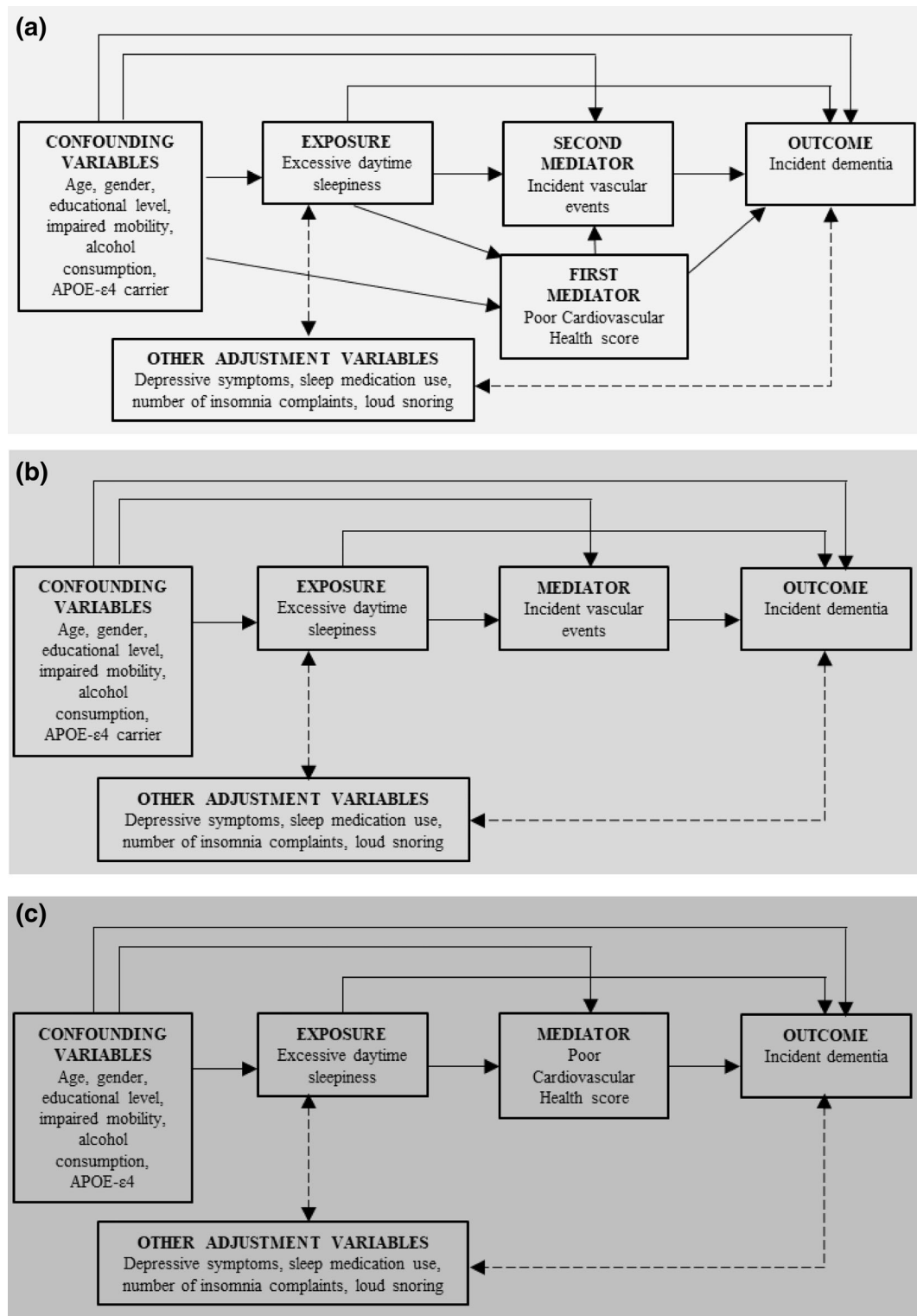
## 3 | RESULTS

### 3.1 | Study sample

The study sample consisted of 6171 subjects (Figure 1). The median (interquartile range [IQR]) age of the sample was 72.7 (69.3–76.9) years at baseline, and 63% were women. Among the included participants, 17.1% reported EDS, and 21.7% used sleep medication (15.9% BZD, 4.7% BZD-like compounds, 1.7% antihistamine compounds, 1.4% sedatives, and 1.2% miscellaneous medication) at baseline. Compared with participants without EDS, those with EDS were older, more frequently men, had a lower educational level, were more confined, took more sleep medication, reported more loud snoring, had more depressive symptoms and insomnia complaints, and had a poorer CVH score (Table 1). The frequencies of participants who had poor levels of cardiovascular health metrics were as follows: smoking, 6.0%; low physical activity, 23.1%; unhealthy diet, 33.9%; obesity, 12.7%; high total cholesterol, 33.7%; high blood pressure, 62.3%; and abnormal fasting plasma glucose, 4.4%. Description of the cardiovascular health metric frequencies according to the CVH score levels are described in supplementary results (Table S1).

### 3.2 | Association between EDS and dementia incidence

After a median (IQR) follow-up of 9.2 (4.3–11.3) years, 9.5% of participants ( $n = 584$ ) developed dementia (including 421 AD and 85 DVC; annual incidence rate = 11.7/1000 person-years) and 6.0% ( $n = 368$ ) reported a vascular event during follow-up (249 CHD and 119 stroke as first event).



**FIGURE 2** Causal frameworks modelling the complex relationship between excessive daytime sleepiness and dementia through mediator variables. (a) Causal framework modelling the relationship between excessive daytime sleepiness and dementia through incident vascular events and poor Cardiovascular Health score (including smoking, physical activity, diet, body mass index, total cholesterol, blood pressure, and fasting plasma glucose) together as mediators. (b) Causal framework modelling the relationship between excessive daytime sleepiness and dementia using only incident vascular events as mediator. (c) Causal framework modelling the relationship between excessive daytime sleepiness and dementia using only poor Cardiovascular Health score as mediator. APOE-ε4, apolipoprotein E-ε4.



Characteristic	No EDS, <i>n</i> = 5114	EDS, <i>n</i> = 1057	<i>p</i> <sup>b</sup>
Gender, women, <i>n</i> (%)	3337 (65.3)	565 (53.5)	<0.0001
Age, years, median (IQR)	72.5 (69.1–76.7)	74.0 (70.1–78.1)	<0.0001
Educational level (years), <i>n</i> (%)			
<6	1128 (22.1)	299 (28.3)	<0.0001
6–12	1903 (37.2)	366 (34.6)	
≥12	2083 (40.7)	392 (37.1)	
Impaired mobility, yes, <i>n</i> (%)	215 (4.2)	75 (7.1)	<0.0001
Alcohol (g/day), <i>n</i> (%)			
<12	3375 (66.0)	663 (62.7)	0.08
12–36	1317 (25.8)	289 (27.3)	
≥36	422 (8.3)	105 (9.9)	
APOE-ε4 carrier, yes, <i>n</i> (%)	1014 (19.8)	188 (17.8)	0.13
Poor cardiovascular health score, yes, <i>n</i> (%)	862 (16.9)	278 (26.3)	<0.0001
Incident vascular events, yes, <i>n</i> (%)	290 (5.7)	78 (7.4)	0.03
Depressive symptoms <sup>a</sup> , yes, <i>n</i> (%)	1171 (23.1)	333 (32.1)	<0.0001
Sleep medication use, yes, <i>n</i> (%)	1066 (20.8)	270 (25.5)	<0.001
Number of insomnia complaints, <i>n</i> (%)			
0	1546 (30.8)	121 (11.6)	<0.0001
1	1489 (29.7)	309 (29.7)	
2–3	1987 (39.6)	610 (58.7)	
Loud snoring, yes	1417 (31.5)	477 (53.2)	<0.0001

Abbreviations: APOE, apolipoprotein E; EDS, excessive daytime sleepiness; IQR, interquartile range.

<sup>a</sup>Center for Epidemiologic Studies-Depression Scale score ≥16 or current antidepressant treatment.

<sup>b</sup>Student test was used for continuous variables and chi-squared test for categorical variables.

Excessive daytime sleepiness was associated with a higher risk of all-cause dementia (HR 1.39, 95% CI 1.13–1.69) and DVC (HR 2.14, 95% CI 1.30–3.51) but not with AD incidence (HR 1.18, 95% CI 0.93–1.51) (Figure 3). Results remained unchanged after further adjustment for sleep medication use, depressive symptoms, number of insomnia complaints, or loud snoring (data not shown). We therefore explored the mediation analyses only for all-cause dementia and DVC.

### 3.3 | Mediation analyses

When we considered poor CVH score at baseline and incident vascular events as potential mediators together (Figure 2a), the TE was decomposed into a NDE HR of 1.38 (95% CI 1.12–1.69) and a NIE HR of 1.01 (95% CI 0.98–1.06) for all-cause dementia (Table 2, Model 1). The combined effect of these two mediators explained 5% (95% CI 4.1–5.2) of the relationship between EDS and incident all-cause dementia. Regarding DVC, we observed higher direct (HR 2.04, 95% CI 1.16–3.24) and indirect effects (HR 1.06, 95% CI 0.96–1.1), with a PM of 11% (95% CI 9.7–11.3) (Table 2, Model 1). All the results remained globally unchanged after adjustment for sleep medication use, depressive symptoms, number of insomnia complaints, or loud snoring (Table 2, Models 2, 3, 4, and 5).

Considering only the incidence of vascular events as a potential mediator (Figure 2b), we found that it explained 3% (95% CI 2.7–3.6)

of the association between EDS and DVC (direct effect HR 2.13, 95% CI 1.22–3.40; indirect effect HR 1.02, 95% CI 0.99–1.07) but it did not contribute to the association between EDS and all-cause dementia (PM = 0%; Table 2, Model 1). All the results remained globally unchanged after several adjustments (models 2–5 in Table 2).

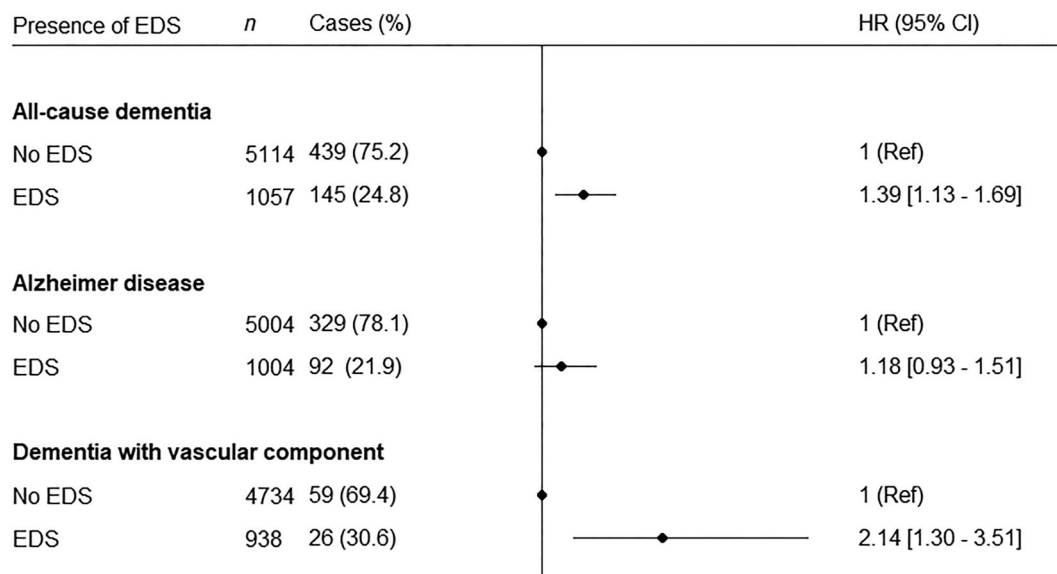
When we considered only poor CVH score as a potential mediator (Figure 2c), it explained respectively 6% (95% CI 5.5–6.7); with direct effect and indirect effect of the association between EDS and all-cause dementia equal to HR 1.37 (95% CI 1.12–1.68) and HR 1.02 (95% CI 0.98–1.06), respectively (Table 2, Model 1). For DVC, poor CVH score alone explained 7% (95% CI 6.7–8.1) of the relation with direct and indirect effects equal to HR 2.08 (95% CI 1.18–3.26) and HR 1.04 (95% CI 0.95–1.16), respectively (Table 2, Model 1). The results remained generally unchanged after adjustment (models 2–5 in Table 2).

No interaction was observed between study centre, gender, APOE-ε4, sleep medication use, depressive symptoms, number of insomnia symptoms, loud snoring, each mediator, and EDS for the risk of dementia.

### 3.4 | Sensitivity analyses

When we examined stroke and CHD separately, stroke events contributed to the relationships between EDS and both all-cause

**TABLE 1** Baseline characteristics of the study population according to presence of excessive daytime sleepiness (*n* = 6171).



**FIGURE 3** Association between excessive daytime sleepiness (EDS) and dementia incidence over a 12-year follow-up (1999–2012). Models adjusted for study centre, gender, educational level, apolipoprotein E- $\epsilon$ 4 carrier, impaired mobility, alcohol consumption, and age as timescale. CI, confidence interval; HR, hazard ratio.

dementia and DVC, with a PM of 1% (95% CI 0.9–1.5) and 6% (95% CI 5.9–7.1), respectively. CHD events did not contribute to such relationships (PM = 0%). Furthermore, the combined effect of CVH score and stroke explained 7% (95% CI 6.8–8.1) and 14% (95% CI 13.2–15.0) of the relationships between EDS and all-cause dementia and DVC, respectively; whereas the combined effect of CVH score and CHD events explained 5% (95% CI 4.3–5.4) and 7% (95% CI 6.6–7.3) of the relationships, respectively.

Results were consistent when: (i) considering differential censoring (Table 2, Model 5), although the PM was smaller; (ii) excluding participants who took sleep medication at baseline (analyses being implemented only for all-cause dementia due to small sample size for DVC; Table S2); and (iii) including participants with vascular events at baseline in the sample of analysis ( $n = 7224$ ) including 742 (10.3%) incident dementia cases (of whom 502 were AD [67.7%] and 150 were DVC [20.2%]; Table S3).

In a supplementary analysis, we assessed the role of vascular events in the relationship between EDS and dementia, considering poor CVH score as a confounding factor instead of a mediator. Similarly to the main analysis, the incidence of vascular events contributed to 3% (95% CI 2.6–3.4) of the association between EDS and DVC, but not to all-cause dementia (Figure S1, Table S4).

## 4 | DISCUSSION

In this large cohort of community-dwelling older adults, we quantified the contribution of cardiovascular health and vascular events in the relationship between EDS and dementia. Cardiovascular burden explained 5% and 11% of the relationship between EDS and all-cause dementia and DVC, respectively. Overall, the cardiovascular burden seems to play a marginal role in this association. For all-cause dementia,

the indirect effect and the proportion mediated by cardiovascular burden were negligible. For DVC, the results suggest that the association between EDS and dementia was mediated by cardiovascular health and stroke events, but this effect was weaker than expected.

Our present results on the effect of EDS on dementia incidence are in line with most longitudinal studies reporting that EDS was associated with a higher risk of dementia (Elwood et al., 2011; Foley et al., 2001; Merlino et al., 2010). However, the mechanisms underlying these associations remain unclear and there may be bidirectional effects between sleep and dementia (Lucey, 2020; Yaffe et al., 2014). EDS may directly influence cognitive functioning because of its associations with global and regional cortical thickness reduction, particularly in the temporal region, which is one of the first regions impacted in dementia (Carvalho et al., 2017). EDS may also impact cognition by increasing the longitudinal  $\beta$ -amyloid accumulation in older population (Carvalho et al., 2018). Furthermore, EDS can be a marker of mental and health factors such as depression, which are themselves associated with dementia incidence (Diniz et al., 2013; Livingston et al., 2020). However, the latter hypothesis appears to be of less concern in our study as we controlled for depressive symptoms (Model 3), and the results remained unchanged from the main results.

An indirect pathway linking EDS and dementia through cardiovascular burden was supported by our mediation analysis. We reported a lower-than-expected contribution for the role of cardiovascular health and stroke incidence in the relationship between EDS and DVC, with negligible involvement for all-cause dementia. EDS can be a proxy of night-time sleep problems such as sleep deprivation, and it is considered as the cardinal symptom of obstructive sleep apnea, which plays a facilitating role in cardiovascular impairment via hypoxaemia and sleep fragmentation (Ryan, 2018; Yoshida & Takeishi, 2019). Insomnia was often associated with an increased risk of cardiovascular diseases



**TABLE 2** Estimated total effect (TE), natural direct effect (NDE), natural indirect effect (NIE), and proportion mediated (PM) using vascular events, Cardiovascular Health score, and their joint effects as mediator for the association of excessive daytime sleepiness with incidence all-cause dementia, and dementia with vascular component over a 12-year follow-up (1999–2012).

EDS	All-cause dementia															
	TE						Dementia with vascular component									
	N	HR	(95% CI)	NDE	HR	(95% CI)	N	PM, %	NIE	HR	(95% CI)	NIE	HR	(95% CI)	PM, %	
Multiple mediators = poor Cardiovascular Health score and incident vascular events																
Model 1	6171	1.39	(1.14; 1.70)	1.38	(1.12; 1.69)	1.01	0.98; 1.06	5	5672	2.16	(1.24; 3.47)	2.04	(1.16; 3.24)	1.06	(0.96; 1.18)	11
Model 2	6171	1.38	(1.13; 1.68)	1.37	(1.11; 1.67)	1.01	(0.98; 1.05)	4	5672	2.14	(1.24; 3.45)	2.03	(1.16; 3.21)	1.06	(0.96; 1.18)	10
Model 3	6100	1.34	(1.09; 1.64)	1.33	(1.08; 1.64)	1.01	(0.97; 1.04)	3	5603	2.05	(1.16; 3.37)	1.94	(1.10; 3.08)	1.06	(0.97; 1.17)	11
Model 4	6062	1.39	(1.13; 1.70)	1.37	(1.12; 1.69)	1.02	(0.98; 1.06)	5	5574	2.10	(1.20; 3.45)	1.97	(1.13; 3.09)	1.07	(0.97; 1.19)	12
Model 5	5398	1.53	(1.23; 1.90)	1.51	(1.22; 1.88)	1.01	(0.98; 1.06)	4	4967	2.24	(1.20; 3.64)	2.14	(1.14; 3.51)	1.05	(0.95; 1.17)	8
Model 6	6147	1.40	(1.12; 1.71)	1.39	(1.12; 1.70)	1.01	(0.97; 1.04)	2	5650	2.07	(1.14; 3.25)	2.02	(1.11; 3.21)	1.03	(0.95; 1.13)	5
Mediator = incident vascular events																
Model 1	6171	1.39	(1.14; 1.70)	1.40	(1.14; 1.71)	0.99	(0.98; 1.00)	0	5672	2.16	(1.24; 3.47)	2.13	(1.22; 3.40)	1.02	(0.99; 1.07)	3
Model 2	6171	1.39	(1.13; 1.67)	1.40	(1.14; 1.68)	0.99	(0.98; 1.00)	0	5672	2.14	(1.24; 3.45)	2.10	(1.22; 3.39)	1.02	(0.99; 1.07)	3
Model 3	6100	1.34	(1.09; 1.63)	1.35	(1.10; 1.64)	0.99	(0.98; 1.00)	0	5603	2.05	(1.16; 3.37)	2.02	(1.13; 3.29)	1.02	(0.99; 1.08)	4
Model 4	6062	1.40	(1.13; 1.71)	1.41	(1.14; 1.72)	0.99	(0.98; 1.00)	0	5574	2.10	(1.20; 3.45)	2.07	(1.19; 3.42)	1.02	(0.99; 1.08)	3
Model 5	5398	1.52	(1.24; 1.89)	1.53	(1.25; 1.89)	0.99	(0.98; 1.00)	0	4967	2.24	(1.20; 3.65)	2.19	(1.16; 3.58)	1.02	(0.99; 1.10)	4
Model 6	6147	1.41	(1.13; 1.72)	1.42	(1.14; 1.74)	0.99	(0.97; 1.00)	0	5650	2.07	(1.14; 3.25)	2.02	(1.12; 3.20)	1.02	(0.98; 1.08)	4
Mediator = poor Cardiovascular Health score																
Model 1	6171	1.39	(1.14; 1.70)	1.37	(1.12; 1.68)	1.02	(0.98; 1.06)	6	5672	2.16	(1.24; 3.47)	2.08	(1.18; 3.26)	1.04	(0.95; 1.16)	7
Model 2	6171	1.38	(1.13; 1.68)	1.36	(1.11; 1.67)	1.02	(0.98; 1.05)	5	5672	2.14	(1.24; 3.45)	2.07	(1.17; 3.23)	1.04	(0.95; 1.16)	7
Model 3	6100	1.34	(1.09; 1.64)	1.32	(1.08; 1.62)	1.01	(0.98; 1.04)	5	5603	2.05	(1.16; 3.37)	1.98	(1.12; 3.13)	1.04	(0.96; 1.14)	7
Model 4	6062	1.39	(1.13; 1.70)	1.36	(1.11; 1.68)	1.02	(0.98; 1.06)	7	5574	2.10	(1.20; 3.45)	2.01	(1.13; 3.14)	1.05	(0.95; 1.16)	9
Model 5	5398	1.53	(1.23; 1.90)	1.50	(1.21; 1.86)	1.02	(0.98; 1.06)	5	4967	2.24	(1.20; 3.65)	2.20	(1.17; 3.58)	1.02	(0.94; 1.14)	4
Model 6	6147	1.40	(1.12; 1.71)	1.38	(1.11; 1.69)	1.01	(0.98; 1.05)	4	5650	2.07	(1.14; 3.25)	2.06	(1.13; 3.25)	1.01	(0.94; 1.09)	1
Stroke																
Multiple mediators = poor Cardiovascular Health score and incident stroke																
Model 1	6171	1.39	(1.14; 1.70)	1.37	(1.11; 1.68)	1.02	(0.99; 1.06)	7	5672	2.16	(1.24; 3.47)	2.00	(1.13; 3.18)	1.08	(0.96; 1.23)	14
Model 2	6171	1.38	(1.13; 1.68)	1.35	(1.10; 1.66)	1.02	(0.98; 1.06)	7	5672	2.14	(1.24; 3.45)	1.99	(1.13; 3.15)	1.08	(0.96; 1.22)	14
Model 3	6100	1.34	(1.09; 1.64)	1.32	(1.07; 1.62)	1.02	(0.98; 1.05)	6	5603	2.05	(1.16; 3.37)	1.91	(1.08; 3.08)	1.07	(0.96; 1.21)	14
Model 4	6062	1.39	(1.13; 1.70)	1.36	(1.10; 1.67)	1.03	(0.99; 1.07)	9	5574	2.10	(1.20; 3.42)	1.92	(1.09; 3.06)	1.10	(0.97; 1.26)	17
Model 5	5398	1.53	(1.23; 1.90)	1.49	(1.20; 1.87)	1.02	(0.99; 1.07)	7	4967	2.24	(1.20; 3.65)	2.08	(1.12; 3.45)	1.08	(0.96; 1.24)	13
Model 6	6147	1.40	(1.12; 1.71)	1.38	(1.11; 1.68)	1.02	(0.99; 1.05)	6	5650	2.07	(1.14; 3.25)	1.96	(1.08; 3.13)	1.06	(0.96; 1.20)	11

TABLE 2 (Continued)

EDS	All-cause dementia										Dementia with vascular component																					
	TE					NDE					NIE					TE					NDE					NIE						
	N	HR	(95% CI)	HR	(95% CI)	N	HR	(95% CI)	HR	(95% CI)	N	HR	(95% CI)	HR	(95% CI)	N	HR	(95% CI)	HR	(95% CI)	N	HR	(95% CI)	HR	(95% CI)	N	HR	(95% CI)	HR	(95% CI)	PM, %	
Mediator = incident stroke																																
Model 1	6171	1.39	(1.14; 1.70)	1.39	(1.13; 1.70)	1.00	(0.99; 1.02)	1.00	(0.99; 1.02)	1	5672	2.16	(1.24; 3.47)	2.09	(1.19; 3.36)	1.04	(0.97; 1.14)	6														
Model 2	6171	1.39	(1.13; 1.67)	1.38	(1.12; 1.67)	1.00	(0.10; 1.02)	1.00	(0.10; 1.02)	1	5672	2.14	(1.24; 3.45)	2.07	(1.18; 3.34)	1.04	(0.97; 1.14)	7														
Model 3	6100	1.34	(1.09; 1.63)	1.33	(1.09; 1.62)	1.00	(0.99; 1.02)	1.00	(0.99; 1.02)	1	5603	2.05	(1.16; 3.37)	1.99	(1.11; 3.25)	1.03	(0.97; 1.14)	6														
Model 4	6062	1.40	(1.13; 1.71)	1.39	(1.13; 1.70)	1.00	(0.99; 1.02)	1.00	(0.99; 1.02)	1	5574	2.10	(1.20; 3.42)	2.01	(1.15; 3.31)	1.04	(0.98; 1.15)	8														
Model 5	5398	1.52	(1.24; 1.89)	1.52	(1.22; 1.88)	1.00	(0.99; 1.02)	1.00	(0.99; 1.02)	1	4967	2.24	(1.20; 3.65)	2.14	(1.13; 3.49)	1.05	(0.98; 1.17)	9														
Model 6	6147	1.41	(1.13; 1.72)	1.41	(1.13; 1.71)	1.00	(0.99; 1.02)	1.00	(0.99; 1.02)	1	5650	2.07	(1.14; 3.25)	1.97	(1.08; 3.11)	1.05	(0.99; 1.16)	9														
Coronary heart disease																																
Multiple mediators = poor Cardiovascular Health score and incident coronary heart disease																																
Model 1	6171	1.39	(1.14; 1.70)	1.38	(1.12; 1.68)	1.01	(0.98; 1.06)	1.01	(0.98; 1.06)	5	5672	2.16	(1.24; 3.47)	2.09	(1.18; 3.28)	1.04	(0.94; 1.16)	7														
Model 2	6171	1.38	(1.13; 1.68)	1.37	(1.11; 1.67)	1.01	(0.98; 1.05)	1.01	(0.98; 1.05)	4	5672	2.14	(1.24; 3.45)	2.08	(1.19; 3.25)	1.03	(0.94; 1.16)	6														
Model 3	6100	1.34	(1.09; 1.64)	1.33	(1.08; 1.63)	1.01	(0.97; 1.04)	1.01	(0.97; 1.04)	2	5603	2.05	(1.16; 3.37)	1.99	(1.13; 3.18)	1.03	(0.95; 1.14)	6														
Model 4	6062	1.39	(1.13; 1.70)	1.37	(1.11; 1.69)	1.02	(0.98; 1.06)	1.02	(0.98; 1.06)	5	5574	2.10	(1.20; 3.42)	2.02	(1.15; 3.18)	1.04	(0.94; 1.17)	8														
Model 5	5398	1.53	(1.23; 1.90)	1.51	(1.22; 1.87)	1.01	(0.98; 1.06)	1.01	(0.98; 1.06)	4	4967	2.24	(1.20; 3.65)	2.21	(1.19; 3.64)	1.02	(0.93; 1.13)	3														
Model 6	6147	1.40	(1.12; 1.71)	1.39	(1.11; 1.70)	1.01	(0.97; 1.04)	1.01	(0.97; 1.04)	3	5650	2.07	(1.14; 3.25)	2.07	(1.13; 3.28)	1.00	(0.93; 1.08)	0														
Mediator = incident coronary heart disease																																
Model 1	6171	1.39	(1.14; 1.70)	1.40	(1.14; 1.71)	0.99	(0.98; 1.01)	0.99	(0.98; 1.01)	0	5672	2.16	(1.24; 3.47)	2.18	(1.25; 3.53)	0.99	(0.97; 1.01)	0														
Model 2	6171	1.39	(1.13; 1.67)	1.40	(1.14; 1.69)	0.99	(0.98; 1.01)	0.99	(0.98; 1.01)	0	5672	2.14	(1.24; 3.45)	2.16	(1.25; 3.45)	0.99	(0.97; 1.01)	0														
Model 3	6100	1.34	(1.09; 1.63)	1.35	(1.10; 1.64)	0.99	(0.97; 1.01)	0.99	(0.97; 1.01)	0	5603	2.05	(1.16; 3.37)	2.07	(1.18; 3.42)	0.99	(0.97; 1.01)	0														
Model 4	6062	1.40	(1.13; 1.71)	1.41	(1.14; 1.72)	0.99	(0.98; 1.01)	0.99	(0.98; 1.01)	0	5574	2.10	(1.20; 3.42)	2.11	(1.21; 3.48)	0.99	(0.97; 1.01)	0														
Model 5	5398	1.52	(1.24; 1.89)	1.53	(1.25; 1.90)	0.99	(0.98; 1.01)	0.99	(0.98; 1.01)	0	4967	2.24	(1.20; 3.65)	2.26	(1.21; 3.69)	0.99	(0.97; 1.01)	0														
Model 6	6147	1.41	(1.13; 1.72)	1.42	(1.14; 1.74)	0.99	(0.97; 1.01)	0.99	(0.97; 1.01)	0	5650	2.07	(1.14; 3.25)	2.08	(1.15; 3.29)	0.99	(0.97; 1.01)	0														

Note: Model 1: adjustment for study centre, gender, age, educational level, apolipoprotein E-e4 carrier, impaired mobility, and alcohol consumption.

Model 2: adjustment for Model 1 plus sleep medication use.

Model 3: adjustment for Model 1 plus depressive symptoms.

Model 4: adjustment for Model 1 plus number of insomnia complaints.

Model 5: adjustment for Model 1 plus loud snoring.

Model 6: adjustment for Model 1 plus inverse probability of censoring weights to account for attrition bias.

Abbreviations: CI, confidence interval; EDS, excessive daytime sleepiness; HR, hazard ratio; NDE, natural direct effect; NIE, natural indirect effect; PM, proportion mediated; TE, total effect.

(Li et al., 2014; Sawadogo et al., 2023); however, its association with dementia remains controversial in the literature and was not associated with dementia onset in the Three-City Study as previously reported (Cavallès et al., 2022). Moreover, in the present study, the relationship between EDS and dementia mediated via cardiovascular health and stroke events remained consistent after controlling for the presence of loud snoring or the number of insomnia symptoms. Sleep fragmentation is often associated with activation of hypothalamic–pituitary–adrenal axis and the sympathetic nervous system leading to subsequent hypertension, oxidative stress, endothelial dysfunction, and elevation of systemic inflammation, which can increase the cardiovascular risk (Mullington et al., 2009; Panossian & Veasey, 2012; Pepin et al., 2014; Vgontzas et al., 2006), cognitive impairment, and DVC. Although we cannot exclude a potential underestimation of the PM due to the potential misclassification of cardiovascular health (as cardiovascular risk factors were not considered prospectively over the follow-up period), the limitation in the study population to older persons (with the impact of cardiovascular risk factors on dementia being more important in midlife than in late life [Livingston et al., 2020]), and the potential bidirectionality of the EDS–cardiovascular burden relationships, these results suggest that there may be several other underlying mechanisms to explain the relationship between EDS and dementia.

The major strengths of this study are the population-based sample using a 12-year follow-up, with extensive evaluations, and validated diagnosis of dementia and vascular events. We performed mediation analysis according to the type of dementia, in particular DVC although statistical power was low. The use of IORW method to explore mediation has the advantage of considering multiple mediators while accounting for their dependence (Tchetgen, 2013). However, this method is statistically less efficient compared with parametric methods (Baron & Kenny, 1986; VanderWeele, 2015). Some limitations need to be acknowledged. Given our study sample, the generalisability of this study was limited to older populations. Future studies in younger populations with larger sample size are needed using other potential mediators (e.g., anxiety, inflammatory markers, hypoxaemia, arousal index) to identify the other pathways underlying the EDS–dementia association. The CVH score was assessed at the same time as the exposure, which may limit the statistical power of the analysis and impact the predicted estimations. However, we tested the hypothesis considering a poor CVH score as a risk factor for EDS, and results remained unchanged. In addition, EDS may rise and fall over time with periods of remission and worsening, often influenced by behavioural characteristics and changes in psychological, metabolic, and night-time sleep patterns, which has not been assessed in our present study. Further studies are thus warranted to confirm our results, with prospective assessment of cardiovascular risk factors and EDS, and with a specific attention to their occurrence and evolution over time. The presence of residual mediators not accounted in the definition of the CVH score as well as unidentified confounders cannot be excluded. Data on obstructive sleep disorder was not available in this study, hence we cannot rule out an underlying confounding effect as this disorder is associated with both EDS and dementia risk (Andrade et al., 2018; Guay-Gagnon et al., 2022;

Pérez-Carbonell et al., 2022). Nevertheless, we took into account snoring that can be used, although imperfect, as a surrogate measure of obstructive sleep disorders, and the results remained unchanged. Future studies might benefit from incorporating objective measures to assess obstructive sleep disorders but also night-time and daytime sleep duration (e.g., actigraphy or polysomnography). Also, bias could have been introduced due to the exclusion of individuals with poorer health than those included, leading to a potential underestimation of the effects. Indeed, subjects excluded from the study were more likely to be older, had a lower educational level, had more frequently impaired mobility, took more sleep medication, complained more of EDS, insomnia complaints, and depressive symptoms, and had a poorer CVH score. However, results accounting for attrition bias and the sensitivity analysis including participants with vascular events at baseline did not change the results. Finally, assessment of EDS was self-reported using a single question, without precise time frame, which may lack precision with potential for misperception.

## 5 | CONCLUSION

The findings of this study provide some insights on the association between EDS, cardiovascular burden, and dementia. The results suggest that strategies focused solely on reducing cardiovascular burden may have limited effectiveness in reducing the impact of EDS on dementia risk in older populations. However, given the evidence linking EDS and dementia, it may be important to explore interventions that directly target EDS itself to potentially reduce the risk of dementia. A better understanding of factors that may explain the association between EDS and dementia will lead to a deeper understanding of the underlying pathophysiology, and potentially lead to highlight more relevant lifestyle interventions to reduce dementia risk in the elderly.

## AUTHOR CONTRIBUTIONS

**Clémence Cavallès:** Conceptualization; formal analysis; methodology; software; visualization; writing – original draft. **Noémie Letellier:** Methodology; software; writing – review and editing. **Claudine Berr:** Resources; writing – review and editing. **Cecilia Samieri:** Resources; writing – review and editing. **Jean-Philippe Empana:** Writing – review and editing. **Christophe Tzourio:** Writing – review and editing; resources. **Jean-François Dartigues:** Resources; writing – review and editing. **Tarik Benmarhnia:** Methodology; software; writing – review and editing. **Yves Dauvilliers:** Conceptualization; supervision; writing – review and editing. **Isabelle Jaussent:** Methodology; conceptualization; software; supervision; writing – review and editing.

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### CONFLICT OF INTEREST STATEMENT

Clémence Cavallès, Noémie Letellier, Claudine Berr, Cecilia Samieri, Jean-Philippe Empana, Christophe Tzourio, Jean-François Dartigues, Tarik Benmarhnia, and Isabelle Jaussent have no competing interests. Yves Dauvilliers participated in the advisory board for UCB Pharma, Jazz, TheraNexus, Avadel, Idorsia and Bioprojet, outside the submitted work.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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