Hypnotics and mortality in an elderly general population: a 12-year prospective study.

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Abstract: 289

References: 45

Words: 3359

Tables: 4

Figure: 1

ABSTRACT

Background

Hypnotics are widely used by the elderly, and their impact on mortality remains controversial. The inconsistent findings could be due to methodological limitations, notably the lack of control for underlying sleep symptoms or illness associated with hypnotic use, *e.g.* insomnia symptoms and excessive daytime sleepiness, depression and anxiety. Our objective was to examine the association between the use of hypnotics and mortality risk in a large cohort of community-dwelling elderly, taking into account a wide range of potential competing risks including sociodemographic characteristics, lifestyle, and chronic disorders as well as underlying psychiatric disorders and sleep complaints.

Methods

Analyses were carried out on 6696 subjects aged 65 years or older randomly recruited from three French cities and free of dementia at baseline. Adjusted Cox proportional hazards models with delayed entry, and age of the participants as the time scale, were used to determine the association between hypnotic use and 12-year survival.

Results

At baseline, 21.7% of the participants regularly used at least one hypnotic. During follow-up, 1307 persons died; 480 from cancer and 344 from cardiovascular disease. Analyses adjusted for study center, age and gender showed a significantly greater risk of all-cause and cardiovascular-related mortality with hypnotics, particularly benzodiazepines, and this increased with the number of hypnotics used. None of these associations were significant in models adjusting for socio-demographic characteristics, lifestyle, chronic disorders including cardiovascular pathologies, sleep and psychiatric disorders. Results remained unchanged

when duration of past-hypnotic intake or persistent *vs* intermittent use during follow-up were taken into account.

Conclusions

When controlling for a large range of potential confounders, the risk of mortality was not significantly associated with hypnotic use regardless of the type and duration. Underlying psychiatric disorders appear to be the principal confounders of the observed association.

KEYWORDS

Cohort studies, Mortality, Hypnotics, Sleep disorders, Elderly

BACKGROUND

Sleep changes with advancing age; however the high prevalence of insomnia in the older adult population is often due to associated age-related medical and psychosocial comorbidities and the frequent use of medications that may impact sleep per se [1]. Insomnia symptoms in older adults are frequently associated with daytime fatigue, excessive daytime sleepiness (EDS), and hypnotics use [2-4]. Insomnia and EDS are also frequently comorbid with other pathologies, notably cardiovascular diseases (CVD) [5, 6] and psychiatric disorder, *e.g.* anxiety and depression [2, 4, 7].

Hypnotics are indicated for treating insomnia symptoms, including those associated with anxiety and depression, and may also be used together with antidepressant treatment. The current use of hypnotics in the general population is estimated to range between 3.5% and 11.7%, and more doubling in elderly populations [8-11]. Hypnotics may produce residual daytime sleepiness and impairment of psychomotor, attention and memory performances the day following bedtime administration, especially with the high dose and long half-life durations [12]. Moreover the use of hypnotics seems associated with excess risk of accidents such as falls and car accidents [12] and may increase mortality risk, especially in elderly people with increased pharmacodynamic alterations.

However, the high rate of insomnia, EDS complaints, and psychiatric disorder in the elderly, their frequent comorbidity and the potential risk of mortality associated with both sleep disorder [13] and psychiatric disorder [14, 15], may override hypnotics *per se* as the cause of increased mortality, independently of the underlying burden of illness.

Overall, evidence suggesting an association between hypnotics consumption and mortality in the elderly, remains controversial. Four observational studies in young adults [16, 17] and elderly people [18, 19] found no significant associations between hypnotics and all-cause

mortality. Other studies reported a significant association with excessive all-cause deaths in adults [20-22]. Two large studies with very wide age ranges from young adult to older elderly [23-25] found significant associations in all age-groups including the elderly. Most of the above studies controlled for socio-demographic characteristics, lifestyle, and some chronic disorders but rarely or not at all for the underlying medical conditions associated with hypnotic prescription *i.e.* depression, antidepressant use, anxiety, insomnia and EDS. Finally, no studies examined the cumulative effect of hypnotics or the impact of its long-term use on mortality risk in an elderly population specifically. Several methodological issues may contribute to the observed inconsistencies, including (i) the design of the study (retrospective or prospective), (ii) the duration of follow-up (between 2.5 and 20 years), (iii) the heterogeneity in sample size and age range, (iv) the type and duration of hypnotic prescription, as well as (v) the lack of control for psychiatric and sleep disorders (prescription/ indication biais).

The aim of the present study is to examine the associations between the use of hypnotics and 12-year mortality risk (all-causes, cancer and cardio-vascular disorders) in a large cohort of community-dwelling elderly, taking into account a wide range of potential competing risks including sociodemographic characteristics, lifestyle, and chronic disorders as well as underlying psychiatric disorders, EDS, and insomnia complaints. The impact of duration and type of hypnotic treatment were also evaluated.

METHODS

Study population

Subjects were recruited as part of the Three-City Study, an ongoing multi-site longitudinal study involving three French cities, Bordeaux, Dijon and Montpellier [26]. Briefly, non-

institutionalized subjects aged 65 years or over were randomly selected from electoral rolls between 1999 and 2001. The acceptance rate was 37%, yielding a sample of 9294 subjects.

The study protocol was approved by the ethical committee of the University Hospital of Kremlin-Bicêtre and CPP Sud Méditérannée III, and written informed consent was obtained from each participant. The participants were administered standardized questionnaires and underwent clinical examinations at baseline and after 2, 4, 8, 10 and 12 years.

Mortality

The exact date of death of the participants was obtained from death registries. The causes of death were collected by the local study centers from medical records and interviews with family physicians, clinicians and other non-medical informants (relatives or caregivers) [27]. A validation committee used all information to classify the cause of death using the tenth revision of International Classification of Diseases (ICD-10) [28] as follows; cancer (ICD-10: C00 to C97 and D37 to D48), CVD and stroke (ICD-10: I00 to I99 and R960 to R961), respiratory (ICD-10: J00 to J99) and ill-defined causes (ICD-10: R00 to R99).

Socio-demographic and clinical variables at baseline

The standardized interview included questions on demographic characteristics, level of education, living alone and on health behaviors (e.g. consumption of alcohol and smoking status). Information on the health of the participants was obtained through detailed medical questionnaires. Case-level depressive symptoms were defined as a score above the 16-point cut-off on the Center for Epidemiological Studies–Depression Scale (CES-D) [29]. Anxiety trait symptoms were measured using the Spielberger's State-Trait Anxiety Inventory (STAI) [30]. In the absence of a validated cut-off score in elderly populations, the state score was divided into tertiles with the highest tertile (higher level of anxiety) being compared to the

two lowest tertiles. Global cognitive function was assessed by the Mini-Mental State Examination (MMSE) [31] and participants scoring less than 26 were classified as cognitively impaired. Confinement was defined as social restriction (confinement to bed, home or outings restricted to the neighborhood) [32]. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). The presence of hypertension was defined by measured systolic blood pressure (BP) ≥160 mmHg or diastolic BP ≥95 mmHg or current antihypertensive treatment. Diabetes was defined as fasting glucose level ≥7.0 mmol/l or treatment for diabetes. Hypercholesterolemia was defined as total cholesterol level ≥6.2 mmol/L or treatment with lipid lowering agents. Detailed medical questionnaires included past history of respiratory and thyroid disorders, and cardio-cerebrovascular disease (angina pectoris, myocardial infarction, cardiovascular surgery, arteritis and stroke) established according to standardized questions.

Sleep complaints at baseline

Sleep complaints were assessed at baseline as part of the clinical interview, followed by the completion of a specific sleep questionnaire [33]. The participants self-rated as "never, rarely, frequently, or often" occurrence of 1) being excessively sleepy during the day (EDS), 2) having difficulties in initiating sleep (DIS), 3) having several awakenings during the night (DMS), 4) having early morning awakening (EMA) without being able to go back to sleep, and 5) snoring loudly. In this analysis, EDS was defined as reporting frequently/often being excessively sleepy. Insomnia complaints based on DIS, DMS and EMA were dichotomized as frequently/often versus never/rarely and summed up to obtain a number of insomnia complaints ranging from 0 to 3. The "risk" of obstructive sleep apnea syndrome (OSAS) was defined clinically as being obese (BMI ≥30kg/m^2), with frequent/often EDS, and frequent/often loud snoring.

Medications and hypnotic use

At baseline and at 2, 4, 8-year follow-up, an inventory of all prescriptions and over-the-counter drugs used during the preceding month was included in a standardized interview. Medical prescriptions and the medications themselves were checked by the interviewer thus minimizing exposure misclassification. Current use of antidepressants and hypnotics were coded according to the World Health Organization's Anatomical Therapeutic Chemical Classification [34]. Hypnotics were classified as; benzodiazepines (BZD), BZD-like compounds (zolpidem, zopiclone), and miscellaneous medications (including barbiturates, antihistaminics, and other pharmacological categories such as neuroleptics). At baseline, the participants currently taking hypnotics were also requested to report the duration of hypnotic intake.

Statistical analyses

Logistic regression models were used to compare the characteristics of participants according to the use of hypnotics at baseline after adjustment for study center, age, and gender. To analyze the associations between hypnotic use and risk of mortality, Cox proportional hazard models with delayed entry and age of the participants as the time scale were used to estimate Hazard Ratios (HR) and their 95% Confidence Intervals (CI). This method gives better adjustment for age and is therefore preferable for an elderly sample over the standard model which uses study time as the time scale as the covariates are strongly associated with age (*e.g.* chronic diseases) [35, 36]. Multivariate models included covariates that were associated with mortality at a conservative level of $p<0.15$. Model 1 was adjusted for study center, age and gender. Model 2 was further adjusted for education, alcohol intake, smoking status, BMI, confinement, respiratory disorder, cognitive impairment, history of CVD, hypertension and diabetes. Two other models were adjusted for diseases associated with hypnotic use in order to take into account possible prescription bias, *e.g.* number of insomnia complaints and EDS

(model 3) and anxiety, depressive symptomatology and antidepressant use (model 4). The multivariate model 5 was adjusted for all possible confounders. All-cause mortality was the principal outcome defined for the analysis. In secondary analyses, cause-specific mortality due to CVD and cancer was analyzed for separate end points. If both CVD and cancer were reported as cause of death, both causes were considered in the analysis. In all final models, significance level was set at $p<0.05$. Analyses were performed using SAS statistical software (version 9.2; SAS Inc, Cary, North Carolina).

RESULTS

Study population

As shown in the study diagram (figure 1), the study sample included 6696 participants free of dementia (58.7% women) with a median (min-max) age of 72.8 years (65.0 to 95.0). The 2382 subjects free of dementia excluded from the study were significantly more likely to be older, had a lower education level, more frequently female and living alone, with confinement, hypertension, diabetes, respiratory disease, hypercholesterolemia, depressive and anxiety symptoms, cognitive impairment, past history of cardio-cerebrovascular disease, and taking more hypnotics ($p<0.05$ for all comparisons). They were also more likely to have died during the follow-up period ($p<0.0001$).

At baseline, 21.7% (n=1454) of the participants were taking at least one hypnotic, 6.9% (n=464)had three insomnia complaints and 3.9% (n=260) no insomnia complaints. More than 3% (n=212) reported taking two or more hypnotics. Regarding the main classes of hypnotics, 16% (n=1070) took BZD, 4.8% (n=321) BZD-like compounds, and 3.0% (n=204) miscellaneous medications (of whom 54.4% antihistaminics, 25.0% non-BZD anxiolytics, 18.6% barbiturates, and 4.4% neuroleptics). With regard to duration, 4.8% (n=304) had been

taking hypnotics for less than 5 years, 3.9% (n=244) between 5 and 10 years, 2.0% (n=127) between 10 and 20 years and 6.0% (n=378) for more than 20 years. .

Baseline sociodemographic and clinical characteristics of the participants according to hypnotic use are described in Table 1. Analysis adjusted for study center, age and gender, showed that participants taking hypnotics had a lower education level, were more likely to be confined to home, had more symptoms of depression, anxiety and cognitive impairment, had more frequently a past history of chronic disease (CVD, thyroid disease, diabetes, hypercholesterolemia), consumed less caffeine and reported more insomnia complaints and EDS ($p<0.05$ for all comparisons).

Association between hypnotic use and 12-year mortality

The median follow-up time for the study was 8.9 years with a range of 0.06 to 11.7 years. During this period, 1307 (19.5%) deaths were observed. They were particularly related to CVD (26.3%), cancer (36.8%), and co-morbid CVD and cancer (3.1%). A substantial number of deaths were due to ill-defined causes (21.6%) as the result of multiple pathologies associated with frailty, and 10.2% died from respiratory diseases.

Baseline socio-demographic and clinical characteristics in relation to follow-up mortality (all causes) are given in Table 2. Participants who died during follow-up were more frequently confined to home, obese, past or current smoker, consuming less alcohol, had hypertension, diabetes mellitus, a past history of CVD, respiratory disease, poorer cognitive performance, EDS, depressive symptoms or were taking antidepressants. They also tended to have a lower level of education, and more frequently reporting insomnia and anxiety symptoms ($p<0.15$). Subsequent analyses were adjusted for these factors. A significant association was also found for subjects “at risk” of OSAS (n=133) (HR=1.76, 95%CI=[1.31-2.36], p=0.0002).

Table 3 shows the associations between hypnotic use at baseline and all-cause mortality over the 12-year follow-up. After adjustment for age, gender, and study center, the risk of all-cause

mortality increased significantly with the use of any hypnotic, the number of hypnotics, and alone for BZD ($p<0.01$ for all comparisons, model 1). When potential lifestyle and chronic disorder confounders were further entered into the model (model 2), the HR were reduced and failed to be significant except for BZD ($p=0.05$) and this was unchanged when further adjusting for sleep complaints (model 3). On the other hand, when adjusting for anxiety and depressive symptomatology (model 4) the associations were not significant even for BZD ($p=0.22$) and this was also the case for the complete multivariate model adjusted for all potential confounders (model 5). BZD-like compounds, and miscellaneous medications intake were not associated with all-cause mortality even in the minimally adjusted model 1. No significant interaction was found for mortality between hypnotic use and 1) EDS, 2) number of insomnia complaints, 3) antidepressant use, 4) chronic diseases and 5) being "at risk" for OSAS.

The relationship between hypnotic intake and the risk of mortality remained unchanged after exclusion of the participants who died during the first two years of follow-up (n= 134), the follow-up rate at two years being 88%.. With regard to specific causes of death, the use of hypnotics and BZD, as well as number of hypnotics were associated with a significantly increased risk of CVD-related death in model 1, but not in the complete multivariate model adjusted for all potential confounders (Table 4). There was no significant association between hypnotics and cancer-related death regardless of covariates, even in the minimally-adjusted model 1 ($p=0.38$).

Duration of hypnotic use and mortality

Sensitivity analyses were performed to examine the relationship between persistent use of hypnotics during the initial 4 years and all-cause mortality. A total of 3496 participants (65.9%) did not report hypnotic use at baseline or at follow-up examination, 773 (14.5%) reported use both at baseline and at all two follow-ups (persistent users) and 1040 (19.6%)

were taking hypnotics at one of two time points (intermittent users). The risk of mortality for the next 8 years was not significantly associated with the persistent use of hypnotics (when compared with non-users, HR=1.03 95% CI=0.84-1.28 for intermittent users, HR=1.11 %CI=0.88-1.39 for persistent users, in multivariate model 5). Similar results were obtained when the analyses focused on persistent BZD users in comparison to non persistent BZD-users or non-BZD-users.

We also examined the impact of past hypnotic intake duration and compared subjects who were not taking sleep medication at baseline with those having previously reported taking sleep medications (i) for less than 5 years, (ii) between 5 and 10 years (iii) between 10 and 20 years and (iii) for more than 20 years. No significant association was observed between duration of hypnotic intake and all-cause mortality, the global p-value ranging from 0.18 (model 1) to 0.76 (model 5) (data not shown).

DISCUSSION

This study examined associations between hypnotic intake and risk of excess mortality (all-causes and specific-causes) over a 12-year period in a large elderly cohort, taking into account a wide range of potential confounding factors. As in several previous studies we observed significant associations between hypnotic use, notably BZDs, and mortality; however these associations became non-significant after adjustment for all potential confounding factors, notably psychiatric disorder. These findings persisted even after taking into account up to 20 years duration of past-hypnotic intake or persistent *vs*. intermittent use.

Previous studies have been inconsistent with some studies observing significant relationships between hypnotic prescriptions and mortality [16, 20-25, 37] and others not [16-19]. Our findings suggest that these differences are probably largely due to failure to take into account confounding associations, notably common affective symptoms and sleep complaints,

although other factors such as study design, participant age, and class of hypnotics probably also influence study outcome.

Insomnia symptoms often lead to the use of hypnotics, a condition frequently associated with EDS, anxiety and mood disorders. Depression and anxiety are also risk factors for mortality [14, 15]. Depressive symptomatology and insomnia are both common in the elderly and in France there are no official guidelines for management, such that antidepressants are often used to treat sleep disorder and hypnotics to treat depression, especially where sleep disturbance is one of the presenting symptoms [2]. EDS is also of multifactorial origin, and commonly associated with depression [7], cognitive decline [38], physical illness (particularly cardiovascular disease), and mortality in older adults [5, 6, 13]. Thus, all these conditions may increase the risk of mortality in elderly subjects through pathways independently of hypnotics. However, few previous studies have controlled for psychological status [17, 18, 22, 23] and in studies where depressive symptoms have been considered, antidepressant use has not been necessarily taken into account. This is important as antidepressant use may relieve depressive symptomatology, but the underlying biological risk factors associated with increased mortality may still be operating. No previous studies have controlled for anxiety or simultaneously for insomnia and EDS symptoms as potential independent confounding factors. To our knowledge, our study is the first one controlling for such a large range of potential confounding factors, especially the underlying diseases associated with hypnotic use, *e.g.* anxiety and depressive symptomatology, antidepressant use, as well as EDS and insomnia complaints. Our finding that psychiatric disorder could be a principal determinant driving the association between hypnotics and mortality risk explains previous inconsistencies.

Chronic use of hypnotic drugs particularly BZD may be associated with the risk of addiction and insomnia-rebound after withdrawal, psychomotor impairment and cognitive problems,

OSAS, EDS, and car accidents [12, 39, 40]. In our sample, only one subject died from a car accident, and this person did not use hypnotics. We did not find any interaction between subjects clinically "at risk" for OSAS, hypnotics intake and mortality, suggesting that if hypnotics may trigger or aggravate OSAS they did not impact on mortality risk. The use of BZD may also favor falls and hip fractures and thus increase the risk for disability and death especially in the elderly [41, 42]. However some studies have suggested that nighttime sleep problems *per se* may also be significant risk factors for falls in the elderly, independently of hypnotic use [43-45]. In our study, the associations between hypnotic use and all-causes or CVD-related death became non-significant after adjustment for health behavior and status variables, plus EDS and insomnia complaints.

An increased incidence risk for cancer was also reported in subjects using hypnotics in some studies [21, 22, 24], even in infrequent hypnotic users [22]. Our study did not report any association between hypnotic use and cancer-related death. Again, differences in adjustment of underlying co-morbid conditions frequently associated with the chronic use of hypnotics appear to explain previous findings.

The present study has some limitations. Unfortunately, data related to hypnotic dose was not available. Bias could have been introduced by the low participation rate at baseline, the non-random exclusion of participants with missing data at baseline, who were older, were more commonly hypnotics users and more often had psychiatric and other chronic disorders that may limit the generalizability of our findings. Although unlikely, the possibility of overadjusment could not be excluded: potential confounding variables should be intermediate variables in the causal pathway between hypnotics intake and mortality. Finally, the absence of significant association between the use of hypnotics and mortality (all-causes, and cardio-vascular disorders) after adjustments for covariables should be interpreted with caution regarding the small number of events per predictor variable.

Our prospective study based on a large community sample has several strengths, including the duration of the follow-up and adjustment for a wide range of possible confounding factors including socio-demographic and lifestyle factors, chronic disorders, sleep complaints as well as depression and anxiety disorders which were found as key confounding factors in this study. Prescriptions and medications themselves were checked by the interviewer and the causes of death were established by an independent committee. Finally, excluding participants who died during the first two years of follow-up did not modify the main results, suggesting a modest confounding effect of severe undiagnosed conditions in relation to hypnotic use and death.

CONCLUSIONS

Our findings suggest that the use of hypnotics is not independently associated with an increased risk of mortality in the elderly, and that previous findings may be largely attributable to failure to take into account confounding variables, notably clinical co-morbidity which is frequent at higher ages, particularly psychiatric disorders. Use of hypnotics might be a marker underlying more complex health issues.

LIST OF ABBREVIATIONS

BMI: Body mass index

BP: Blood pressure

BZD: benzodiazepines

CES-D: Center for Epidemiological Studies–Depression Scale

CI: Confidence interval;

CVD: cardiovascular diseases

DIS: Difficulties in initiating sleep

DMS: Difficulties in maintaining sleep

EMA: Early morning awakening

EDS: excessive daytime sleepiness

HR: Hazard Ratios

ICD-10: International Classification of Diseases

MMSE: Mini-Mental State Examination

OSAS: Obstructive sleep apnea syndrome

STAI: Spielberger's State-Trait Anxiety Inventory

COMPETING INTERESTS

The authors have nothing to disclose in relation to this paper.

Dr Isabelle Jaussent, Dr Marie-Laure Ancelin, Dr Karine Pérès and Dr Alain Besset report no disclosures. Dr. Ritchie has received honoraria from Novartis and Glaxo Smith-Kline, is on the scientific advisory boards for the Biomedical Research Centre, King's College London, and the MRC Strategic Steering Committee (Longitudinal Health and Aging Research Unit); and serves on the editorial boards of the International Journal of Geriatric Psychiatry, Dementia, International Psychogeriatrics, Journal of Clinical and Experimental Gerontology, Psychogeriatrics, Neuronale, Neurologie-Psychiatrie-Gériatrie, and Gerontology. Dr Claudine Berr serves on advisory boards of the British Journal of Nutrition and Revue d'épidemiologie et de santé publique. Prof. Dauvilliers has received speaker's honoraria and support for travel to meetings from UCB Pharma, JAZZ and Bioprojet. Prof. Dauvilliers participated in advisory boards of UCB Pharma, JAZZ and Bioprojet

AUTHORS' CONTRIBUTIONS

IJ, MLA, and YD participated in the conception and design of the study. IJ conducted the analyses and wrote the first draft of the manuscript. IJ, MLA, AB, YD participated in the

interpretation of the data. IJ, MLA, CB, KP, JS, AB, KR and YD contributed to the writing of the manuscript. MLA, CB, KP, JS, KR and YD participated in the acquisition of the data. All authors approved the final manuscript.

ACKNOWLEDGEMENTS

The 3C Study is conducted under a partnership agreement between Inserm, the Victor Segalen – Bordeaux II University and Sanofi-Synthélabo. The Fondation pour la Recherche Médicale funded the preparation and first phase of the study. The 3C-Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Agence Française de Sécurité Sanitaire des Produits de Santé, the Regional Governments of Aquitaine, Bourgogne and Languedoc-Roussillon and, the Fondation de France, the Ministry of Research-Inserm Programme "Cohorts and collection of biological material". The Lille Génopôle received an unconditional grant from Eisai. Part of this project is financed by grants from the Agence Nationale de la Recherche (ANR) and Fondation Plan Alzheimer. None of the sponsors had any further involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication

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Figure. Flow diagram

Table 1. Sociodemographic and clinical characteristics of participants according to hypnotic use at baseline

		Hypnotic use					
		No N=5242		Yes N=1454			
Variable		n	%	n	%	OR [95% CI][1]	p[1]
High level of education[2]	No	4136	78.90	1245	85.63	1	0.0006
	Yes	1106	21.10	209	14.37	0.75 [0.63;0.88]	
Living alone	Yes	1610	30.71	605	41.61	1	0.06
	No	3632	69.29	849	58.39	0.88 [0.77;1.01]	
Confinement	No	5025	95.86	1314	90.37	1	<0.0001
	Yes	217	4.14	140	9.63	1.90 [1.51;2.40]	
Alcohol intake (g/day)	<12	955	18.22	349	24.00	1	0.14
	12-36	3799	72.47	1012	69.60	0.86 [0.75;1.00]	
	>36	488	9.31	93	6.40	0.92 [0.70;1.22]	
Caffeine intake (mg/day)	≤125	1310	24.99	423	29.09	1	0.007
	125-375	3103	59.19	836	57.50	0.83 [0.73;0.95]	
	>375	829	15.81	195	13.41	0.76 [0.62;0.92]	
Smoking status	Never	3033	57.86	969	66.64	1	0.38
	Past	1901	36.26	402	27.65	0.99 [0.85;1.15]	
	Current	308	5.88	83	5.71	1.19 [0.92;1.55]	
History of CVD	No	3902	74.44	945	64.99	1	<0.0001
	Yes	1340	25.56	509	35.01	1.59 [1.40;1.81]	
Respiratory disease	No	4945	94.33	1364	93.81	1	0.35
	Yes	297	5.67	90	6.19	1.13 [0.88;1.44]	
Thyroid disease	No	4823	92.01	1286	88.45	1	0.009
	Yes	419	7.99	168	11.55	1.29 [1.07;1.57]	
Depressive symptomatology	No	4295	81.93	897	61.69	1	<0.0001
	Yes	947	18.07	557	38.31	2.76 [2.41;3.15]	

		Hypnotic use					
		No N=5242		Yes N=1454			
Variable		n	%	n	%	OR [95% CI][1]	p[1]
Antidepressants intake	No	5081	96.93	1196	82.26	1	<0.0001
	Yes	161	3.07	258	17.74	6.32 [5.12;7.81]	
Spielberger trait anxiety	<43	3688	70.35	715	49.17	1	<0.0001
	≥43	1554	29.65	739	50.83	2.33 [2.06;2.64]	
MMSE Score	≥ 26	4559	86.97	1190	81.84	1	<0.0001
	<26	683	13.03	264	18.16	1.40 [1.20;1.65]	
Body Mass Index (kg/m^2)	Normal (<25)	2477	47.25	747	51.38	1	0.41
	Overweight (25-29)	2106	40.18	515	35.42	0.92 [0.81;1.05]	
	Obese (≥30)	659	12.57	192	13.20	1.00 [0.83;1.20]	
Hypertension	No	2175	41.49	538	37.00	1	0.08
	Yes	3067	58.51	916	63.00	1.12 [0.99;1.27]	
Diabetes mellitus	No	4777	91.13	1314	90.37	1	0.03
	Yes	465	8.87	140	9.63	1.25 [1.02;1.54]	
Hypercholesterolemia	No	3349	63.89	859	59.08	1	0.005
	Yes	1893	36.11	595	40.92	1.19 [1.05;1.34]	
Snoring loudly (n=5972)	Never/Rarely	3021	64.30	863	67.74	1	0.63
	Frequently/Often	1677	35.70	411	32.26	0.97 [0.84;1.11]	
DIS[4]	Never/Rarely	3760	71.73	641	44.09	1	<0.0001
	Frequently/Often	1482	28.27	813	55.91	2.85 [2.51;3.24]	
DMS[5]	Never/Rarely	2029	38.71	455	31.29	1	<0.0001
	Frequently/Often	3213	61.29	999	68.71	1.29 [1.14;1.47]	
EMA[6]	Never/Rarely	3565	68.01	740	50.89	1	<0.0001
	Frequently/Often	1677	31.99	714	49.11	1.85 [1.64;2.09]	
Number of insomnia complaints[7]	0	1586	30.26	260	17.88	1	<0.0001
	1	1729	32.98	326	22.42	1.15 [0.96;1.38]	
	2	1138	21.71	404	27.79	2.02 [1.70;2.41]	

		Hypnotic use					
		No N=5242		Yes N=1454			
Variable		n	%	n	%	OR [95% CI][1]	p[1]
	3	789	15.05	464	31.91	3.07 [2.56;3.68]	
EDS[8]	Never/Rarely	4384	83.63	1165	80.12	1	0.005
	Frequently/Often	858	16.37	289	19.88	1.25 [1.07;1.47]	

[1] Adjustment for center study, age and gender.

[2] University level

[3] History of cardio-vascular disease (stroke or coronary heart disease)

[4] DIS: Difficulty with initiating sleep

[5] DMS: Difficulty in maintaining sleep

[6] EMA: Early morning awakening

[7] Number of insomnia complaints : DIS + DMS + EMA

[8] EDS: Excessive daytime sleepiness

Table 2. Baseline predictors of deaths from all causes during follow-up.

		Deaths-all causes					
		No N=5389		Yes N=1307			
Variable		n	%	n	%	HR [95% CI][1]	p[1]
High level of education[2]	No	4337	80.48	1044	79.88	1	0.06
	Yes	1052	19.52	263	20.12	0.87 [0.76;1.00]	
Living alone	Yes	1782	33.07	433	33.13	1	0.84
	No	3607	66.93	874	66.87	1.01 [0.89;1.15]	
Confinement	No	5181	96.14	1158	88.60	1	0.0001
	Yes	208	3.86	149	11.40	1.78 [1.49;2.13]	
Alcohol intake (g/day)	<12	1062	19.71	242	18.52	1.23 [1.06 ;1.42]	0.01
	12-36	3900	72.37	911	69.70	1	
	>36	427	7.92	154	11.78	1.14 [0.96;1.36]	
Caffeine intake (mg/day)	≤125	1362	25.27	371	28.39	1	0.86
	125-375	3164	58.71	775	59.30	0.97 [0.85;1.09]	
	>375	863	16.01	161	12.32	0.97 [0.81;1.17]	
Smoking status	Never	3368	62.50	634	48.51	1	<0.0001
	Past	1740	32.29	563	43.08	1.22 [1.07;1.40]	
	Current	281	5.21	110	8.42	1.73 [1.41;2.14]	
History of CVD[3]	No	4079	75.69	768	58.76	1	0.0001
	Yes	1310	24.31	539	41.24	1.49 [1.33;1.67]	
Respiratory disease	No	5121	95.03	1188	90.90	1	0.0001
	Yes	268	4.97	119	9.10	1.64 [1.36;1.98]	
Thyroid disease	No	4890	90.74	1219	93.27	1	0.19
	Yes	499	9.26	88	6.73	1.16 [0.93;1.45]	
Depressive symptomatology	No	4209	78.10	983	75.21	1	0.0005
	Yes	1180	21.90	324	24.79	1.26 [1.11;1.43]	
Antidepressant use	No	5072	94.12	1205	92.20	1	0.0002
	Yes	317	5.88	102	7.80	1.47 [1.20;1.80]	

		Deaths-all causes					
		No N=5389		Yes N=1307			
Variable		n	%	n	%	HR [95% CI][1]	p[1]
Spielberger trait anxiety	<43	3509	65.11	894	68.40	1	0.13
	≥43	1880	34.89	413	31.60	1.10 [0.97;1.23]	
MMSE Score	≥ 26	4666	86.58	1083	82.86	1	0.005
	<26	723	13.42	224	17.14	1.23 [1.07;1.43]	
Body Mass Index (kg/m2)	Normal (<25)	2611	48.45	613	46.90	1	0.0007
	Overweight (25-29)	2118	39.30	503	38.49	1.01 [0.90;1.14]	
	Obese (≥30)	660	12.25	191	14.61	1.36 [1.15;1.60]	
Hypertension	No	2313	42.92	400	30.60	1	0.002
	Yes	3076	57.08	907	69.40	1.21 [1.07;1.36]	
Diabetes mellitus	No	4965	92.13	1126	86.15	1	0.0001
	Yes	424	7.87	181	13.85	1.58 [1.35;1.85]	
Hypercholesterolemia	No	3333	61.85	875	66.95	1	0.99
	Yes	2056	38.15	432	33.05	1.00 [0.89;1.12]	
Snoring loudly (n=5972)	Never/Rarely	3114	64.93	770	65.48	1	0.90
	Frequently/Often	1682	35.07	406	34.52	1.01 [0.89;1.14]	
DIS[4]	Never/Rarely	3506	65.06	895	68.48	1	0.20
	Frequently/Often	1883	34.94	412	31.52	0.92 [0.81;1.04]	
DMS[5]	Never/Rarely	2055	38.13	429	32.82	1	0.26
	Frequently/Often	3334	61.87	878	67.18	1.07 [0.95;1.20]	
EMA[6]	Never/Rarely	3434	63.72	871	66.64	1	0.12
	Frequently/Often	1955	36.28	436	33.36	0.91 [0.81;1.02]	
Number of insomnia complaints[7]	0	1526	28.32	320	24.48	1	0.07
	1	1595	29.60	460	35.20	1.14 [0.99;1.31]	
	2	1227	22.77	315	24.10	1.08 [0.92;1.26]	
	3	1041	19.32	212	16.22	0.92 [0.77;1.11]	
EDS[8]	Never/Rarely	4555	84.52	994	76.05	1	0.003

	Deaths-all causes					
	No N=5389		Yes N=1307			
Variable	n	%	n	%	HR [95% CI][1]	p[1]
Frequently/Often	834	15.48	313	23.95	1.23 [1.07;1.40]	

[1] adjusted for center study, gender and age

[2] university degree

[3] History of cardio-vascular disease (stroke or coronary heart disease)

[4] DIS: Difficulty with initiating sleep

[5] DMS: Difficulty in maintaining sleep

[6] EMA: Early morning awakening

[7] Number of insomnia complaints: DIS + DMS + EMA

[8] EDS: Excessive daytime sleepiness

TABLE 3. Risks of death from all causes over 12-year according to hypnotic use

	All-cause death													
	No N=5389		Yes N=1307		Model 1[(1)]		Model 2[(2)]		Model 3[(3)]		Model 4[(4)]		Model 5[(5)]	
Variable	n	%	n	%	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p
Hypnotic use														
No	4261	79.07	981	75.06	1	0.007	1	0.16	1	0.12	1	0.50	1	0.43
Yes	1128	20.93	326	24.94	1.19 [1.05;1.36]		1.10 [0.96;1.25]		1.12 [0.97;1.29]		1.05 [0.92;1.20]		1.06 [0.92;1.23]	
Number of hypnotics														
0	4261	79.07	981	75.06	1	0.003	1	0.13	1	0.13	1	0.44	1	0.47
1	970	18.00	272	20.81	1.14 [0.99;1.31]		1.06 [0.93;1.22]		1.09 [0.94;1.26]		1.02 [0.89;1.18]		1.04 [0.89;1.21]	
≥2	158	2.93	54	4.13	1.53 [1.16;2.01]		1.32 [1.00;1.74]		1.33 [0.98;1.81]		1.20 [0.90;1.60]		1.21 [0.88;1.65]	
BZD														
No	4557	84.56	1069	81.79	1	0.003	1	0.05	1	0.05	1	0.22	1	0.21
Yes	832	15.44	238	18.21	1.24 [1.08;1.44]		1.15 [1.00;1.33]		1.17 [1.00;1.37]		1.10 [0.95;1.28]		1.11 [0.94;1.30]	
BZD-like compounds														
No	5135	95.29	1240	94.87	1	0.93	1	0.56	1	0.76	1	0.40	1	0.55
Yes	254	4.71	67	5.13	1.01 [0.79;1.29]		0.93 [0.72;1.19]		0.96 [0.74;1.25]		0.90 [0.70;1.15]		0.92 [0.71;1.20]	
Miscellaneous medications														
No	5241	97.25	1251	95.72	1	0.15	1	0.30	1	0.32	1	0.49	1	0.49

	All-cause death														
	No N=5389		Yes N=1307		Model 1[(1)]		Model 2[(2)]		Model 3[(3)]		Model 4[(4)]		Model 5[(5)]		
Variable	n	%	n	%	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	
Yes	148	2.75	56	4.28	1.22 [0.93;1.60]		1.15 [0.88;1.51]		1.16 [0.87;1.55]		1.10 [0.84;1.45]		1.11 [0.83;1.48]		

[(1)] Model 1 adjusted for age, study center and gender

[(2)] Model 2 adjusted for age, study center, gender, level of education, confinement, alcohol intake, smoking status, history of cardio and cerebrovascular disease, respiratory disease, MMSE score, BMI, hypertension and diabetes mellitus.

[(3)] Model 3 was adjusted for all the covariates in model 2, plus excessive daytime sleepiness and number of insomnia complaints

[(4)] Model 4 was adjusted for all the covariates in model 2, plus depressive symptoms, antidepressant use and Spielberger trait anxiety score.

[(5)] Model 5 was adjusted for all the covariates in model 3 plus depressive symptoms, antidepressants use and Spielberger trait anxiety score.

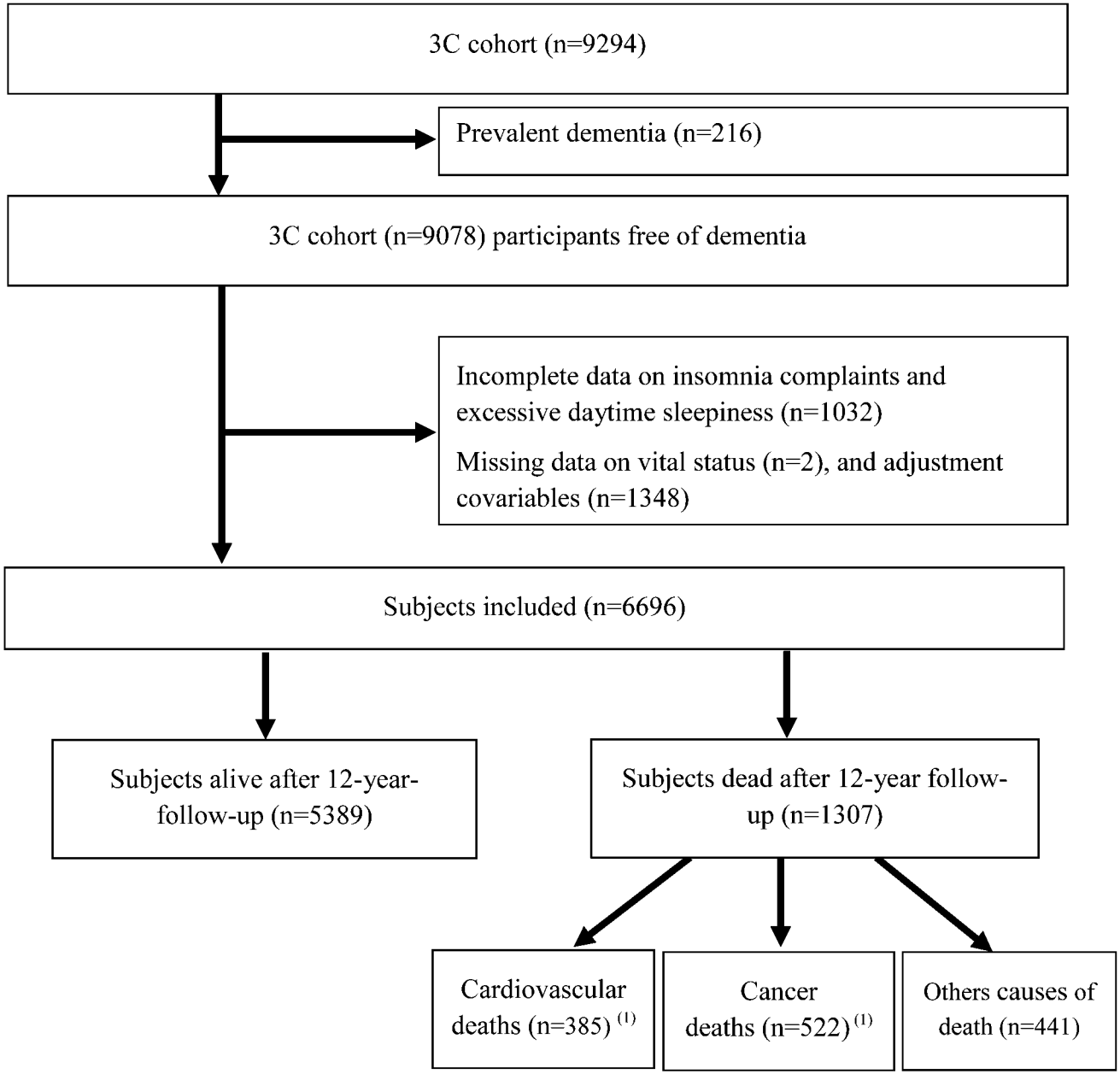
TABLE 4. Risks of cardiovascular (CVD) and cancer as causes of death over 12-year according hypnotic use

	CVD Deaths								Cancer Deaths							
	No		Yes						No		Yes					
	n=6311		N=385		Model 1[(1)]		Model 2[(2)]		n=6174		N=522		Model 1[(1)]		Model 2[(2)]	
Variable	n	%	n	%	HR [95% CI]	p	HR [95% CI]	p	n	%	n	%	HR [95% CI]	p	HR [95% CI]	p
Hypnotic use																
No	4962	78.62	280	72.73	1	0.02	1	0.56	4818	78.04	424	81.23	1	0.38	1	0.73
Yes	1349	21.38	105	27.27	1.32 [1.04;1.66]		0.92 [0.71;1.20]		1356	21.96	98	18.77	0.90 [0.72;1.13]		0.96 [0.74;1.23]	
Number of hypnotics																
0	4962	78.62	280	72.73	1	0.03	1	0.78	4818	78.04	424	81.23	1	0.67	1	0.94
1	1154	18.29	88	22.86	1.26 [0.99;1.61]		0.94 [0.72;1.23]		1157	18.74	85	16.28	0.91 [0.72;1.15]		0.96 [0.74;1.25]	
≥2	195	3.09	17	4.42	1.69 [1.03;2.76]		0.83 [0.45;1.52]		199	3.22	13	2.49	0.89 [0.51;1.54]		0.93 [0.50;1.72]	
BZD																
No	5321	84.31	305	79.22	1	0.004	1	0.60	5170	83.74	456	87.36	1	0.27	1	0.42
Yes	990	15.69	80	20.78	1.45 [1.13;1.87]		1.08 [0.81;1.43]		1004	16.26	66	12.64	0.86 [0.66;1.12]		0.89 [0.66;1.19]	
BZD-like compounds																
No	6008	95.20	367	95.32	1	0.65	1	0.12	5879	95.22	496	95.02	1	0.78	1	0.44
Yes	303	4.80	18	4.68	0.90 [0.56;1.44]		0.67 [0.40;1.11]		295	4.78	26	4.98	1.06 [0.71;1.57]		1.18 [0.77;1.82]	
Miscellaneous medications																
No	6123	97.02	369	95.84	1	0.64	1	0.43	5986	96.95	506	96.93	1	0.88	1	0.95

	CVD Deaths							Cancer Deaths						
	No		Yes					No		Yes				
	n=6311		N=385		Model 1[(1)]		Model 2[(2)]	n=6174		N=522		Model 1[(1)]		Model 2[(2)]	
Variable	n	%	n	%	HR [95% CI]	p	HR [95% CI]	p	n	%	n	%	HR [95% CI]	p	HR [95% CI]	p
Yes	188	2.98	16	4.16	1.13 [0.68;1.87]		0.80 [0.45;1.41]		188	3.05	16	3.07	0.96 [0.58;1.59]		1.02 [0.59;1.74]	

[(1)] Model 1 adjusted for age, study center and gender.

[(2)] Model 2 adjusted for model 1 plus high level of education, confinement, alcohol intake, smoking status, history of cardio-cerebrovascular disease, respiratory disease, MMSE score, body mass index, hypertension and diabetes mellitus, depressive symptoms, antidepressants use, Spielberger trait anxiety score, excessive daytime sleepiness and number of insomnia complaints.



(1) For 41 participants, the cause of death was related to both cardiovascular and cancer

Additional files provided with this submission:

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