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Claire Berticat, Frédéric Thomas, Yves M Dauvilliers, Isabelle Jaussent, Karen Ritchie, Catherine Helmer, Christophe Tzourio, Michel Raymond, Sylvaine Artero

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1 **Excessive daytime sleepiness and antipathogen drug consumption**
2 **in the elderly: a test of the immune theory of sleep**

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9 Berticat Claire ^{1¶}, Thomas Frédéric ^{2¶}, Dauvilliers Yves^{3,4}, Jaussent Isabelle⁴, Ritchie Karen^{4,5},

10 Helmer Catherine⁶, Tzourio Christophe⁷, Raymond Michel¹, Artero Sylvaine ^{4*}

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12

13 [¶]co-first authors

14

15 * Corresponding author

16 E-mail: sylvaine.artero@inserm.fr

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19¹Institute of Evolutionary Sciences, University of Montpellier, Montpellier, France. (CNRS, IRD, EPHE)

20²IRD, MIVEGEC, (UMR CNRS/IRD/), Montpellier Cedex 5, France;

21³Centre de Référence Maladies Rares Narcolepsie et Hypersomnie Idiopathique, Service de Neurologie, Unité
22des Troubles du Sommeil, Hôpital Gui-de-Chauliac, CHU Montpellier, France ;

23⁴Inserm, U1061, Montpellier, France; Université de Montpellier, Montpellier, France

24⁵Faculty of Medicine, Imperial College, St Mary's Hospital, London, United Kingdom

25⁶INSERM, ISPED, U897, Bordeaux, France; Univ. Bordeaux, Bordeaux, France;

26⁷INSERM, ISPED, U897, Bordeaux, France; Univ. Bordeaux, Bordeaux, France; Service de Neurologie,

27Department of Clinical Neurosciences, CHU Pellegrin, Bordeaux, France.

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32Abstract

33

34The evolutionary reasons for sleep remain controversial. The immune theory of sleep suggests
35that sleep is essential to the immune system, allowing organisms to allocate more energy to
36their immunity. This hypothesis was tested by exploring the links between excessive daytime
37sleepiness (EDS) and vulnerability to infectious diseases in a large (n = 9294) cohort of
38elderly individuals, with information on socio-demographics, daily habits, and medical
39characteristics. At the two-year and four-year follow-ups, we obtained individual data from
40the national healthcare insurance about all medications prescribed to the participants between
412001 and 2003 (n = 2865). We found an independent positive association between EDS and
42the consumption of some anti-pathogen drugs. This relationship was mostly explained by
43fungal and parasitic infections rather than by viral and bacterial ones. These results, although
44based on correlations, are consistent with the idea that EDS as a proxy of altered sleep
45quality/quantity may affect the efficiency of the immune system, and hence vulnerability to
46infections.

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58Introduction

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60 Sleep is widespread in the animal kingdom, being described in insects, fish, birds, and
61mammals [1-6]. From an evolutionary perspective, it is predicted that sleep must be
62associated to substantial benefits to outweigh the multiple costs that are associated with
63dormancy states. While it is relatively easy to identify several of these costs (e.g., no mating
64or foraging opportunities, vulnerability to insect vectors and/or predators, low ability to detect
65and respond to changing environmental conditions), the benefits are more difficult to
66determine. However, sleep deprivation is usually rapidly accompanied by highly detrimental
67health consequences, indicating that sleep is a strict necessity in a great number of species.
68Currently, the main theories regarding the function of sleep [7] propose that it plays an
69important role in brain development, clearance, or repair [8-10], and in consolidating
70memories and learning [11] Sleep could also be beneficial because it maximizes energy
71saving when other activities bring no, or little, fitness benefits [12, 13]. Alternatively, there is
72an increasing body of evidence that sleep is essential to the immune system, allowing
73organisms to allocate more energy to their immunity [14, 15]. To function properly, the
74immune system indeed requires a significant proportion of our daily energy budget [16]. An
75efficient way of allocating more energy to the immune system is to place all the other
76functions in 'rest mode', in other words, put them to sleep. In accordance with this hypothesis,
77it is a common belief that sleep deprivation is linked to increased vulnerability to infections
78[17, 18, 19] and that sleep duration usually increases in sick individuals [20], which
79significantly accelerates their recovery [21, 22]. A recent interspecific study on mammals also
80supports the immune theory of sleep: the more the organisms sleep, the better their immune
81system functions and the fewer parasites they have [23]. This immunity hypothesis for the
82role of sleep still needs to be explored, particularly at the intraspecific level.

83 Here, we tested the immune theory of sleep in humans by exploring the links between
84 excessive daytime sleepiness (EDS) and vulnerability to infectious diseases. We focused our
85 study on elderly individuals because the effects of sleep changes are expected to be especially
86 elevated in populations at particular risk of infections, like older adults [14]. In addition, aging
87 is often associated with a decrease in both the quality and quantity of sleep, with large
88 variations among individuals [24-27], and EDS is frequently reported in the elderly [28, 29].
89 To estimate changes in sleep quality/quantity, we focused on the complaint of EDS because
90 although subjective it represents a unique relative individual estimate of sleep alteration
91 whatever the total daily amount of time spent sleeping. Thus we use EDS in this analysis as a
92 proxy of altered sleep quality/quantity. Using a four-year longitudinal study based on an
93 elderly population, we examined whether EDS was associated with the consumption of anti-
94 pathogen drugs.

95

96 **Results**

97

98 **Baseline characteristics**

99 The present analysis was carried out on 2,865 subjects 1,108 males and 1,757 females
100 from three centres (Bordeaux, Toulouse, Montpellier; 31% of the subjects initially recruited at
101 baseline) for whom all data were available, including follow-up data for medications and who
102 did not have dementia or narcolepsy. The ages of the subjects in 2000 ranged from 65 to 93
103 years, with an average of 73.2 ± 4.9 years (Table 1). Overall 54% (1,538/2,865) reported
104 having EDS (58% of men [647/1,108] and 51% of women [891/1,757]; Table 1). The mean
105 consumption of the different types of drugs from CNAM-TS is detailed in Table 1.

106

107 **Relationship between EDS and anti-infectious medicine consumption**

108 The relationship between excessive daytime sleepiness and drug consumption for the
109 different models fitted is provided in Table 2. The quantity of antibiotics taken was not
110 significantly linked to EDS ($\chi^2 = 0.92$, $df = 1$, $P = 0.34$; 15% of the variance was explained by
111 the model). Similarly, no significant association between EDS and the frequency of antiviral
112 consumption was detected ($\chi^2 = 1.86$, $df = 1$, $P = 0.17$; 5% of the variance was explained by
113 the model). However, EDS was significantly associated with an increased frequency of
114 antifungals consumption ($\chi^2 = 5.33$, $df = 1$, $P = 0.02$; 5% the variance was explained by the
115 model) and the frequency of antiparasitics consumption ($\chi^2 = 4.43$, $df = 1$, $P = 0.03$; 9% of the
116 variance was explained by the model). The sum of these four categories of anti-infectious
117 drugs was not significantly influenced by EDS ($\chi^2 = 0.77$, $df = 1$, $P = 0.38$; 16.5% of the
118 variance was explained by the model). This was probably largely caused by the antibiotics
119 category, which represents 79% of all anti-infectious drugs consumed. Interestingly, the
120 quantity of all non-infectious and non-psychotropic drugs was not significantly influenced by
121 EDS ($\chi^2 = 0.86$, $df = 1$, $P = 0.35$; 16% of the variance was explained by the model). See the
122 Supplementary Information for details on all regression models (Tables S2-S7).

123

124 **Discussion**

125

126 We detected a positive relationship between the consumption of some anti-pathogen
127 drugs and excessive daytime somnolence, which is consistent with the idea that sleep
128 deprivation may affect immune system efficiency and hence vulnerability to infections [15].
129 The correlations were significant for parasitic and fungal infections but not for bacterial and
130 viral infections.

131 Several hypotheses could be invoked to explain these findings. First, it is possible that
132sleep deprivation increases vulnerability to all infectious agents, but that depending on the
133pathogens considered, drug consumption may not be an entirely reliable proxy of the real
134infection frequency. For instance, while people are frequently infected by viruses, anti-viral
135drug consumption is low because it is rarely effective, e.g., the common cold and influenza
136are usually not treated with antiviral drugs. The correlation is presumably also weak with
137bacterial infections because antibiotics are often overprescribed [30], thereby weakening the
138correlation between real bacterial infection rates and antibacterial drug consumption.
139However, pathologies due to fungal or parasitic infections are more specific, leading infected
140people to more systematically consult physicians and obtain targeted drugs [31]. Interestingly,
141prescribed antifungals were mainly (70%) dermatological, suggesting that there was no
142relationship here between consumption of antibiotics and antifungals [32]. The lack of a
143significant correlation between EDS and viral/bacterial infections could also suggest that the
144immune state is a rather poor predictor of the infection outcome when in contact with those
145pathogenic agents, that is, people with a poor immunity are not the only ones to get sick when
146in contact with a virus.

147 This study is strengthened by the large sample size, the population-based design, the
148four-year follow-up, and the adjustment with a wide range of covariates. However, we cannot
149exclude several alternative explanations, including a reverse causality, where somnolence
150would result from the detrimental effects of frequent infections on sleep quality/quantity. For
151instance, while influenza viruses increase sleep duration during the symptomatic period, they
152may conversely reduce it during the incubation period [33]. Several infections are also known
153to directly induce daytime somnolence without necessarily altering sleep quality itself [14].
154We do not currently favour hypotheses suggesting that infections (indirectly or directly) cause
155somnolence, because daytime sleepiness most likely reflects a chronic rather than acute
156problem. Consequently, as suggested by the absence of correlation between consumption of

157anti-infectious drugs and EDS at baseline, even frequent infection episodes may remain too
158infrequent over the survey period to influence the self-rated level of somnolence of
159participants.

160 Certain illnesses, like depression, diabetes and chronic organic diseases, can also affect
161both sleep and immunity, and could then potentially lead to a spurious correlation between
162these two variables. Nevertheless, our results do not change even after adjusting for these
163potential confounding elements. As people get older, they have comorbid conditions more
164frequently and particularly high rates of depressive symptoms leading to immunosenescence
165[34]. In our study, the effects of these comorbidities were controlled. We cannot exclude that
166there is no infectious specificity in the response detected since daytime sleepiness is
167significantly associated with a wide range of lethal disorders in the elderly [35, 36, 37].

168 Finally there are several limitations in this study. First all the results presented here are
169only correlations. Second, the infection was qualitatively detected by the presence of
170treatments, although its severity could not be quantitatively estimated. Thus, low grade
171infections, generally without specific treatments, could not be considered here. Despite
172extensive adjustments for socio-demographic and lifestyle factors, chronic diseases, and sleep
173medication, we cannot exclude the possibility that unmeasured confounding factors may
174explain part of any association detected in observed data. The assessment of sleep complaints
175was self-reported, and that remains the most common method for initial diagnosis and
176management in the primary healthcare setting. The measurement of EDS in this study was
177based on only one question, but its severity was examined using a four-point scale. However,
178an assessment of sleep apnea was not available, and the possibility remains that our results on
179EDS may be driven by these variables as we also hypothesized for sleep restriction per se.
180Finally, sleep disturbance was assessed only once (at the baseline examination). We therefore
181could not assess the evolution of sleep disturbances in relation to antipathogen medication

182intake and thus determine whether sleep problems were stable, decreased, or increased in
183parallel with the drug intake.

184 Further long-term studies are needed to extend these findings and explore the role of
185EDS and sleep alteration in immunity and its consequences on the probabilities of specific
186infections. This is especially important in humans who suffer from sleep restriction and non-
187restorative sleep; over recent decades, these have been increasingly recognized as a public-
188health preoccupation for both individuals and the population as a whole [14]. A possible
189explanation for the link between EDS, sleep quality/quantity and the immune state is that
190change in the sleep profile may alter molecular processes that drive cellular immune
191activation and induce inflammatory cytokines [38, 15]. Unraveling the molecular and cellular
192pathways by which sleep and the immune system are interrelated also appears to be a
193promising direction for understanding how sleep alterations could be more beneficial to some
194pathogens than others.

195 This question is of considerable public health interest given the high prevalence and
196secondary complication of infection in the elderly.

197

198**Materials and Methods**

199

200**Participants**

201 Between 1999 and 2001, non-institutionalized subjects were recruited as part of a
202multisite cohort study (Three City study, or 3C) of subjects aged at least 65 years old who
203were randomly selected from the electoral roll of three French cities (Bordeaux, Dijon, and
204Montpellier). Health-related data were collected during face-to-face interviews using
205standardized questionnaires. For the details of the study protocol, see [39]. A total of 9,294

206 subjects were included in the study (4,931 from Dijon, 2,104 from Bordeaux, and 2,259 from
207 Montpellier). The study protocol was approved by the ethical committee of the university
208 hospital of Kremlin-Bicêtre. Each participant signed legal consent forms.

209 The present study uses data collected at baseline (1999–2000) and at the two-year
210 (2001–2002) and four-year (2003–2004) follow-up examinations for medication.

211

212 **Sleep complaint**

213 At baseline, we defined EDS as the self-report of having a feeling of being excessively
214 sleepy during the day. Participants were invited to answer ‘never, rarely, frequently, or often’
215 to the question, ‘Do you feel very sleepy during the day?’. Other information related to sleep
216 were also recorded, including the prescription of hypnotic, antidepressant, and anxiolytic
217 medications due to their action on sleep per se and snoring. Insomnia was also recorded; it
218 was defined as the number of insomnia complaints self-reported when participants answered
219 the following questions: ‘Do you have any difficulty in falling asleep?’ (difficulty in initiating
220 sleep), ‘Do you wake up during the night?’ (difficulty in maintaining sleep), ‘Do you often
221 wake up early in the morning without being able to go back to sleep?’ (early morning
222 awakening) [28, 40].

223

224 **Medication**

225 About half of the 3C cohort participants were affiliated with the French national
226 health-care insurance for active or retired salaried workers (Caisse Nationale d'Assurance
227 Maladie des Travailleurs Salariés; CNAM-TS). For these persons, we obtained individual data
228 from the CNAM-TS about all drugs prescribed between 2001 and 2003. Drug names were

229 coded according to the Anatomical Therapeutic Chemical classification of the World Health
230 Organization and classified into one of five categories: antibiotics, antivirals, antifungals,
231 antiparasitics, or non-infectious and non-psychotropic drugs (anxiolytics, hypnotics, and
232 antidepressants) (see Supplementary Table S1). In this study, antipathogen drug consumption
233 was considered as a proxy of infection rate and hence of immune system efficacy.

234

235 **Baseline data collection and examination**

236 Data were collected by training nurses and psychologists during face-to-face
237 interviews using standardized questionnaires at baseline (1999–2000). For the purpose of our
238 study, baseline control variables were selected that included socio-demographic
239 characteristics (age, sex, educational level, income, and if they were living alone), weight and
240 height, and daily habits such as smoking and alcohol, coffee, and tea consumption. Depressive
241 symptoms were defined by a score ≥ 16 on the Center for Epidemiological Studies Depression
242 scale questionnaire [41]. Past history of cardiovascular heart disease included a history of
243 angina pectoris, myocardial infarction, or revascularization procedures. Diabetes was defined
244 as a fasting blood glucose level ≥ 7 mmol/l and/or drug treatment for diabetes. Blood pressure
245 was measured twice with a digital electronic tensiometer. Information about asthma was also
246 recorded.

247 A diagnosis of dementia was made by a neurologist according to DSM-IV [42] criteria
248 and validated by an independent national panel of neurologists. Mild Cognitive Impairment
249 (MCI) (which is considered a prodrome to dementia) was diagnosed according to the
250 currently used revised criteria (MCI-R) proposed by an international consensus group [43].
251 The detailed MCI definition has been reported elsewhere [44]. Verbal neurocognitive
252 functioning and premorbid IQ estimate were assessed through the National Adult Reading

253Test (NART) [45]. All medication used during the previous month were recorded by
254interviewers. Participants were asked to show medical prescriptions and drug packages. Drug
255names were coded according to the Anatomical Therapeutic Chemical classification of the
256World Health Organization. There was no significant association between the consumption of
257anti-infectious drugs recorded at baseline and EDS, suggesting that these two variables were
258not directly influencing each other at baseline (Fisher exact tests; antibiotics: $P = 0.32$,
259antivirals: $P = 0.33$, antifungals: $P = 0.23$, antiparasitics: $P = 0.44$).

260

261Statistical analyses

262 The quantity of each anti-infectious drug category (antibiotics, antivirals, antifungals,
263and antiparasitics) was considered as a dependent variable in a regression, with EDS (two
264levels: never, at least one) as the explanatory variable. The quantity of antibiotics followed a
265left-bounded error distribution (antibiotics consumption cannot be negative), thus a censored
266regression models (Tobit) was used. For the other drug categories, consumption was pooled
267into two categories (two levels: never, at least one), and logistic regressions were used. The
268sum of all anti-infectious drugs was also considered as a dependent variable, and a Tobit
269regression model was used (anti-infectious drugs consumption cannot be negative). For all
270models, the control variable was the sum of all drugs consumed (CNAM-TS record), and the
271potential confounding variables were sampling location (three levels: Bordeaux, Dijon,
272Montpellier), sex (binary), age (quantitative), educational level (four levels), income (five
273levels), snoring level (four levels), smoking (binary), alcohol consumption (three levels:
274drinker, abstainer, ex-drinker), mg of caffeine per day (quantitative), asthma (binary), high
275blood pressure (binary), lifestyle (two levels: alone/not alone), past history of cardiovascular
276heart disease (binary), depressive symptoms (binary), diabetes (binary), MCI score (binary),
277NART score (six levels), BMI (or weight/height², quantitative), consumption of anxiolytic,

278antidepressant, and hypnotic drugs from the interview (two levels: never, at least one), and
279insomnia (two levels: never/rarely; frequently/often). The interaction terms of sex and age
280with the dependent variables, educational level, income, MCI score, insomnia, consumption
281of anxiolytic, consumption of antidepressant, and consumption of hypnotic drugs were
282considered and removed when non-significant (see Supplementary Information for details).
283The quantity of all non-infectious and non-psychotropic drugs consumed was also considered
284as a dependent variable, with the same explanatory, control, and confounding variables as
285above. All statistical analyses were performed with R 2.11.1 software (www.r-project.org).

286

287Ethics Statement

288 The study protocol was approved by the ethical committee of the university hospital of
289Kremlin-Bicêtre. The methods were carried out in accordance with the approved guidelines.
290Each participant signed legal consent forms. Informed consent was obtained from all subjects.

291

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404

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406

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419

420 **Author contributions**

421

422C.B. analysed data and wrote the paper; F.T., M.R. and S.A. conceived the study and wrote
423the paper; Y.D. and I.J. wrote the paper; K.R., C.H. and C.T. supervised data collection from
4243C cohort.

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427

428**Table 1. Baseline characteristics of the study sample.** Sex, sample size (N), age, excessive daytime
 429sleepiness (EDS), and consumption of the different types of medicines from 2001 to 2003 recorded
 430from CNAM-TS. For the medicines, ‘n’ refers to the number of individuals taking at least one of that
 431type of drug during the period considered. For the consumption of drugs described by a quantitative
 432variable, the mean and standard deviation of the global distribution is given. For EDS, the number and
 433the percentage of individuals reporting sleep deficit is indicated. See Methods for details.

434

Sex	Age	Antivirals	Antiparasitics	Antifungals	Antibiotics	Non anti-infectious and psychotropic drugs	Complaint of EDS
	mean (SD)	n	n	n	mean (SD)	mean (SD)	n (%)
Men (N=1108)	73.1 (4.8)	42	58	382	3.7 (4.5) n=916	120 (80) n=1108	647 (58)
Women (N=1757)	73.2 (4.9)	112	95	668	4.1 (4.9) n=1484	132 (79) n=1757	891 (51)
All (N=2865)	73.2 (4.9)	154	153	1050	3.97 (4.7) n=2400	127 (80) n=2865	1,538 (54)

435 **Table 2. Influence of excessive daytime sleepiness (EDS) on consumption of drugs for the**
 436 **different models fitted, all things being equal** (n=2,865). For each model, estimate of the effect of
 437 EDS relative to its absence, standard error (SE), χ^2 statistic, degree of freedom (df), and *P*-value of the
 438 χ^2 test are given. Items in bold showed significant effects.

Explained variable of the model	Estimate of effect from EDS	SE	χ^2	df	<i>P</i> ($>\chi^2$)
Anti-infectious (Tobit)	+ 0.20	0.27	0.55	1	0.46
Antibiotics (Tobit)	+ 0.19	0.20	0.92	1	0.34
Antivirals (Logistic)	+ 0.28	0.18	2.49	1	0.11
Antifungals (Logistic)	+ 0.19	0.08	5.12	1	0.02
Antiparasitics (Logistic)	+ 0.39	0.19	4.40	1	0.03
Non anti-infectious and psychotropics (Tobit)	-0.22	0.24	0.81	1	0.37

439

440Supplementary Information

441**Table S1. Classification of drugs.** Classification of drugs according to the Anatomical Therapeutic
442Chemical classification of the World Health Organization into categories: antibiotics, antivirals,
443antifungals, antiparasitics, anxiolytics, hypnotics, antidepressants, and non-infectious and non-
444psychotropic drugs.

Drugs	ATC Classification
Antibiotics	A07AA-A07AB-A07-A07AX03-A07AX04-D06A-D06C- D07C-G01AA-G01AB-G01AC-G01AE-G01BA-G01BC- G01BD-G04AB-G04AC -G04AG-G04AH-J01-J04-S01AA- S01AB
Antivirals	J05-S01AD
Antifungals	A07AC-D01A-D01B-G01AF-G01AG-G01BE-G01BF-J02
Antiparasitics	A07AX01-A07AX02-P01-P02
Antidepressants	N06A
Anxiolytics	N05B
Antihypnotics	N05C
Non-infectious and non- psychotropic drugs	A01-A02-A03-A04-A05-A06 -A09-A10-A11-A12-A13-A16- B-C-D02-D03-D04-D05-D06B-D07A-D07B-D11A-G01AD- G01AX-G02-G03-G04AA-G04AD-G04BD-G04C-H-J06-J07- L-M-N01-N02-N03-N04-N05A-N06B-N06C-N06D-N07-P03- R-S01AX-S01B-S01C-S01E-S01F-S01G-S01H-S01J-S01K- S01X-S02-S03-V

445

446Table S2. Tobit regression model of the quantity of antibiotics consumed as a function of
 447excessive daytime sleepiness (EDS), totality of medicines taken, and potential confounding
 448variables (n=2,865). For each variable, the estimate, standard error of the mean (SE), *P*-value of the
 449Student's test of the mean, χ^2 statistic (Likelihood Ratio Test), and *P*-value of the χ^2 test are given. For
 450categorical variables, the estimates are for one category compared to the reference category
 451(underlined term). Items in bold showed significant effects.

452

	Estimate	SE	<i>P</i> (> t)	χ^2	<i>P</i> (> χ^2)
Intercept	7.28	6.33	0.25		
EDS	0.19	0.20	0.38	0.92	0.34
Totality of drugs	0.02	0.0015	<10 ⁻⁵	305	<10 ⁻⁵
Insomnia (frequently/ <u>rarely</u>)	0.18	0.2	0.38	0.77	0.38
Snoring				4.23	0.24
rarely/ <u>never</u>	0.345	0.24	0.16		
regularly/ <u>never</u>	-0.12	0.27	0.67		
frequently/ <u>never</u>	0.35	0.33	0.29		
Age	0.07	0.08	0.41		
Sex	-0.24	0.42	0.57		
Body mass Index (BMI)	-0.05	0.024	0.04	4.38	0.04
Educational level (lower to higher)					
2/ <u>1</u>	-1.07	0.42	0.01		
3/ <u>1</u>	-0.61	0.49	0.21		
4/ <u>1</u>	-0.35	0.50	0.48		
Income (1 to 4: lower to higher, 5: do not wish to reply)					
2/ <u>1</u>	-2.66	6.64	0.69		
3/ <u>1</u>	-7.58	6.77	0.26		
4/ <u>1</u>	3.82	6.70	0.57		
5/ <u>1</u>	-6.70	1.1	0.54		
National Adult Reading Test (NART) score (lower to higher)				14.64	0.01
2/ <u>1</u>	-0.61	6.637	0.19		
3/ <u>1</u>	-0.69	0.47	0.16		
4/ <u>1</u>	-0.92	0.49	0.05		
5/ <u>1</u>	-0.20	0.47	0.68		
6/ <u>1</u>	-1.20	0.49	0.02		
Mild Cognitive Impairment :MCI (yes/ <u>no</u>)	0.04	0.20	0.85	0.04	0.85
Lifestyle (not alone/ <u>alone</u>)	0.33	0.25	0.19	1.74	0.19
Alcohol consumption				0.54	0.76
drinker/ <u>abstainer</u>	0.006	0.26	0.98		

ex-drinker/abstainer	0.46	0.66	0.48		
History of cardiovascular disease (yes/no)	-0.57	0.34	0.10	2.73	0.10
Depressive symptoms (yes/no)	0.60	0.30	0.04	4.12	0.04
Smoker (yes/no)	0.24	0.23	0.30	1.05	0.30
mg of caffeine per day	0.0009	0.0006	0.16	1.97	0.16
Asthma (yes/no)	1.59	0.37	<10 ⁻⁵	18.5	<10 ⁻⁵
High blood pressure (yes/no)	-0.85	0.21	<10 ⁻⁵	15.9	<10 ⁻⁵
Diabetes (yes/no)	0.38	0.35	0.28	1.16	0.28
hypnotic drugs (yes/no)	0.05	0.33	0.88	0.02	0.88
Anxiolytic drugs (yes/no)	0.12	0.28	0.65	0.20	0.65
Antidepressant drugs (yes/no)	-12.3	5.53	0.03		
Centre				0.30	0.86
Dijon/Bordeaux	-0.09	0.28	0.72		
Montpellier/Bordeaux	0.03	0.33	0.93		
Sex*Educational level				8.32	0.04
female/male*2/1	0.95	0.5	0.06		
female/male*3/1	0.91	0.59	0.12		
female/male*4/1	-0.07	0.64	0.91		
Age * Income				10.15	0.04
Age*2/1	0.03	0.09	0.74		
Age*3/1	0.10	0.09	0.25		
Age*4/1	-0.05	0.09	0.25		
Age*5/1	0.09	0.15	0.53		
Age*Antidepressant drugs (yes/no)	-0.16	0.07	0.03	4.80	0.03

453

454 **Table S3. GLM with error binomial predicting the quantity of antiviral drugs consumed as a**
455 **function of excessive daytime sleepiness (EDS) and potential confounding variables (n=2,865).**
456 For each variable, the estimate, standard error of the mean (SE), *P*-value of the Student's test of the
457 mean, χ^2 statistic, and *P*-value of the χ^2 test are given. For categorical variables, the estimates are for
458 one category compared to the reference category (underlined term).

	Estimate	SE	<i>P</i> (> t)	χ^2	<i>P</i> (> χ^2)
Intercept	1.09	1.78	0.54		
EDS	0.28	0.18	0.12	2.49	0.11
Totality of drugs	0.004	0.0011	<10 ⁻³	0.02	0.88
Insomnia (frequently/ <u>rarely</u>)	0.02	0.18	0.88	0.02	0.87
Snoring				0.008	0.93
rarely/ <u>never</u>	-0.18	0.21	0.40		
regularly/ <u>never</u>	-0.08	0.24	0.73		
frequently/ <u>never</u>	0.07	0.28	0.81		
Age	-0.05	0.02	0.01		
Sex	0.43	0.24	0.07	3.55	0.06
Body Mass Index (BMI)	-0.06	0.02	0.007	7.38	0.006
Educational level (lower to higher)				4.44	0.22
2/ <u>1</u>	0.06	0.22	0.78		
3/ <u>1</u>	-0.33	0.32	0.30		
4/ <u>1</u>	0.33	0.32	0.30		
Income (1 to 4: lower to higher, 5: do not wish to reply)				3.9	0.42
2/ <u>1</u>	0.36	0.43	0.39		
3/ <u>1</u>	0.17	0.46	0.71		
4/ <u>1</u>	-0.08	0.48	0.86		
5/ <u>1</u>	0.51	0.63	0.42		
National Adult Reading test (NART) score (lower to higher)				1.13	0.95
2/ <u>1</u>	-0.14	0.39	0.72		
3/ <u>1</u>	-0.39	0.43	0.37		
4/ <u>1</u>	-0.19	0.40	0.63		
5/ <u>1</u>	-0.15	0.42	0.71		
6/ <u>1</u>	-0.11	0.43	0.80		
Mild Cognitive Impairment (MCI) (yes/ <u>no</u>)	-0.11	0.18	0.54	0.32	0.57
Lifestyle (not alone/ <u>alone</u>)	-0.05	0.22	0.81	0.04	0.84
Alcohol consumption				8.94	0.01
drinker/abstainer	0.52	0.25	0.04		
ex-drinker/abstainer	-1.15	1.04	0.27		
History of cardiovascular disease (yes/ <u>no</u>)	-0.13	0.32	0.69	0.16	0.68
Depressive symptoms (yes/ <u>no</u>)	-0.16	0.26	0.54	0.32	0.57

smoker (yes/ <u>no</u>)	-0.10	0.21	0.61	0.25	0.62
mg of caffeine per day	-0.0001	0.0006	0.82	0.04	0.84
Asthma (yes/ <u>no</u>)	0.04	0.31	0.89	0.02	0.87
High blood pressure (yes/ <u>no</u>)	0.0001	0.19	0.99	<10 ⁻⁵	0.99
Diabetes (yes/ <u>no</u>)	-0.22	0.35	0.53	0.48	0.49
Antihypnotic drugs (yes/ <u>no</u>)	0.29	0.26	0.26	1.22	0.27
Anxiolytic drugs (yes/ <u>no</u>)	-7.8	3.23	0.01		
Antidepressant drugs (yes/ <u>no</u>)	0.22	0.33	0.50	0.45	0.50
Centre				0.60	0.74
Dijon/Bordeaux	0.15	0.26	0.55		
Montpellier/Bordeaux	0.23	0.30	0.45		
Age*Anxiolytic drugs (yes/ <u>no</u>)	0.1060	0.04686	0.023718		

459

460 Table S4. GLM with error binomial predicting the quantity of antifungal drugs consumed as a
 461 function of excessive daytime sleepiness (EDS) and potential confounding variables (n=2,865).
 462 For each variable, the estimate, standard error of the mean (SE), P-value of the Student's test of the
 463 mean, χ^2 statistic, and P-value of the χ^2 test are given. For categorical variables, the estimates are for
 464 one category compared to the reference category (underlined term). Items in bold showed significant
 465 effects.

466

	Estimate	SE	$P(> t)$	χ^2	$P(>\chi^2)$
Intercept	-0.38	0.82	0.64		
EDS	0.19	0.08	0.02	5.12	0.02
Totality of drugs	0.006	0.00067	<10 ⁻⁵	103.6	<10 ⁻⁵
Insomnia (frequently/ <u>rarely</u>)	0.008	0.09	0.92	0.006	0.94
Snoring				0.26	0.61
rarely/ <u>never</u>	0.06	0.10	0.56		
regularly/ <u>never</u>	-0.10	0.12	0.39		
frequently/ <u>never</u>	-0.006	0.14	0.96		
Age	-0.02	0.008	0.03	4.98	0.02
Sex	-0.52	0.38	0.18		
Body Mass Index (BMI)	0.02	0.01	0.02	5.21	0.02
Educational level (lower to higher)				5.97	0.11
2/ <u>1</u>	-0.09	0.11	0.37		
3/ <u>1</u>	0.07	0.14	0.60		
4/ <u>1</u>	0.25	0.16	0.12		
Income (1 to 4: lower to higher, 5: do not wish to reply)				5.50	0.24
2/ <u>1</u>	-0.31	0.20	0.12		
3/ <u>1</u>	-0.23	0.21	0.28		
4/ <u>1</u>	-0.09	0.22	0.68		
5/ <u>1</u>	-0.06	0.31	0.84		
National Adult Reading (NART) score (lower to higher)					
2/ <u>1</u>	-0.27	0.32	0.39		
3/ <u>1</u>	-0.37	0.33	0.27		
4/ <u>1</u>	-0.12	0.31	0.69		
5/ <u>1</u>	-0.50	0.33	0.13		
6/ <u>1</u>	-0.36	0.33	0.27		
Mild Cognitive Impairment (MCI) (yes/ <u>no</u>)	0.32	0.14	0.02		
Lifestyle (not alone/ <u>alone</u>)	-0.13	0.10	0.22	1.51	0.22
Alcohol consumption				2.07	0.35

drinker/abstainer	0.16	0.11	0.16		
ex-drinker/abstainer	0.22	0.27	0.42		
History of cardiovascular disease (yes/no)	-0.51	0.15	<10 ⁻³	11.64	<10 ⁻³
Depressive symptoms (yes/no)	0.04	0.12	0.74	0.10	0.75
Smoker (yes/no)	-0.09	0.09	0.37	0.79	0.37
mg of caffeine per day	0.0002	0.0003	0.53	0.35	0.56
Asthma (yes/no)	0.13	0.15	0.41	0.64	0.42
High blood pressure (yes/no)	-0.23	0.09	0.01	6.20	0.01
Diabetes (yes/no)	0.0007	0.15	0.99	8.10 ⁻⁵	0.99
Antihypnotic drugs (yes/no)	0.05	0.14	0.70	0.15	0.70
Anxiolytic drugs (yes/no)	0.06	0.12	0.62	0.23	0.63
Antidepressant drugs (yes/no)	-0.08	0.18	0.65	0.19	0.66
Centre				0.48	0.79
Dijon/Bordeaux	0.06	0.12	0.64		
Montpellier/Bordeaux	0.02	0.14	0.89		
Sex (female/male)*NART score				11.85	0.04
female/male*2/1	1.00	0.41	0.01		
female/male*3/1	0.91	0.43	0.03		
female/male*4/1	0.54	0.40	0.17		
female/male*5/1	1.13	0.41	0.006		
female/male*6/1	0.71	0.41	0.08		
Sex (female/male)*MCI	-0.36	0.17	0.03340	4.55	0.03

467

468 Table S5. GLM with error binomial predicting the quantity of antiparasitic drugs consumed as a
 469 function of excessive daytime sleepiness (EDS) and potential confounding variables (n=2,865).
 470 For each variable, the estimate, standard error of the mean (SE), P-value of the Student's test of the
 471 mean, χ^2 statistic, and P-value of the χ^2 test are given. For categorical variables, the estimates are for
 472 one category compared to the reference category (underlined term). Items in bold showed significant
 473 effects.

474

	Estimate	SE	$P(> t)$	χ^2	$P(>\chi^2)$
Intercept	0.55	1.82	0.76		
EDS	0.39	0.19	0.040	4.40	0.03
Totality of drugs	0.006	0.0012	<10 ⁻⁵	27.8	<10 ⁻⁵
Insomnia (frequently/ <u>rarely</u>)	0.17	0.19	0.36	0.83	0.36
Snoring				5.12	0.16
Rarely/ <u>never</u>	0.007	0.23	0.978		
Regularly/ <u>never</u>	0.46	0.24	0.06		
Frequently/ <u>never</u>	0.016	0.30	0.96		
Age	-0.05	0.02	0.01		
Sex	-2.15	0.90	0.02		
Body Mass Index (BMI)	0.002	0.02	0.92	0.008	0.92
Educational level (lower to higher)				5.52	0.14
2/ <u>1</u>	0.30	0.25	0.22		
3/ <u>1</u>	0.61	0.30	0.04		
4/ <u>1</u>	0.69	0.34	0.04		
Income (1 to 4: lower to higher, 5: do not wish to reply)				1.05	0.90
2/ <u>1</u>	-0.03	0.44	0.94		
3/ <u>1</u>	0.04	0.46	0.93		
4/ <u>1</u>	0.22	0.48	0.65		
5/ <u>1</u>	0.03	0.75	0.96		
National Adult Reading test (NART) score (lower to higher)					
2/ <u>1</u>	-0.49	0.58	0.40		
3/ <u>1</u>	-0.79	0.63	0.21		
4/ <u>1</u>	-0.79	0.57	0.17		
5/ <u>1</u>	-0.68	-0.60	0.26		
6/ <u>1</u>	-1.78	0.71	0.01		
Mild Cognitive Impairment (MCI) (yes/ <u>no</u>)	-0.04	0.18	0.81	0.06	0.81
Lifestyle (couple/ <u>alone</u>)	0.23	0.22	0.29	1.10	0.29
Alcohol consumption				4.88	0.09

drinker/abstainer	-0.50	0.22	0.03		
ex-drinker/abstainer	-0.16	0.53	0.75		
History of cardiovascular disease (yes/ <u>no</u>)	-0.06	0.29	0.83	0.05	0.83
Depressive symptoms (yes/ <u>no</u>)	-0.09	0.36	0.72	0.13	0.72
Smoker (yes/ <u>no</u>)	-0.35	0.21	0.10	2.73	0.10
mg of caffeine per day	9.6 10 ⁻⁵	6.1 10 ⁻⁴	0.87	0.02	0.88
Asthma (yes/ <u>no</u>)	-0.34	0.35	0.33	1.01	0.31
High blood pressure (yes/ <u>no</u>)	-0.45	0.19	0.02	5.33	0.02
Diabetes (yes/ <u>no</u>)	-0.20	0.32	0.54	0.39	0.53
Antihypnotic drugs (yes/ <u>no</u>)	0.54	0.24	0.03		
Anxiolytic drugs (yes/ <u>no</u>)	0.70	0.38	0.07		
Antidepressant drugs (yes/ <u>no</u>)	-10.2	4.30	0.02		
Centre				17.74	<10 ⁻³
Dijon/Bordeaux	0.02	0.26	0.93		
Montpellier/Bordeaux	0.90	0.28	0.001		
Sex (female/ <u>male</u>)*NART score				17.62	0.003
female/ <u>male</u> *2/ <u>1</u>	1.16	0.10	0.24		
female/ <u>male</u> *3/ <u>1</u>	1.98	0.99	0.05		
female/ <u>male</u> *4/ <u>1</u>	2.03	0.94	0.03		
female/ <u>male</u> *5/ <u>1</u>	2.05	0.95	0.03		
female/ <u>male</u> *6/ <u>1</u>	2.91	1.02	0.004		
Sex (female/ <u>male</u>)*Anxiolytic drugs (yes/ <u>no</u>)	-0.96	0.48	0.04	4.32	0.04
Sex (female/ <u>male</u>)*Antidepressant drugs (yes/ <u>no</u>)	2.21	1.18	0.06	5.47	0.02
Age*Antidepressant drugs (yes/ <u>no</u>)	0.11	0.05	0.04	5.0	0.02

475

476**Table S6. Tobit regression model of the quantity of anti-infectious drugs consumed as a function**
477**of excessive daytime sleepiness (EDS), totality of medicines taken, and potential confounding**
478**variables (N=2.865).** For each variable, the estimate, standard error of the mean (SE), p-value of the
479Student's test of the mean, χ^2 statistic (Likelihood Ratio Test), and P-value of the χ^2 test are given. For
480categorical variables, the estimates are for one category compared to the reference category
481(underlined term).

482

	Estimate	SE	$P(> t)$	χ^2	$P(>\chi^2)$
Intercept	3.95	8.24	0.63		
EDS	0.20	0.27	0.46	0.55	0.46
Totality of drugs	0.04	0.002	<10 ⁻⁵	369	<10 ⁻⁵
Insomnia (frequently/ <u>rarely</u>)	0.09	0.27	0.74	0.09	0.75
Snoring				2.76	0.10
Rarely/ <u>never</u>	0.49	0.32	0.12		
Regularly/ <u>never</u>	0.17	0.36	0.64		
Frequently/ <u>never</u>	0.91	0.43	0.03		
Age	-0.04	0.11	0.68		
Sex	0.51	0.34	0.13	2.23	0.13
Body Mass Index (BMI)	-0.04	0.03	0.21	1.71	0.19
Educational level (lower to higher)				5.51	0.14
2/ <u>1</u>	-0.74	0.33	0.03		
3/ <u>1</u>	-0.19	0.43	0.66		
4/ <u>1</u>	-0.41	0.49	0.40		
Income (1 to 4: lower to higher, 5: do not wish to reply)					
2/ <u>1</u>	2.23	8.72	0.80		
3/ <u>1</u>	-5.27	8.88	0.55		
4/ <u>1</u>	13.42	8.81	0.13		
5/ <u>1</u>	-1.12	14.45	0.94		
National Adult reading test (NART) score (lower to higher)				13.12	0.02
2/ <u>1</u>	0.10	0.62	0.87		
3/ <u>1</u>	-0.04	0.66	0.94		
4/ <u>1</u>	-0.33	0.62	0.59		
5/ <u>1</u>	0.73	0.65	0.26		
6/ <u>1</u>	-0.61	0.68	0.37		
Mild Cognitive Impairment (MCI) (yes/ <u>no</u>)	0.16	0.27	0.55	0.33	0.56
Lifestyle (couple/ <u>alone</u>)	0.29	0.33	0.38	0.78	0.37
Alcohol consumption				0.90	0.64

drinker/abstainer	0.34	0.35	0.33		
ex-drinker/abstainer	0.29	0.87	0.74		
History of cardiovascular disease (yes/no)	-1.41	0.46	0.002	9.35	0.002
Depressive symptoms (yes/no)	0.84	0.39	0.03	4.46	0.03
Smoker (yes/no)	-0.06	0.31	0.85	0.03	0.86
mg of caffeine per day	6.10 ⁻⁴	8.10 ⁻⁴	0.48	0.43	0.51
Asthma (yes/no)	1.74	0.49	< 10 ⁻³	12.6	<10 ⁻³
High blood pressure (yes/no)	-1.17	0.28	< 10 ⁻⁴	17.08	<10 ⁻⁵
Diabetes (yes/no)	0.17	0.47	0.71	0.13	0.72
Antihypnotic drugs (yes/no)	0.26	0.43	0.55	0.34	0.56
Anxiolytic drugs (yes/no)	0.13	0.37	0.71	0.11	0.73
Antidepressant drugs (yes/no)	-0.35	0.56	0.53	0.38	0.54
Centre				0.82	0.66
Dijon/Bordeaux	0.03	0.37	0.94		
Montpellier/Bordeaux	0.30	0.43	0.49		
Age * Income				15.7	0.003
Age*2/1	-0.04	0.12	0.73		
Age*3/1	0.07	0.12	0.54		
Age*4/1	-0.17	0.12	0.13		
Age*5/1	-0.03	0.19	0.89		

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484**Table S7. Tobit regression model of the quantity of all non-infectious drugs consumed as a**
485**function of excessive daytime sleepiness (EDS), totality of medicines taken, and potential**
486**confounding variables** (n=2,865). For each variable, the estimate, standard error of the mean (SE), p-
487value of the Student's test of the mean, χ^2 statistic (Likelihood Ratio Test), and p-value of the χ^2 test are
488given. For categorical variables, the estimates are for one category compared to the reference category
489(underlined term).

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	Estimate	SE	$P(> t)$	χ^2	$P(>\chi^2)$
Intercept	-6.69	7.43	0.37		
EDS	-0.22	0.24	0.37	0.81	0.37
Totality of drugs	0.97	0.001	<10 ⁻⁵	13000	<10 ⁻⁵
Insomnia (frequently/ <u>rarely</u>)	-0.09	0.24	0.72	0.11	0.73
Snoring				2.96	0.08
Rarely/ <u>never</u>	-0.42	0.29	0.15		
Regularly/ <u>never</u>	-0.17	0.33	0.59		
Frequently/ <u>never</u>	-0.83	0.39	0.03		
Age	0.07	0.10	0.50		
Sex	-0.48	0.30	0.11	2.47	0.12
Body Mass Index (BMI)	0.04	0.03	0.17	2.06	0.15
Educational level (lower to higher)				4.76	0.19
2/ <u>1</u>	0.63	0.30	0.04		
3/ <u>1</u>	0.21	0.39	0.58		
4/ <u>1</u>	0.23	0.44	0.60		
Income (1 to 4: lower to higher, 5: do not wish to reply)					
2/ <u>1</u>	0.07	7.85	0.99		
3/ <u>1</u>	6.65	8.01	0.41		
4/ <u>1</u>	-9.12	7.94	0.25		
5/ <u>1</u>	2.10	12.9	0.87		
National Adult Reading test NART score (lower to higher)				11.8	0.04
2/ <u>1</u>	-0.12	0.56	0.83		
3/ <u>1</u>	0.05	0.59	0.93		
4/ <u>1</u>	0.34	0.56	0.55		
5/ <u>1</u>	-0.60	0.59	0.30		
6/ <u>1</u>	0.51	0.61	0.41		
Mild Cognitive Impairment (MCI) (<u>yes/no</u>)	-0.06	0.24	0.81	0.06	0.81
Lifestyle (couple/ <u>alone</u>)	-0.26	0.29	0.38	0.79	0.37

Alcohol consumption				1.45	0.48
drinker/abstainer	-0.37	0.32	0.24		
ex-drinker/abstainer	-0.53	0.78	0.50		
History of cardiovascular disease (yes/no)	1.22	0.41	0.003	8.62	0.003
Depressive symptoms (yes/no)	-0.71	0.36	0.05	3.94	0.05
Smoker (yes/no)	0.08	0.28	0.76	0.08	0.77
mg of caffeine per day	-4.10 ⁻⁴	8.10 ⁻⁴	0.64	0.18	0.67
Asthma (yes/no)	-1.53	0.44	<10 ⁻³	11.83	<10 ⁻³
High blood pressure (yes/no)	0.93	0.25	<10 ⁻³	13.58	<10 ⁻³
Diabetes (yes/no)	-0.06	0.43	0.88	0.02	0.89
Antihypnotic drugs (yes/no)	-0.17	0.39	0.65	0.20	0.66
Anxiolytic drugs (yes/no)	-0.07	0.33	0.82	0.04	0.84
Antidepressant drugs (yes/no)	0.20	0.50	0.68	0.15	0.69
Centre				1.25	0.53
Dijon/Bordeaux	0.03	0.33	0.91		
Montpellier/Bordeaux	-0.30	0.39	0.44		
Age * Income				13.84	0.008
Age*2/1	0.006	0.10	0.95		
Age*3/1	-0.09	0.11	0.40		
Age*4/1	0.12	0.11	0.26		
Age*5/1	-0.04	0.17	0.81		

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