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To cite this version:
Claire Berticat, Frédéric Thomas, Yves Dauvilliers, Isabelle Jaussent, Karen Ritchie, et al.. Excessive daytime sleepiness and antipathogen drug consumption in the elderly: a test of the immune theory of sleep. Scientific Reports, Nature Publishing Group, 2016, 6, pp.23574. 10.1038/srep23574. hal-01867593v2
Excessive daytime sleepiness and antipathogen drug consumption in the elderly: a test of the immune theory of sleep

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The evolutionary reasons for sleep remain controversial. The immune theory of sleep suggests that sleep is essential to the immune system, allowing organisms to allocate more energy to their immunity. This hypothesis was tested by exploring the links between excessive daytime sleepiness (EDS) and vulnerability to infectious diseases in a large (n = 9294) cohort of elderly individuals, with information on socio-demographics, daily habits, and medical characteristics. At the two-year and four-year follow-ups, we obtained individual data from the national healthcare insurance about all medications prescribed to the participants between 2001 and 2003 (n = 2865). We found an independent positive association between EDS and the consumption of some anti-pathogen drugs. This relationship was mostly explained by fungal and parasitic infections rather than by viral and bacterial ones. These results, although based on correlations, are consistent with the idea that EDS as a proxy of altered sleep quality/quantity may affect the efficiency of the immune system, and hence vulnerability to infections.

Sleep is widespread in the animal kingdom, being described in insects, fish, birds, and mammals1–6. From an evolutionary perspective, it is predicted that sleep must be associated to substantial benefits to outweigh the multiple costs that are associated with dormancy states. While it is relatively easy to identify several of these costs (e.g., no mating or foraging opportunities, vulnerability to insect vectors and/or predators, low ability to detect and respond to changing environmental conditions), the benefits are more difficult to determine. However, sleep deprivation is usually rapidly accompanied by highly detrimental health consequences, indicating that sleep is a strict necessity in a great number of species. Currently, the main theories regarding the function of sleep7 propose that it plays an important role in brain development, clearance, or repair8–10, and in consolidating memories and learning11. Sleep could also be beneficial because it maximizes energy saving when other activities bring no, or little, fitness benefits12,13. Alternatively, there is an increasing body of evidence that sleep is essential to the immune system, allowing organisms to allocate more energy to their immunity14,15. To function properly, the immune system indeed requires a significant proportion of our daily energy budget16. An efficient way of allocating more energy to the immune system is to place all the other functions in ‘rest mode’, in other words, put them to sleep. In accordance with this hypothesis, it is a common belief that sleep deprivation is linked to increased vulnerability to infections17–19 and that sleep duration usually increases in sick individuals20, which significantly accelerates their recovery21,22. A recent interspecific study on mammals also supports the immune theory of sleep: the more the organisms sleep, the better their immune system functions and the fewer parasites they have23. This immunity hypothesis for the role of sleep still needs to be explored, particularly at the intraspecific level.

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Here, we tested the immune theory of sleep in humans by exploring the links between excessive daytime sleepiness (EDS) and vulnerability to infectious diseases. We focused our study on elderly individuals because the effects of sleep changes are expected to be especially elevated in populations at particular risk of infections, like older adults\textsuperscript{14}. In addition, aging is often associated with a decrease in both the quality and quantity of sleep, with large variations among individuals\textsuperscript{24–27}, and EDS is frequently reported in the elderly\textsuperscript{28,29}. To estimate changes in sleep quality/quantity, we focused on the complaint of EDS because although subjective it represents a unique relative individual estimate of sleep alteration whatever the total daily amount of time spent sleeping. Thus we use EDS in this analysis as a proxy of altered sleep quality/quantity. Using a four-year longitudinal study based on an elderly population, we examined whether EDS was associated with the consumption of the different types of medicines from 2001 to 2003 recorded from CNAM-TS. For whom all data were available, including follow-up data for medications and who did not have dementia or narcolepsy. The ages of the subjects in 2000 ranged from 65 to 93 years, with an average of 73.2 ± 4.9 years (Table 1). Overall 54% (1,538/2,865) reported having EDS (58% of men [647/1,108] and 51% of women [891/1,757]; Table 1). The mean consumption of the different types of drugs from CNAM-TS is detailed in Table 1.
Discussion
We detected a positive relationship between the consumption of some anti-pathogen drugs and excessive daytime somnolence, which is consistent with the idea that sleep deprivation may affect immune system efficiency and hence vulnerability to infections. The correlations were significant for parasitic and fungal infections but not for bacterial and viral infections.

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

This study is strengthened by the large sample size, the population-based design, the four-year follow-up, and the adjustment with a wide range of covariates. However, we cannot exclude several alternative explanations, including a reverse causality, where somnolence would result from the detrimental effects of frequent infections on sleep quality/quantity. For instance, while influenza viruses increase sleep duration during the symptomatic period, they may conversely reduce it during the incubation period. Several infections are also known to directly induce daytime somnolence without necessarily altering sleep quality itself. We do not currently favour hypotheses suggesting that infections (indirectly or directly) cause somnolence, because daytime sleepiness most likely reflects a chronic rather than acute problem. Consequently, as suggested by the absence of correlation between consumption of anti-infectious drugs and EDS at baseline, even frequent infection episodes may remain too infrequent over the survey period to influence the self-rated level of somnolence of participants.

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

Finally there are several limitations in this study. First all the results presented here are only correlations. Second, the infection was qualitatively detected by the presence of treatments, although its severity could not be quantitatively estimated. Thus, low grade infections, generally without specific treatments, could not be considered here. Despite extensive adjustments for socio-demographic and lifestyle factors, chronic diseases, and sleep medication, we cannot exclude the possibility that unmeasured confounding factors may explain part of any association detected in observed data. The assessment of sleep complaints was self-reported, and that remains the most common method for initial diagnosis and management in the primary healthcare setting. The measurement of EDS in this study was based on only one question, but its severity was examined using a four-point scale. However, an assessment of sleep apnea was not available, and the possibility remains that our results on EDS may be driven by these variables as we also hypothesized for sleep restriction per se.

Finally, sleep disturbance was assessed only once (at the baseline examination). We therefore could not assess the evolution of sleep disturbances in relation to antipathogen medication intake and thus determine whether sleep problems were stable, decreased, or increased in parallel with the drug intake.

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

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

Materials and Methods
Participants. Between 1999 and 2001, non-institutionalized subjects were recruited as part of a multisite cohort study (Three City study, or 3C) of subjects aged at least 65 years old who were randomly selected from the electoral roll of three French cities (Bordeaux, Dijon, and Montpellier). Health-related data were collected during face-to-face interviews using standardized questionnaires. For the details of the study protocol, see. A total of 9,294 subjects were included in the study (4,931 from Dijon, 2,104 from Bordeaux, and 2,259 from Montpellier). The study protocol was approved by the ethical committee of the university hospital of Kremlin-Bicêtre. The methods were carried out in accordance with the approved guidelines. Each participant signed legal consent forms.
Sleep complaint. At baseline, we defined EDS as the self-report of having a feeling of being excessively sleepy during the day. Participants were invited to answer ‘never, rarely, frequently, or often’ to the question, ‘Do you feel very sleepy during the day?’ Other information related to sleep were also recorded, including the prescription of hypnotic, antidepressant, and anxiolytic medications due to their action on sleep per se and snoring. Insomnia was also recorded; it was defined as the number of insomnia complaints self-reported when participants answered the following questions: ‘Do you have any difficulty in falling asleep?’ (difficulty in initiating sleep), ‘Do you wake up during the night?’ (difficulty in maintaining sleep), ‘Do you often wake up early in the morning without being able to go back to sleep?’ (early morning awakening).

Medication. About half of the 3C cohort participants were affiliated with the French national health-care insurance for active or retired salaried workers (Caisse Nationale d’Assurance Maladie des Travailleurs Salarisés; CNAM-TS). For these persons, we obtained individual data from the CNAM-TS about all drugs prescribed between 2001 and 2003. Drug names were coded according to the Anatomical Therapeutic Chemical classification of the World Health Organization and classified into one of five categories: antibiotics, antivirals, antifungals, and antiparasitics, or non-infectious and non-psychoactive drugs (anxiolytics, hypnotics, and antidepressants) (see Supplementary Table S1). In this study, antipathogen drug consumption was considered as a proxy of infection rate and hence of immune system efficacy.

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

A diagnosis of dementia was made by a neurologist according to DSM-IV criteria and validated by an independent national panel of neurologists. Mild Cognitive Impairment (MCI) (which is considered a prodrom to dementia) was diagnosed according to the currently used revised criteria (MCI-R) proposed by an international consensus group. The detailed MCI definition has been reported elsewhere. Verbal neurocognitive functioning and premorbid IQ estimate were assessed through the National Adult Reading Test (NART). Past history of cardiovascular heart disease included a history of angina pectoris, myocardial infarction, or revascularization procedures. Diabetes was defined as a fasting blood glucose level ≥7 mmol/l and/or drug treatment for diabetes. Blood pressure was measured twice with a digital electronic tensiometer. Information about asthma was also recorded.

Ethics Statement. The study protocol was approved by the ethical committee of the university hospital of Kremlin-Bicêtre. The methods were carried out in accordance with the approved guidelines. Each participant signed legal consent forms. Informed consent was obtained from all subjects.
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Acknowledgements
This is contribution ISEM 2016-055 of the Institute of Evolutionary Science of Montpellier. The 3C Study is conducted under a partnership agreement between Inserm, the Victor Segalen–Bordeaux II University, and Sanofi-Synthelabo. 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, the 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’. None of the funding organizations or sponsors played a role in the design and conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

Author Contributions
C.B. analysed data and wrote the paper; F.T., M.R. and S.A. conceived the study and wrote the paper; Y.D. and I.J. wrote the paper; K.R., C.H. and C.T. supervised data collection from 3C cohort.

Additional Information
Supplementary information accompanies this paper at http://www.nature.com/srep

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Berticat, C. et al. Excessive daytime sleepiness and antipathogen drug consumption in the elderly: a test of the immune theory of sleep. Sci. Rep. 6, 23574; doi: 10.1038/srep23574 (2016).

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