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Are primary care consultations for insomnia associated with dementia in later life? (ISAC Protocol)

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A) Study title

Are primary care consultations for insomnia associated with dementia in later life?

B) Lay summary

Insomnia has been defined as a difficulty initiating or maintaining sleep, leading to sleep that is either insufficient or unrefreshing. It is well-established that insomnia is more common in people with dementia, but it is not clear if insomnia predates dementia in these individuals. This latter question is an important one: if it can be shown that people with insomnia are more likely to develop dementia in later life, this may improve our ability to predict an individual's dementia risk, and possibly to help manage that risk. Several recent studies have found a link between insomnia and later dementia, but typically give little information about the time between the onset of insomnia and the onset of dementia, raising the possibility that the insomnia is an early symptom of dementia, rather than a risk factor or potential cause of the disease. Furthermore, in some studies the link between insomnia and dementia becomes weaker when factors such as depression and sleeping tablet use are taken into account.

The proposed study uses primary care records to learn whether people with dementia are more likely to have consulted with their general practitioner (GP) about insomnia 5-10 years earlier, compared to those who do not have dementia.

C) Technical summary

We propose a 1:1 matched case-control study, using 8414 anonymised GP records already acquired for our main study (Protocol 15_111R). The study aims to explore the association between insomnia and later dementia.

Insomnia consultations will be identified using relevant Read codes. Our measure of insomnia will be the number of months in which the patient consulted the GP about insomnia, during the period 5-10 years before the index date (defined for cases as the first coded diagnosis of dementia). This 5-10 year exposure window will help address the problem of 'reverse causality', whereby we might record insomnia episodes which are merely an early symptom of dementia, rather than a risk factor for later disease.

We will use conditional logistical regression to estimate the odds ratio (OR) of developing dementia in those exposed compared to those not exposed, and to control for covariates including benzodiazepine and z-drug use, mental and physical health comorbidities, and GP visit frequency.

D) Objectives, Specific Aims and Rationale

Our objective is to understand the association between dementia and previous insomnia, as measured by the number of months in which the patient consults the GP about insomnia.

We aim to answer the following research questions:

RQ1. In the period 5-10 years prior to the index date (i.e. first diagnosis of dementia), do people with dementia consult their GP about insomnia more frequently than controls?

RQ2. Does any association between insomnia and dementia remain significant after controlling for variables such as benzodiazepine and z-drug use, physical health comorbidities and history of mental illness?

RQ3. If a sensitivity analysis is performed, looking at different exposure windows (6-11 and 7-12 years prior to the index date), does any association between insomnia and dementia remain?

E) Study background

The prevalence of insomnia among patients in primary care ranges from 10 to 50% (1). A strong association between duration of insomnia and later dementia would be of clinical relevance, with the possibility of using insomnia as a prognostic marker for dementia, or even a treatable risk factor.

But while it is well-established that insomnia is common in dementia (2), it is less clear whether the insomnia predates the development of dementia. Here is a summary of some important papers:

- A recent meta-analysis of prospective cohort studies reported significantly higher risk ($RR=1.53$) of all-cause dementia in the elderly with previous insomnia (3). However, little information on the latency between the onset of insomnia and the onset of dementia is available.
- A longitudinal study (4) found that reduced sleep was associated with a 75% increase in risk of dementia, but results were no longer significant after adjusting for depressive symptoms, respiratory problems and pain.
- A large prospective cohort study using the Caerphilly Cohort (5) found no significantly increased risk of either Alzheimer's disease or vascular dementia in those reporting insomnia 10 years previously (although those reporting daytime sleepiness and sleep apnoea had an increased risk of vascular dementia).
- A study of midlife sleep (mean age = 52) and cognitive impairment and dementia 18 to 26 years later in >2,300 Finnish twins found no association with Alzheimer's for poor sleep or hypnotic use (6).

In a recent retrospective cohort study from Taiwan, those with insomnia prescribed hypnotics were more likely to develop dementia during three years of follow-up than those with insomnia not prescribed hypnotics (7). This highlights the confounding role that hypnotics may play when analysing the relationship between sleep and dementia.

F) Study type

The study is hypothesis-testing. The null hypothesis is that there is no association between dementia and previous insomnia.

G) Study design

The study has a matched case-control design.

H) Feasibility counts

We will be using data already obtained for the main study (Protocol 15_111R), which comprised 50,000 cases and 50,000 controls. However, due to new exclusion criteria (most notably the requirement that patients have ten years of data preceding their index date), the total number of cases and controls eligible for the new study is 8414.

I) Sample size considerations

Cross-sectional studies estimate the prevalence of insomnia among patients attending primary care as 10-50% (1). If we take the lower estimate of 10%, and assume conservatively that half of these patients receive an insomnia-related clinical code, then of our 8414 patients, we will find evidence of exposure to insomnia in at least 421 patients, while 7993 will be recorded as not exposed.

According to the Sampsize power calculator (8), our study would be able to detect an odds ratio of 1.3 with 80% power and 5% alpha risk, assuming a 5% rate of exposure among controls. Furthermore, our study will have a larger sample size than four of the five longitudinal studies judged suitable for inclusion in the aforementioned systematic review (3). It is therefore likely that our study will have adequate power to detect a clinically significant effect.

J) Data Linkage Required:

No data linkage is required for this study.

K) and L) Study population and selection of controls

A subsample of the data already acquired for the main study (Protocol 15_111R) will be used for the current study.

Both cases and controls were originally drawn from the CPRD population. Dementia cases were defined on the basis of 1) a dementia code in their GP record in the period 2000-2012; and 2) an age of 65 years or older at the time of diagnosis. All patients in the CPRD who met this criteria were included (N = 47858). Controls were then drawn at random from the same CPRD population, and were matched on date of birth, sex and GP practice, with one control per case.

For the current study, two new exclusion criteria will be applied:

- Existing controls must not have been prescribed an antidementia drug (memantine, donepezil, galantamine, rivastigmine or tacrine) at any point in their record, up to two years after index date. This is to reduce the number of cases misclassified as controls.
- Existing cases and controls must have at least 10 years of available data prior to the index date.

Although it is a matched design, we will performed a standard, rather than a matched, analysis, following advice set out by Pearce (9), as this may lead to greater precision. The matching factors (age, gender and GP practice) will still be controlled for in the logistic regression.

M) Exposures, Health Outcomes and Covariates

The outcome of interest is dementia diagnosis, as defined by the code list in [Appendix 2](#).

The exposure of interest is insomnia, as measured by the number of months during the study period characterised by at least one insomnia consultation with the GP. An exposure window of 5-10 years prior to the index date has been chosen to reduce the possibility of a reverse causality bias.

For RQ1, insomnia consultations will be identified by Read codes indicating insomnia, defined for this study as a difficulty initiating or maintaining sleep, leading to an insufficient amount of sleep and subjective

complaints of non-restorative sleep (6,7,10). A tentative list of suitable Read codes is given in [Appendix 1](#), but this will be added to and refined following consultation with clinical experts (GPs). We will not use Read codes indicating hypersomnia, disturbances of the sleep-wake cycle, sleep apnoea or abnormal behaviours during sleep.

Table 1 lists possible confounding variables which may be controlled for in our analysis. The final list of adjustment variables will be refined after performing chi-squared tests of association with our outcome for each variable, as well as testing for collinearity.

Covariate	Comments
Age	
Gender	
GP practice	
Benzodiazepine and Z-drug use	<p>Possible confounder, as these drugs are often prescribed for insomnia, but may increase risk of dementia in people with insomnia (7).</p> <p>Our list of benzodiazepines and z-drugs will be derived from the BNF subsection 'Hypnotics and Anxiolytics' (we will look at older editions to ensure that we do not miss drugs no longer in use). Following a method described by Gray et al (11), we will calculate a standardized daily dose (SDD) for each prescription by multiplying drug strength with the number of tablets dispensed, and then dividing the result by the minimum effective dose of that drug; we will then sum the SDD for all benzodiazepines and z-drugs prescribed during the exposure period to create the total standardized daily dose for that patient.</p>
Alcohol misuse	<p>Potential confounder, as implicated with both insomnia and dementia.</p> <p>Alcohol code list to be based on existing clinical codes for 'clinically significant alcohol misuse' (12).</p>
History of mental illness (excluding SMI)	<p>Mental illness is a possible risk factor for dementia (13), and likely to confound the relationship between insomnia and dementia, as insomnia is more common in mental illness (14).</p> <p>Will use the existing anxiety, depression (mild and moderate codes only), eating disorder and personality disorders code lists from (15)</p>
History of severe mental illness (SMI, i.e. bipolar disorder, schizophrenia and severe depression)	<p>Considered separately from non-schizophrenia/bipolar mental disorders, due to differing treatment approaches.</p> <p>We will use the existing depression (severe codes only), schizophrenia spectrum and bipolar code lists from (15)</p>

Learning disability	We will use existing learning disability codelist from (16)
Chronic respiratory disease	We will use existing 'chronic pulmonary disease' codelist from (17)
Diabetes	We will use existing diabetes code list from (18)
Hypertension	We will use existing hypertension code list from (18)
Renal disease	We will use existing CKD stages 3-5 codes lists from (18)
CHD, vascular disease and heart failure	We will use existing CHD, peripheral arterial disease and heart failure codelists from (18)
Stroke	We will use existing stroke code list from (18)
Obstructive sleep apnoea	<p>Implicated as a risk factor for dementia (19), and may confound our results as may be incorrectly coded as 'insomnia'.</p> <p>Code list to be drawn up following consultation with clinical experts.</p>
Smoking status	<p>Implicated as a risk factor for both dementia (20) and insomnia (21).</p> <p>Will use existing smoking codelist from (22)</p>
GP visit frequency	<p>Whether or not a patient sees their GP about insomnia may reflect their pattern of health use. By adjusting for GP visit frequency, we can reduce the potentially confounding effect of underlying problems such as health anxiety and physical comorbidity.</p> <p>Patients will be classified as 'infrequent', 'moderate' and 'frequent' GP users, based on the frequency of their non-insomnia-related GP consultations.</p>

Table 1: List of potential confounding variables which may need to be controlled for logistic regression analysis. The exposure period for these variables will be the 5-10 years prior to the index date, unless otherwise stated.

N) Data/ Statistical Analysis

We will initially explore associations using cross-tabulations and chi-squared tests.

We will use conditional logistical regression to estimate the odds ratio (OR) of developing dementia in those exposed compared to those not exposed, and to control for the aforementioned covariates. We will analyse the exposure in its continuous state rather than grouping the exposure into quantiles (e.g. '0-5 months characterised by insomnia').

If insomnia and z-drug/benzodiazepine are found to be highly collinear, it may be necessary to repeat to repeat the analysis excluding all patients who have used these drugs, in order to understand whether insomnia is a risk factor for dementia independent of its association with z-drugs/benzodiazepines.

For RQ3, a sensitivity analysis will be performed, repeating the analysis using different exposure windows: 6-11 year prior to index date, and 7-12 years. The aim here is to ensure that any apparent association between insomnia and dementia is not the result of an arbitrary definition of the exposure period.

O) Plan for addressing confounding

Confounding will be partially addressed by the matched design, where cases and controls will be matched on sex, year of birth and general practice. Matching by practice will address differences in attitudes, recording, and provision of clinical care between GP practices.

In addition, confounding will be addressed at the analysis stage through logistic regression.

P) Plans for addressing missing data

Given the nature of CPRD data, when a clinical entity is not recorded in a set time period, it is treated as “not present” rather than missing. If in a patient record there is no code for insomnia during the 5-10 years prior to dementia diagnosis, we would say that the patient did not have insomnia in that period, rather than that data on insomnia is missing. Only socio-demographic or lifestyle data may be considered missing if not recorded, e.g. BMI. If appropriate, we will use multiple imputation to address missingness in socio-demographic or lifestyle factors.

Q) Patient or user group involvement

There is no patient or user group involvement.

R) Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The study will result in the following outputs:

1. Academic publications
2. Presentations at health informatics and academic primary care conferences.
3. Important clinical results may be disseminated to the public through Alzheimer’s Society talks and conferences and through Brighton Science Festival.

We will give due consideration to preserving confidentiality in our dissemination and publications. We will adhere to CPRD policy that, when reporting the data, no cell should contain <5 events.

S) Limitations of the study design, data sources, and analytic methods

Our measure of insomnia does not give any indication of its severity (e.g. how many hours per night of sleep they are getting), and only a partial indication of its duration (a patient who sees their GP once about an episode of insomnia lasting several months would be considered in this study to have experienced a single ‘insomnia month’).

Furthermore, It is likely that the extent of insomnia will be underestimated, as a UK study found that only 30% of those complaining of insomnia went on to have either a primary care consultation or prescription in the next 12 months about either mood or insomnia (23). Similarly, surveys in the US and Australia have found that respectively only 30% and 52% of those complaining of insomnia seek medical help for their complaint (24,25), while .

In addition, GPs may record insomnia as free text (or not at all) rather than with a Read code, particularly where the consultation primarily focused on another problem.

By requiring all patients to have at least 10 years of available records prior to the index date, we are introducing a bias, as this will favour patients who have stayed at the same GP practice for 10 years, indicating greater geographical stability. Patients who, for example, have to move to a care home in the years before dementia diagnosis, for example, would be excluded if this necessitates a change of GP practice.

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List of Appendices

Appendix 1. Insomnia codes from CPRD data dictionary

Appendix 2. Dementia codes from CPRD data dictionary

Appendix 1: Codes relating to insomnia in CPRD data dictionary

Read code	Frequency of codes	Read term
R005200	587291	[D]Insomnia NOS
1B1B.11	449676	C/O - insomnia
R005.00	188663	[D]Sleep disturbances
E274111	117094	Insomnia NOS
Fy00.00	55901	Disorders of initiating and maintaining sleep
1B1B.00	51359	Cannot sleep - insomnia
663N.00	43757	Asthma disturbing sleep
R005.11	7563	[D]Insomnia - symptom
663N200	7459	Asthma disturbs sleep frequently
663N100	6673	Asthma disturbs sleep weekly
E274100	5018	Transient insomnia
1B1B200	4208	Late insomnia
1B1B000	3875	Initial insomnia
Eu51000	2458	[X]Nonorganic insomnia
1BX0.00	1450	Delayed onset of sleep
E274200	1354	Persistent insomnia
1B1B100	726	Middle insomnia
E274D11	648	Restless sleep
E274.12	169	Insomnia due to nonorganic sleep disorder
E274E00	95	'Short-sleeper'
1BX9.00	19	Light sleep
Total codes	1290892	

Appendix 2: Codes relating to dementia in CPRD data dictionary

Read code	Read term
Eu00..12	Senile/Presenile dementia
E00..11	Senile dementia
F110.00	Alzheimer's disease
Eu024	Dementia in HIV disease
Eu02z	Unspecified dementia
Eu01	Vascular dementia
E000	Uncomplicated senile dementia
F116	Lewy body disease
Eu00	Dementia in Alzheimer's disease
Eu00z11	[X]Alzheimer's dementia unspec
Eu011	Multi-infarct dementia
Eu012	Subcortical vascular dementia
Eu023	Dementia in Parkinson's disease
Eu01100	[X] Multi-infarct dementia
Eu00112	[X]Senile dementia,Alzheimer's type
E001	Presenile dementia
F1100	Alzheimer's disease with early onset
E0020	Senile dementia with paranoia
Eu01z	Vascular dementia unspecified
E004	Arteriosclerotic dementia
E0021	Senile dementia with depression
E041.00	Dementia in conditions EC
Eu00011	[X]Presenile dementia,Alzheimer's type
Eu025	Lewy body dementia
Eu10711	[X] Alcoholic dementia NOS
Eu10711	Alcoholic dementia NOS
E0013	Presenile dementia with depression
Eu020	Dementia in Pick's disease
Eu00z	Dementia in Alzheimer's disease unspecified
F112	Senile degeneration of the brain, not elsewhere classified
E0012	Presenile dementia with paranoia
Eu002	Dementia in Alzheimer's disease, atypical or mixed type
Eu013	Mixed cortical and subcortical vascular dementia
F1101	Alzheimer's disease with late onset
Eu022	Dementia in Huntingdon's disease
E003	Senile dementia with delirium

E0014	Presenile dementia NOS
Eu001	Dementia in Alzheimer's disease with late onset
E002z	Senile dementia with depressive or paranoid features NOS
Eu004z	Arteriosclerotic dementia NOS
Eu0040	Uncomplicated arteriosclerotic dementia
Eu0043	Arteriosclerotic dementia with depression
Eu00113	[X]Primary degen dementia of Alzheimer's type, senile onset
E002	Senile dementia with depressive or paranoid features
E0010	Uncomplicated presenile dementia
Eu01000	[X]Vascular dementia of acute onset
Eu00111	[X]Alzheimer's disease type 1
Eu02z11	[X] Presenile dementia NOS
Eu000	Dementia in Alzheimer's disease with early onset
E0011	Presenile dementia with delirium
Eu041	Delirium superimposed on dementia
Eu021	Dementia in Creutzfeldt-Jakob disease
E012	Other alcoholic dementia
Eu01y	Other vascular dementia
Eu0042	Arteriosclerotic dementia with paranoia
Eu01111	[X]Predominantly cortical dementia
Eu0041	Arteriosclerotic dementia with delirium
Eu00012	[X]Primary degen dementia, Alzheimer's type, presenile onset
Eu00013	[X]Alzheimer's disease type 2
E02y100	Drug-induced dementia
Eu02y00	[X] Dementia in other diseases classified elsewhere
F111	Circumscribed brain atrophy including Pick's disease