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## **Are symptoms of insomnia in primary care associated with subsequent onset of dementia? A matched retrospective case-control study**

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## **Disclosure of interest**

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: support for the submitted work as described above; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work. NH reports personal fees and non-financial support from Rosch, grants and personal fees from Eli-Lily, and personal fees from GE Healthcare, all outside the submitted work. JC reports grants from NIHR and Wellcome Trust and other financial activities with BMJ Publishing and NHS Swale Clinical Commissioning Group, all outside the submitted work .

## **Data availability statement**

Only the authors have access to the CPRD data. Codelists have been made available by the authors and deposited in the clinical codes repository (Hoile, 2019). Researchers should contact the CPRD's Independent Scientific Advisory Committee (ISAC) to obtain access to data. The programming code used for data preparation and statistical analysis is available from the corresponding author's Github repository (Hoile, 2018).

## **Ethical approval**

Ethical approval was given by the CPRD Independent Scientific Advisory Committee (ISAC 17\_057).

## **Authorship**

RH is the lead author and guarantor. RH and NT developed the hypothesis. RH and EF developed the study design. EF acquired the data. HS and RH developed the codelists. RH reviewed the literature, cleaned the data and performed the statistical analysis, with further statistical input from SB. All authors contributed to critical revision of the manuscript.

The lead author (RH) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

# **Are symptoms of insomnia in primary care associated with subsequent onset of dementia? A matched retrospective case-control study**

## **Abstract**

### *Objective*

There is evidence from neuroimaging studies of an association between insomnia and early dementia biomarkers, but observational studies have so far failed to show a clear association between insomnia and the later development of dementia. We investigated the association between dementia diagnosis and recording of insomnia symptoms 5-10 years earlier in primary care.

### *Method*

A case-control study using data from the Clinical Practice Research Datalink. 15,209 cases with dementia (either Alzheimer's, vascular, mixed or non-specific subtypes) at least 65 years old at time of diagnosis, were matched with the same number of controls on year of birth and gender. We ascertained the presence of insomnia symptoms during a five-year period starting 10 years before the index date. Odds ratios for developing dementia were estimated using logistic regression after controlling for hypnotic exposure and physical and mental health comorbidities.

### *Results*

The adjusted odds ratio for dementia in those with previous insomnia was 1.34 (95% CI = 1.20 to 1.50).

### *Conclusion*

There is an association between dementia and previous insomnia. It may be possible to incorporate insomnia into predictive tools for dementia.

## ***Keywords***

Dementia; insomnia; sleep; case–control study; Clinical Practice Research Datalink (CPRD); primary care.

## **Introduction**

The prevalence of dementia among over-65s in the UK has been estimated at 7.1% (Prince et al., 2014). It is thought that in 2015 about 850,000 people were living with dementia in the UK, a figure set to increase to 2 million by 2051 (Prince et al., 2014). The annual cost of dementia to UK society has been estimated to be £32,250 per person with dementia, of which more than a third comprises unpaid work provided by carers (Prince et al., 2014). With no disease-modifying treatments imminent (Godyń, Jończyk, Panek, & Malawska, 2016), the search for modifiable risk factors during the preclinical stage of dementia (Ramakers et al., 2007) has taken on great importance.

One suspected risk factor for dementia is insomnia. Insomnia is a common problem, with one longitudinal study reporting that 37% of UK adults were experiencing it at baseline (Morphy, Dunn, Lewis, Boardman, & Croft, 2007). Insomnia is frequently encountered by general practitioners (GPs): an Australian study found that over a quarter of those with insomnia consulted their GP about it (Bartlett, Marshall, Williams, & Grunstein, 2008). If it were shown to predate the clinical onset of dementia, insomnia could become a prognostic marker for dementia, and even, depending on the nature of the association, a target for disease prevention.

Several studies have already found a link between sleep problems and amyloid plaque formation, one of the pathological hallmarks of Alzheimer's disease (AD), the most common type of dementia (Prince et al., 2014). Individuals who are cognitively normal but have evidence of amyloid plaques, a state sometimes referred to as preclinical AD, have been

shown to have poorer sleep quality on actigraphy (Ju, McLeland, et al., 2013). Similarly, self-reported sleep disturbances have been found to be associated with greater amyloid burden on amyloid PET imaging in cognitively normal adults (Spira et al., 2013). A recent meta-analysis of observational studies and randomised controlled trials (RCTs) found that insomnia and poor sleep quality (measured either subjectively or using actigraphy and other objective techniques) were respectively associated with a 1.38- and 1.62-times greater risk of having AD or cognitive decline (Bubu et al., 2016). However, most of the studies considered were cross-sectional or had a duration of 1-3 years, such that it remains unclear whether insomnia predates clinical features of dementia such as cognitive decline. The extent to which confounders were controlled for in the various studies also varied.

We hypothesised that dementia would be more common in those who had reported insomnia symptoms to their GP 5-10 years earlier. Our case-control study used prospectively-collected UK primary care data to investigate this association, while controlling for potentially confounding physical and mental health comorbidities and hypnotic exposure.

## **Methods**

### ***The dataset***

Study data were drawn from the primary care dataset of the UK's Clinical Practice Research Datalink (CPRD). This dataset comprises anonymised primary care health records of over 11.3 million patients and has been shown to be broadly representative of the UK with regards to age, sex and ethnicity (Herrett et al., 2015). The CPRD dataset includes structured data in the form of prescriptions and Read codes. The Read code system is a coded thesaurus of clinical terms and includes diagnoses, test results, specialty referrals and symptoms, and has been in use since the 1980s (Benson, 2011). Each Read code is accompanied by a descriptive term (for example, G30..00, "Acute myocardial infarction").

### ***Study population and case definition***

We obtained an initial dataset comprising all 47,618 cases patients in the CPRD with a first diagnosis of dementia between 2000 and 2012 (as indicated by the earliest Read code indicating a dementia diagnosis) and an age of at least 65 at the time of diagnosis. An equal number of controls was randomly selected from the source population, none of whom had a dementia Read code anywhere in their record.

Having obtained this dataset, we refined our case definition such that any control who had been prescribed anti-dementia medication (donepezil, rivastigmine, galantamine or memantine) was reclassified as a case; for these patients, the date of the first prescription became the index date. 321 controls were reclassified in this way as cases.

We then removed 6442 cases with final Read codes pertaining to rarer dementia subtypes (including frontotemporal lobe dementia; dementia with Lewy bodies; Creutzfeldt-Jakob disease; and dementias secondary to Parkinson's disease, drug and alcohol use, and human immunodeficiency virus). This was intended to make our findings more generalisable to over-65s with dementia in the general population, who are more likely to have an Alzheimer's, vascular or mixed subtype (Lobo et al., 2000). All remaining cases of dementia had one of 56 Read codes corresponding to either an Alzheimer's, vascular, mixed or non-specific subtype. These dementia Read codes, as well as the 13 rarer dementia Read codes excluded from the study, can be viewed at our clinical code repository (Hoile, 2019).

In addition, we removed from the dataset all cases who did not have at least ten continuous years of data available prior to index date. 24,157 cases were removed in this way.

Cases were then re-matched with controls on year of birth and gender. During the rematching stage, controls without ten continuous years of data available prior to their newly-created



index date were removed. In addition, cases and controls which could not be matched were also removed. 34,418 controls and a further 4101 cases were removed during this stage.

The final dataset contained 12,879 cases and an equal number of controls.

### ***Exposure assessment***

For the purpose of this study, a patient was considered to have insomnia symptoms if they met one of two criteria. The first criterion was the presence of a Read code indicating insomnia. In line with Thorpy (Thorpy, 2012), we defined insomnia as difficulty initiating or maintaining sleep, leading to nocturnal wakefulness or insufficient sleep. We searched for Read codes containing the following strings: “sleep\*”; “insomn\*”; “wak\*”; “rest\*”; “noct\*”; and “night\*”, and from the results identified 18 which indicated insomnia. We excluded Read codes which indicated hypersomnia, sleep apnoea or abnormal behaviours during sleep, such as rapid eye movement disorder.

The second criterion according to which a patient was considered to have insomnia symptoms was the presence of a hypnotic medication in the prescribing history. The September 2000 (Joint Formulary Committee, 2000) and the March 2017 (Joint Formulary Committee, 2017) editions of the British National Formulary were used to identify hypnotic medications. The following hypnotics were then used in our study: chloral hydrate; clomethiazole; diazepam; flurazepam; flunitrazepam; loperazolam; lorazepam; lormetazepam; melatonin; nitrazepam; oxazepam; temazepam; triclofos sodium; zaleplon; zolpidem; zolpidem; and zopiclone.

The window period for exposure measurement was 5 to 10 years prior to the index date. As insomnia is known to be an early symptom of dementia (Ju, Lucey, & Holtzman, 2013), using a window that predates dementia diagnosis by several years aims to prevent the problem of reverse causality, whereby the outcome, rather than being caused by the exposure, in fact precedes and causes the exposure. For our main analysis, we chose not to use a window

period dating back further than ten years, as only a minority of our cases had more than 10 years of continuous clinical data predating their index date. To determine whether our conclusions would be affected by this decision, two sensitivity analyses were performed, in which the exposure window was re-defined as, firstly, the period 12-7 year prior to the index date, and secondly the period 8-3 years prior.

### ***Confounding variables***

Chronic pulmonary disease (comprising asthma, chronic obstructive pulmonary disease and interstitial lung disease), stroke, heart failure, sleep apnoea and mental illness have all been implicated in both insomnia and dementia (Burton, Campbell, Jordan, Strauss, & Mallen, 2013; Cukic, Lovre, & Dragisic, 2011; Harvey, 2001; Hayes, Anstead, Ho, & Phillips, 2008; Heckman et al., 2007; Im et al., 2016; Keezer, Sisodiya, & Sander, 2016; Leppävuori, Pohjasvaara, Vataja, Kaste, & Erkinjuntti, 2002; Luyster, Buysse, & Strollo, 2010; Rusanen et al., 2013; Shastri, Bangar, & Holmes, 2015; Zilkens, Bruce, Duke, Spilsbury, & Semmens, 2014), and were therefore considered potential confounders. To define sleep apnoea, we created a codelist by searching for Read codes containing the string “apnoe\*”. For the other confounders, we used Read codelists already created for other studies: (Kontopantelis, Reeves, Valderas, Campbell, & Doran, 2013) for stroke and heart failure; (Zhong et al., 2018) for chronic pulmonary disease; and (Windfuhr et al., 2016) for mental illness. The mental illness codelists are divided into six categories: schizophrenia-spectrum disorders, bipolar disorder, depression, anxiety disorders, personality disorders, and eating disorders.

In addition, total exposure to hypnotics during the 5-10 year period prior to diagnosis was also considered a potential confounder, as several hypnotics have been linked to dementia (Chen, Lee, Sun, Oyang, & Fuh, 2012; Islam et al., 2016). Medication exposure was measured using units of 100 prescribed daily doses (PDDs). A PDD for a given drug was defined as the

average daily dose that was prescribed for the study population during the exposure window (i.e., 5-10 years prior to index date).

Hypnotic exposure and insomnia symptoms were ascertained only during the exposure window. However, confounding medical conditions (e.g. chronic pulmonary disease, mental illness) were considered present if there was a relevant Read code either during the exposure window or earlier, since patients with these chronic conditions could potentially have received the Read code prior to the exposure window, and never again afterwards.

### ***Codelists***

The Read codelists used to define outcome, exposure and confounders were drawn up by two doctors (RH, a psychiatrist, and HS, a GP), and have been made available in a clinical codes repository (Hoile, 2019).

### ***Data processing and statistical analysis***

Derived variables, such as PDD, were calculated using the Pandas package (version 0.19.2) for the Python programming language. We assessed each variable for multicollinearity by calculating the variance inflation factor (VIF) using Statsmodels (version 0.8.0) for Python.

The association between dementia and insomnia was explored through multivariable logistic regression using Statsmodels. Despite the matched design of the study, the logistic regression analysis itself was not matched or conditional, as per recently published guidance (Pearce, 2016).

We calculated unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CIs) to estimate the association between our covariates and dementia.

## **Results**

### ***Study population***

We identified 12,879 cases and matched them with 12,879 controls. See Table 1 for the characteristics of the cases and controls.

### ***Association between insomnia and subsequent development of dementia***

The association between dementia and insomnia is shown in Table 2. Individuals who complained of insomnia were more likely later to develop dementia: adjusted OR 1.34 (95% CI 1.20-1.50).

In addition, the table shows the association between dementia and the various confounding variables. As none of the confounding variables had high levels of collinearity, defined in this study as VIFs greater than 5 (O'Brien, 2007), all were used in the analysis.

### ***Sensitivity analyses***

When the exposure window for insomnia was brought forward (3-8 years prior to index date), the adjusted OR for dementia was 1.25 (95% CI 1.12-1.40).

When the exposure window for insomnia was pushed backwards (7-12 years prior to index date), the adjusted OR for dementia was 1.19 (95% CI 1.06-1.34).

## **Discussion**

### ***Summary***

In this study, we have identified a small, positive association between dementia and symptoms of insomnia recorded in primary care 5 to 10 years earlier. The association remains even after adjusting for hypnotic exposure and physical and mental health comorbidities.

### *Strengths and limitations*

Strengths of the current study include a large patient sample representative of the wider UK population, and prospectively-gathered prescribing and diagnostic data.

There are, however, several limitations to the study. Our measure of insomnia gives little indication of its severity or duration, nor whether it meets criteria for established ICD-10 insomnia diagnoses (for example, primary insomnia, ICD F51.01). Furthermore, since not all those with insomnia will consult their GP, its true prevalence will be underestimated. It is also unclear how consistently GPs use an insomnia Read code when documenting consultations, or whether the presence of mental illness or dementia affects the likelihood of a GP using such a code.

In addition, drug exposure is likely to be underestimated, as medications prescribed in secondary care may not be recorded in the CPRD dataset (Herrett et al., 2015).

Our study also relies on unverified diagnoses of dementia, and it is unclear whether the diagnoses were made by specialists or by GPs, and which diagnostic criteria were used. Furthermore, it is likely that many cases of dementia are missed: one study found that the observed prevalence of diagnosed dementia in UK primary care is less than half the expected prevalence (Connolly, Gaehl, Martin, Morris, & Purandare, 2011). Because of this underdiagnosis, it is likely that there are many false negatives among our controls.

It is also possible that many of the patients presenting with insomnia in the years before dementia diagnosis already had undiagnosed clinical dementia. If this were the case, our findings would be less interesting, as insomnia is already known to be more common in clinical dementia (Bubu et al., 2016). However, our sensitivity analysis did not show a trend towards a stronger association between insomnia and dementia when the exposure window is brought closer to the index date. This suggests that insomnia may be a symptom of

preclinical, rather than clinical, dementia, and as such may have a role in predicting clinical dementia.

This study cannot determine whether insomnia has a causative role in dementia, largely due to its case-control design, and also because the pathological changes associated with Alzheimer's dementia may precede the clinical syndrome by more than 5-10 years (Ju, Lucey, et al., 2013). Determining whether insomnia causes dementia will require further basic scientific research elucidating possible mechanisms, and clinical trials to assess the efficacy of insomnia interventions in preventing cognitive decline.

### ***Comparison with existing literature***

This study adds to a small body of observational studies reporting an association between insomnia and related sleep disorders and later dementia. One longitudinal study (Hahn, Wang, Andel, & Fratiglioni, 2014) found that reduced sleep was associated with a 75% increase in AD risk 6-9 years after baseline, but results were no longer significant after adjusting for depressive symptoms, respiratory problems and pain. Another study, which adjusted for numerous confounders including depressive symptoms and sedative use, followed up participants for up to six years and found that those with sleep fragmentation had a hazard ratio of 1.2 for developing AD (Lim, Kowgier, Yu, Buchman, & Bennett, 2013). Although much of the research into sleep and dementia has focused on AD, one prospective study found an association between self-reported insomnia and vascular dementia 10 years later, with an adjusted OR of 1.34 (Elwood et al., 2011), although mental health comorbidity and sedative medication exposure were not controlled for.

In addition to insomnia, our analysis showed statistically significant associations between dementia and a number of physical and mental health comorbidities. Some of these associations (in particular stroke and mental illness) are in accordance with findings from our

team's meta-analysis of predictive primary care risk factors for dementia (Ford et al., 2018). Although some studies have reported an increased risk of dementia in those on z-drugs (Chen et al., 2012) and benzodiazepines (Billioti de Gage et al., 2014; Chan et al., 2017; Chen et al., 2012; Gallacher et al., 2012; Islam et al., 2016), we found only a very weak association (OR 1.01) for the class of hypnotics (which includes the z-drugs and certain benzodiazepines) taken as a whole.

### ***Implications for research and/or practice***

Predictive tools for dementia could be developed incorporating insomnia as a predictive factor. Furthermore, in those who are found to be at risk of dementia, interventions to improve sleep quality, such as advice on sleep hygiene (Morin, 2011), could potentially be delivered by primary care clinicians, although further research is needed into the efficacy of this. Interestingly, our study suggests that hypnotics neither increase nor reduce dementia risk meaningfully in those suffering from insomnia.

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## Tables

Table 1. Characteristics of cases and controls, 5-10 years prior to index date. Figures are numbers (percentages) of patients.

Characteristic	Cases (n=12879)	Controls (n=12879)
Age at index date (years):		
65-69	452 (3.5%)	452 (3.5%)
70-74	1161 (9.0%)	1161 (9.0%)
75-79	2513 (19.5%)	2513 (19.5%)
80-84	3621 (28.1%)	3621 (28.1%)
85-89	3385 (26.3%)	3385 (26.3%)
90-99	1429 (11.1%)	1429 (11.1%)
>99	18 (0.1%)	18 (0.1%)
Gender:		
Male	4327 (33.6%)	4327 (33.6%)
Female	8552 (66.4%)	8552 (66.4%)
Insomnia	926 (7.2%)	580 (4.5%)
Stroke	1431 (11.1%)	959 (7.4%)
Heart failure	764 (5.9%)	618 (4.8%)
Mental illness	4766 (37.0%)	3019 (23.4%)
Sleep apnoea	22 (0.2%)	17 (0.1%)
Chronic pulmonary disease	2944 (22.9%)	2114 (16.4%)
Hypnotic PDDs		
0	11063 (85.9%)	11546 (89.6%)
1-10	235 (1.8%)	199 (1.5%)
11-100	675 (5.2%)	521 (4.0%)
101-1000	428 (3.3%)	308 (2.4%)
1001-10000	478 (3.7%)	303 (2.4%)
>10000	0 (0.0%)	2 (0.0%)
Dementia subtype:		
Alzheimer's	4513 (35.0%)	0 (0%)
Vascular	3679 (28.6%)	0 (0%)
Mixed	120 (0.9%)	0 (0%)
Unspecified	4567 (35.5%)	0 (0%)

Table 2. Risk of dementia associated with all covariates used in our final model compared to controls.

Characteristic	Unadjusted OR, 95% CI	Adjusted OR, 95% CI
Insomnia	1.60, (1.44, 1.77)	1.34, (1.20, 1.50)
Age at index date	1.00, (1.00, 1.00)	1.00, (1.00, 1.00)
Heart failure	1.24, (1.11, 1.38)	1.14, (1.02, 1.28)
Female gender	1.00, (0.97, 1.03)	0.95, (0.90, 1.00)
Mental illness	1.58, (1.51, 1.65)	1.79, (1.70, 1.89)
Stroke	1.49, (1.38, 1.62)	1.47, (1.35, 1.61)
Chronic pulmonary disease	1.39, (1.32, 1.47)	1.42, (1.33, 1.51)
Hypnotics (100 PDDs)	1.02, (1.01, 1.03)	1.01, (1.00, 1.02)
Sleep apnoea	1.35, (0.72, 2.53)	0.95, (0.50, 1.81)