Sleep Disorders and the Development of Alzheimer's Disease among U.S. Medicare Beneficiaries

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Introduction

Alzheimer's disease (AD) is a leading cause of disability, affecting over 6 million Americans; this burden is projected to rise to 13 million Americans by 2050 leading to an estimated cost of $355 billion annually.[1] Chronic insufficient sleep has been suggested as a modifiable risk factor for the development of AD with an emerging body of science suggesting that Tau and amyloid plaques accumulate at an increased rate in the setting of insufficient sleep.[2] Therefore, we quantified the role of sleep disorders on the development of AD among Medicare beneficiaries who aged 65 and older.

Methods

We conducted a matched-pair case-control analysis using Medicare fee-for-service claims data. We identified beneficiaries newly diagnosed with AD between January 1, 2013 and December 31, 2020 (ICD-9 code 331.0 or ICD-10 code G30).[3] Potential control subjects were beneficiaries who never had a diagnosis of AD over the same time period.

Each AD case was matched with a control based on age, sex, race, and coverage start date (absolute difference 3 months) using methodology previously described.[4] For cases who had multiple matching controls, we randomly selected one control from all potential matches. Controls were required to be enrolled at the time of the case's first AD diagnosis date. Sleep disorder diagnosis was defined as the presence of at least one inpatient, outpatient, or carrier claim with ICD-9/10 codes according to American Sleep Association (Supplementary Table S1). For each pair, we searched for any sleep disorder diagnosis prior to the AD diagnosis date, excluding the diagnosis of hypersomnia, as far back as January 1, 2010.[3]

We reported patients' demographics and used the asymptotic and exact odds ratio estimate from a logistic regression model to calculate the odds ratio for the matched pairs data. All statistical analyses were performed using SAS Enterprise Version 7.1 (SAS, Inc., Cary, NC).

Results

Of the 1,769,622 older adults (65) with a diagnosis of AD, the median age was 84 (IQR 78-89) years, 63.9% (n=589,238) were female, 10.3% (n=95,457) were black or Hispanic, and 52.1% (n=922,591) had a prior sleep disorder (Table). There were 886,019 discordant pairs (634,646 pairs where case had sleep loss and control did not have sleep loss, and 251,373 pairs where case did not have sleep loss and control had sleep loss). AD cases' odds of having sleep disorders prior to diagnosis was 2.5 times higher than controls' odds of having sleep disorders (Matched odds ratio=2.52, 95% confidence interval: 2.51-2.54, p<0.001) (Supplementary Table S2).

Discussion

We identified an association between sleep disorders and the development of AD in 3,539,244 Medicare beneficiaries. This finding is consistent with animal studies that have suggested a causal inference between chronic poor sleep and AD.[5] The mechanism proposed by these reports is a reduced clearance of brain plaques by the glial-lymphatic system which is more active during slow-wave sleep.[6]

There are some limitations in this analysis. First, patients who had sleep disorders diagnosed prior to Medicare coverage might not be captured. Second, the severity of a sleep disorder cannot be measured in claims data. Third, the data may be susceptible to coding inaccuracies which is a common limitation using claims data. A prior analysis described a 79% sensitivity of sleep disorder codes.[7]

Sleep disorders affect 35-40% of adults, and may be increasing.[8] Similarly, AD is increasing in incidence, which may or may not be correlated. Prospective research is needed to explore the signal of an association we describe in claims data. Formal elucidation of chronic poor sleep as a modifiable risk factor in the develop of AD may represent an opportunity to address this chronic disease through prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

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Table.

Demographic characteristics of 3,539,244 Medicare beneficiaries aged 65 and older by whether they had Alzheimer's Diagnosis and previous sleep disorder.

	No Alzheimer's Diagnosis				Alzheimer's Diagnosis			
	No sleep disorder		Sleep disorder		No sleep disorder		Sleep disorder	
	N	(%)	N	(%)	N	(%)	N	(%)
N	1,230,304	(69.52)	539,318	(30.48)	847,031	(47.87)	922,591	(52.13)
Age								
Median (IQR)	84	(78,89)	84	(78,87)	84	(78, 89)	84	(78, 89)
65-74	183,217	(14.89)	75,760	(14.05)	120,904	(14.27)	138,073	(14.97)
75-84	503,073	(40.89)	228,107	(42.30)	344,618	(40.69)	386,562	(41.90)
85 or older	544,014	(44.22)	235,451	(43.66)	381,509	(45.04)	397,956	(43.13)
Sex								
Female	790,338	(64.24)	351,959	(65.26)	553,059	(65.29)	589,238	(63.87)
Male	439,966	(35.76)	187,359	(34.74)	293,972	(34.71)	333,353	(36.13)
Race								
Asian	24,894	(2.02)	8,213	(1.52)	15,489	(1.83)	17,618	(1.91)
Black	122,095	(9.92)	38,664	(7.17)	86,326	(10.19)	74,433	(8.07)
Hispanic	33,330	(2.71)	8,082	(1.50)	20,388	(2.41)	21,024	(2.28)
Other/Unknown	3,737	(0.30)	2,180	(0.40)	2,612	(0.31)	3,305	(0.36)
White	1,046,248	(85.04)	482,179	(89.41)	722,216	(85.26)	806,211	(87.39)
Metropolitan								
Rural	227,150	(18.46)	103,716	(19.23)	151,786	(17.92)	179,080	(19.41)
Urban	1,003,154	(81.54)	435,602	(80.77)	695,245	(82.08)	743,511	(80.59)
Region								
Midwest	288,392	(23.44)	128,752	(23.87)	204,613	(24.16)	212,531	(23.04)
Northeast	233,223	(18.96)	102,381	(18.98)	171,480	(20.24)	164,124	(17.79)
Other	5,404	(0.44)	2,088	(0.39)	5,305	(0.63)	2,187	(0.24)
South	514,490	(41.82)	224,698	(41.66)	336,445	(39.72)	402,743	(43.65)
West	188,795	(15.35)	81,399	(15.09)	129,188	(15.25)	141,006	(15.28)