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Sleep/wake cycle alterations as a cause of neurodegenerative diseases: A Mendelian randomization study

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ABSTRACT

Sleep and/or wake cycle alterations are common in neurodegenerative diseases (ND). Our aim was to determine whether there is a causal relationship between sleep and/or wake cycle patterns and ND (Parkinson's disease (PD) age at onset (AAO), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS)) using two-sample Mendelian Randomization (MR). We selected 12 sleep traits with available Genome-Wide Association Study (GWAS) to evaluate their causal relationship with the ND risk through Inverse-Variance Weighted regression as main analysis. We used as outcome the latest ND GWAS with available summary-statistics: PD-AAO (N = 17,996), AD (N = 21,235) and ALS (N = 40,136). MR results pointed to a causal effect of subjective and objective-measured morning chronotype on later PD-AAO (95%CI:0.33-1.81, $p = 8.47\times10^{-09}$ and 95%CI:-7.28 to -4.44, $p = 5.87\times10^{-16}$, respectively). Sleep efficiency was causally associated with a decreased AD risk (95%CI:-20.408 to -0.66, p = 0.04) and daytime sleepiness with an increased ALS risk (95%CI:0.15 to 1.61, p = 0.01). Our study suggests that sleep and/or wake patterns have causal relationship with ND. Given that sleep and/or wake patterns are modifiable risk factors, sleep interventions should be investigated as a potential treatment in PD-AAO, AD and ALS.

1. Introduction

Neurodegenerative diseases (ND) constitute a heterogeneous group of conditions for which the time of symptom onset varies between patients. Sleep and/or wake cycle alterations are very common in ND and are present in up to 60% of patients

Abbreviations: ND, neurodegenerative disease; MR, Mendelian Randomization; AAO, Age at onset; GWAS, Genome-Wide Association Study; AD, Alzheimer disease; PD, Parkinson disease; IVW, Inverse variance weighted; ALS, Amyotrophic Lateral Sclerosis; SNVs, single nucleotide variants; REM, rapid eye movement; RBD, REM sleep behavior disorder; OSA, obstructive sleep apnea; LD, linkage disequilibrium; WM, Weighted-Median; MBE, mode-based estimate; M10, most-active 10 hours; MIDP, Sleep midpoint timing.

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(Malhotra, 2018). In many cases sleep and/or wake cycle alterations occur in the prodromal stage of the disease, before manifestation of the main symptoms and final diagnosis (Iranzo, 2016; Malhotra, 2018). Due to the uncertainty regarding the starting point of ND, it is difficult to establish whether sleep and/or wake cycle alterations are an early manifestation of ND or whether these disorders are a causal risk factor for ND (Videnovic and Abbott, 2016).

Different studies support an idea that sleep and/or wake cycle alterations are an underlying symptom of ND. Degeneration of the cerebral nuclei involved in sleep and wake cycle leads to sleep loss and disruption (Peter-Derex et al., 2015). For example, degeneration of the locus coeruleus and raphe nucleus occurs in the preclinical Braak stages I and II of Parkinson's disease (PD) and correlates temporally with the onset of sleep alterations, such as insomnia or parasomnias (Braak and Del Tredici, 2008). Degeneration of specific neurons, such as motor neurons in Amyotrophic Lateral Sclerosis (ALS) is related with breathing-related sleep disorders (Boentert, 2020). Neuronal loss is commonly associated with a reduction in relevant neurotransmitters involved in the sleep and/or wake cycle (Ono et al., 2012). Melatonin in Alzheimer's disease (AD) (Shukla et al., 2017) and orexin in PD (Baumann et al., 2008; Wienecke et al., 2012) are reduced as part of the neurodegenerative process and are linked to disruption and fragmentation of sleep.

However, a causal role of specific sleep and/or wake cycle patterns in the risk and progression of ND is also plausible (Videnovic and Abbott, 2016). The presence of sleep abnormalities, such as sleep disruption and fragmentation, has a negative effect on cognition. The "glymphatic system" (Videnovic and Abbott, 2016) has been described as a potential key factor involved in the causal effect of sleep and/or wake cycle alterations in ND. The glymphatic system consists of a perivascular network involved in the clearance of proteins from the interstitial fluid to the cerebrospinal fluid (Nedergaard, 2013). Abnormal accumulation of amyloid-β and tau is a hallmark in AD. A similar process occurs with α-synuclein in PD and TDP-43, among others, in ALS. The glymphatic system flow is reduced in the above diseases, increasing brain accumulation of these proteins (Boland et al., 2018). The efficiency of the clearance system increases during sleep (Xie et al., 2013). Thus, certain sleep and/or wake cycle patterns could result in an accumulation of products, such as amyloid-β, tau, α-synuclein or TDP-43, which could trigger the onset of ND.

Given the difficulty to establish a causal relationship between sleep and/or wake cycle alterations and ND and the challenge of conducting clinical trials that alter the sleep and/or wake cycle, Mendelian randomization (MR) analysis could be useful. MR is an epidemiological method that uses the same principle of randomization as clinical trials (Allman et al., 2018). MR uses genetic factors that are randomized at conception as instruments to elucidate the causal relationship between a risk factor (exposure) and a disease risk (outcome). It calculates the proportion of the change explained by genetics (usually polymorphisms or single nucleotide variants (SNV)) in the exposure and the change explained by the same genetic factors on the outcome (Emdin et al., 2017; Koellinger and de Vlaming, 2019). It is possible to calculate how changes in the exposure influences the outcome. This approach is useful to avoid reverse causality issues, such as the possibility that the outcome may not cause any changes in genetics. Moreover, genetic instruments are independent of any confounding factors (Grover et al., 2017).

Previous MR studies analyzed the causal relationship between sleep traits and cognitive outcomes, cognitive decline, dementia and the risk of AD. It was found that there is a significant causal relationship between sleep duration and slower reaction time (Henry et al., 2019), and between the longer sleep duration and cortical thickness and lower AD risk (Andrews et al., 2021). A potential causal association of daytime napping and AD risk was identified by Anserson et al. The causal relationship between some sleep-related traits and the risk of PD or ALS have been also evaluated (Noyce et al., 2019; Bandres-Ciga et al., 2019). However, PD age at onset (AAO) was not evaluated. Moreover, the association between the risk of PD, AD and ALS and some objective measures of sleep quality such as sleep efficiency or obstructive sleep apnea (OSA) has not been studied.

The objective of this study was to analyze the causality of different sleep and/or wake patterns and PD-AAO, AD and ALS. If some sleep and/or wake traits are identified as causing the ND, their diagnosis would be important for early intervention in these patients and could help prevent or delay the onset and progression of ND (Loddo et al., 2017).

2. Methods

2.1. Selection of exposure and instruments

To select proper genetic instruments, we searched the GWAS Catalog and the Sleep Disorder Knowledge Portal (Sleep Disorder KP)("Sleep Disorder Genomics," n.d.; "The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019," n.d.) for published Genome-Wide Association Studies (GWAS) on sleep and/or wake patterns with the aim of finding genetic tools for our analysis. We considered the most common sleep and/or wake cycle disorders in ND: insomnia, excessive daytime sleepiness, circadian rhythm changes, rapid eye movement (REM) sleep behavior disorder (RBD), periodic leg movements in sleep, restless legs syndrome, OSA, and nocturnal stridor (Kutscher et al., 2014). Moreover, we considered chronotype as a sleep and/or wake cycle pattern that could be a causal risk factor for ND. These sleep and/or wake traits were selected with the summary statistics available in the GWAS Catalog or in the Sleep disorder KP. We identified the following traits: insomnia, daytime sleepiness, subjective and objective (using accelerometer device measures) chronotype, sleep duration and OSA (Table 1). Summary statistics for insomnia (Lane et al., 2019), chronotype (Jones et al., 2019a), accelerometer measures (Jones et al., 2019b) and sleep duration (Braak and Del Tredici, 2008) were downloaded from the GWAS Catalog ("The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019," n.d.). OSA (Chen et al., 2018) and daytime sleepiness (Wang et al., 2019) data were downloaded from the Sleep disorder KP. We considered the genome-wide significant variants with $p < 5\times10^{-8}$ in the selected GWAS as genetic instruments. For OSA, for which no SNV reached these p-values, we selected all the variants with $p < 10^{-6}$ as instruments.

Further information regarding the exposure variables is set out in Supplementary Methods and Table 1.

Heritability was calculated using the LD SCore (LDSC) (Bulik-Sullivan et al., 2015) for all the GWAS considered as exposure variables to ensure the plausible use of the traits in MR. We calculated the F-statistics to additionally test that the instruments selected were strongly associated with the exposure. A F-statistic greater than 10 was used as a threshold for sufficient instrument strength (Sanderson et al., 2019). The people in charge of the above-mentioned GWAS studies were responsible for obtaining informed consent.

Table 1
Description of sleep traits used as exposure

	Trait	Variable definition	Subjects (*N*)	Cohort	Ancestry	Significant SNV	SNV pruned AD	SNV pruned PD	SNV pruned ALS
	Self-reported								
	Chronotype	Continuous variable considering: morning person, more a morning than evening person, more an evening person than morning, evening person	449,734	UK Biobank	European	15155	152	137	151
	Insomnia	Dicothomic variable considering: never/rarely vs. sometimes/usually	453,379 (345,022 cases/108,357 controls)	UK Biobank	European	2500	38	38	40
	Sleep duration	Continous variable: number of hours	446,118	UK Biobank	European	433	9	9	9
	Daytime Sleepiness	Continuous variable considering: never, sometimes, often, all of the time	452,071	UK Biobank	European	5659	36	36	37
	Objective Measures								
	OSA	Continuous variable: AHI	19,733	ARIC, CFS, FHS, HCHS/SIL, MESA, MrOS, Starr	Multi-ethnic	20[a]	1	5	1
Chronotype measures	M10	Continous variable: most active's 10 hours	85,670	UK Biobank	European	129	1	1	1
	L5	Continous variable: least active 5 hours	85,205	UK Biobank	European	75	6	3	6
	Sleep efficiency	Continous variable: total time of sleeping divided by the total SPW	84,810	UK Biobank	European	17	2	1	2
	Sleep duration	Continous variable: total hours in all the sleep episodes during SPW	85,449	UK Biobank	European	264	9	9	9
	Number of sleep episodes	Continous variable: number sleep episodes during SPW	84,810	UK Biobank	European	853	20	20	21
	MIDP	Continous variable: number of hours from the previous midnight	84,810	UK Biobank	European	1	1	1	1
	Diurnal inactivity	Continous variable: otal daily duration of estimated bouts of inactivity that fell outside of the SPW	84,757	UK Biobank	European	31	2	2	2

Main characteristics of the sleep traits analyzed by MR. 'Significant SNV' column show the number of SNV with p-value $< 5\times10-08$ in the GWAS and 'SNV pruned' the number of SNV after pruning by LD.
AHI, apnea-hypoapnea index; MIDP, midnight period; OSA, obstructive sleep apnea; SPW, sleep period window
[a] SNV had p-val $< 10-7$

2.2. Outcome selection

To select outcomes for the MR analysis we searched for GWAS in different ND: PD-AAO, AD, ALS, hereditary spinocerebellar ataxia, multiple sclerosis, Lewy body dementia, multiple system atrophy, progressive supranuclear palsy, Huntington disease and frontotemporal dementia. We selected diseases with available GWAS summary statistics in the GWAS catalog that had not been previously evaluated for causality between sleep and/or wake cycle patterns and the risk of disease and that were the most recent in the field. Finally, the traits that met these criteria and that were therefore selected as outcomes were PD-AAO, AD, and ALS (Table 2). For PD, we selected a GWAS that had not been included in previous MR analyses and for which summary statistics were available. The selected GWAS analyzed PD-AAO as a PD phenotype (Blauwendraat et al., 2019). This GWAS included only PD patients with information regarding AAO of the disease. The available summary statistics in GWAS catalog from Blauwendraat et al. did not include the 23andMe cohort. Among the latest available GWAS for AD risk, we selected the most recently published by Moreno-Grau et al., because they did not include samples from the UK Biobank. Considering that almost all the GWAS selected for the exposure traits were conducted in patients from this cohort, the selection of an outcome GWAS including samples from the UK Biobank could have suppose bias due to overlapping in the two-sample MR analysis (Burgess et al., 2016). The Moreno-Grau et al. GWAS used the analysis of endophenotypes plus the meta-analysis of previous GWAS for AD to identify new loci associated with AD. For ALS, we used data from the latest GWAS (Nicolas et al., 2018) including sporadic ALS cases and controls. More information regarding the GWAS used as outcome is shown in Table 2.

2.3. Mendelian randomization analysis

We performed two-sample MR analysis following the Two SampleMR package (Hemani et al., 2018) pipeline in R (*version 3.6.2*).

A description of the workflow used for MR analysis is shown in Fig. 1.

For each sleep trait, we selected genome-wide significant polymorphisms ($p < 5\times10^{-08}$) as the instrument and extracted these instruments in each of the 3 selected GWAS as outcomes. We then harmonized the exposure and outcome data. We clumped the SNV

Table 2
Description of GWAS used as outcome

Outcome	Total Subjects	Cases / Controls	Ancestry	Reference
Parkinson's age of onset	17,996	17,996	NR	(Blauwendraat et al., 2019)
Alzheimer Disease	21,235	7,879 / 5,947 4,120 / 3,289	NR European	(Moreno-Grau et al., 2019)
Amiotrophic lateral sclerosis	80,610	20,806 / 59,804	European	(Nicolas et al., 2018)

Description of the GWAS used as outcome.
NR, not-reported

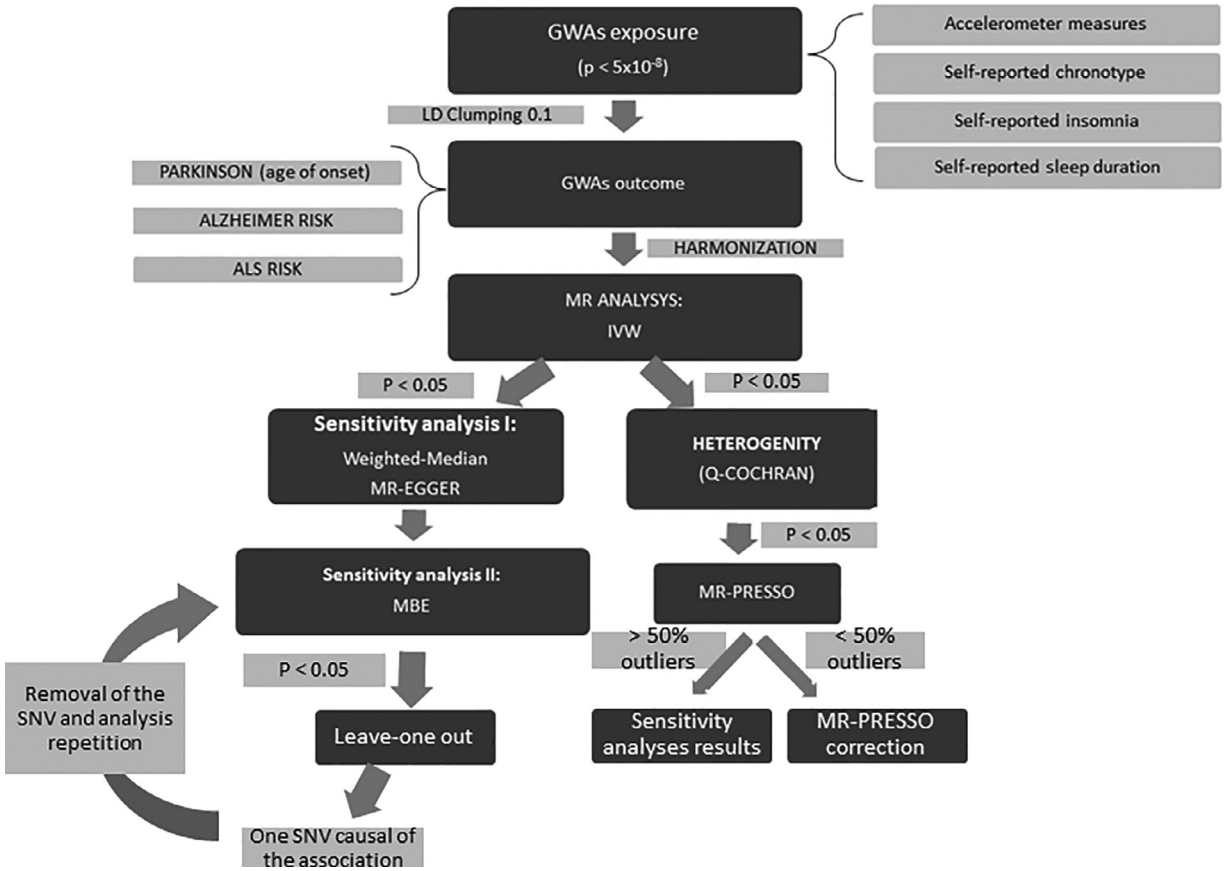

Fig. 1. Methodological workflow. Scheme of the workflow followed for the MR analysis. IVW, inverse variance weighted, MBE, mode-based estimate

by linkage disequilibrium (LD) with an $R^2 < 0.001$ and kb = 10,000. The clumping step was run after harmonization of the data to ensure a minimum loss of SNV due to no overlap between exposure GWAS and outcome GWAS.

For the MR analysis, we selected Inverse Variance Weighted (IVW) regression as previously described (Marini et al., 2020) to infer for a causal relationship between sleep traits and outcomes considering the 3 assumptions in MR: (1) genes are assigned randomly, (2) there are genes that influence the exposure studied and (3) these genes influence outcome directly due to the effect on exposure (no horizontal pleiotropy) (Bowden et al., 2017). For analyses with only 1 SNV as an instrument, we used the Wald ratio test. For traits with many weak instruments, which occurred when SNV had p-values $> 5\times10^{-8}$, we conducted the MR RAPS test, a more robust method in these situations (Zhao et al., 2019).

2.4. Sensitivity analyses

For traits with an IVW *p*-value <0.05 and 2 or more SNV used as instruments, we performed heterogeneity tests to estimate the variability in the effect estimated by each variant using Cochran's Q test and the I^2 index. Cochran's Q *p*-value < 0.05 and $I^2 > 50\%$ were considered statistically significant for heterogeneity.

Then, as additional sensitivity analyses, we tested the Weighted-Median (WM) and MR-Egger to confirm the results obtained with IVW for traits with >2 valid instruments. These tests are valid in different situations: WM can provide valid estimates when 50% or more of the information in the analysis comes from SNV that are valid instrumental variables (Bowden et al., 2016). MR-Egger is more conservative when pleiotropic variants are present (Burgess and Thompson, 2017). For results with a *p*-value < 0.05 in all the previous MR tests, we also performed an MR test with mode-based estimate (MBE), which is robust to horizontal pleiotropy, as a third sensitivity analysis (Hartwig et al., 2017).

For traits with heterogeneity (Cochran's Q *p*-value < 0.05), we performed the MR-PRESSO test, which is valid for identifying horizontal pleiotropic outliers in analyses with multiple instruments

(Verbanck et al., 2018). The specific strategy used to determine the effect of outliers is described in Supplementary Methods.

Moreover, we performed leave-one-out analysis for traits with multiple instruments to ensure the causal effect was not driven by a single genetic variant. We assessed whether the assumption that exposure causes outcome was valid using the Steiger test with the function directionality_test from the TwoSampleMR package.

Taking into account all the different tests, we applied workflows from a recently published MR study (Marini et al., 2020) to consider causal relationships. We accepted causality when IVW was significant and only 1 of the following assumptions was met: (1) No heterogeneity was detected and the WM, MR-Egger and MBE tests were in the same direction; (2) Heterogeneity was detected but was corrected by MR-PRESSO (when <50% of the instruments are considered outliers) (Verbanck et al., 2018), or 3) Heterogeneity was detected and the MR-PRESSO test detected >50% of outliers but MR Egger and WM were significant and had the same effect direction and MBE had the same direction of effect (Verbanck et al., 2018).

2.5. Reverse causality

We studied reverse causality to test whether ND were causally associated with sleep and/or wake cycle pattern traits. We performed MR analyses following the above-described steps to study the causal relationship: (1) MR testing with IVW; (2) Heterogeneity tests; (3) Sensitivity analysis: additional MR tests; (4) MR-PRESSO testing for traits with detected heterogeneity; (5) Leave-one-out tests, and (6) Steiger analysis.

2.6. Genetic correlation

To explore genetic correlation between traits, we used the LDSCsoftware (Bulik-Sullivan et al., 2015). We assessed genetic correlations between the 3 analyzed ND traits and all the different sleep and/or wake cycle traits.

2.7. Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

3. Results

In total, 12 sleep and/or wake pattern traits were analyzed as exposure factors to assess causality for the risk of 3 outcomes: PD-AAO, AD, and ALS. Tables 1 and 2 describe the exposure and outcomes analyzed in detail. All but 1 GWAS included for the selection of instruments for MR analysis were based on the UK Biobank cohort (Table 1). A full description of the variables used in the exposure GWAS and the significant variants before and after LD pruning is shown in Table 1.

We assessed the heritability (h^2) of the different GWAS used as exposure variables to ensure the plausibility of the MR analysis. All traits but 1 (M10) had 4% or higher heritability (Table S1). Diurnal inactivity measured with an accelerometer was the most heritable trait (44%). The M10 measure had negative h^2, indicating inaccuracy in this heritability estimation. Moreover, we assessed the F-statistic to ensure the exposure strength. The F-statistic for all the exposures was higher than 10, the rule-of-thumb cut-off (Table S2).

3.1. MR for PD-AAO

When we considered PD-AAO as an outcome, we identified causality for chronotype, insomnia, OSA, M10 and sleep duration measured with accelerometer (IVW p = 4.33×10^{-3}, 1.29×10^{-7}, 2.28×10^{-3}, 5.87×10^{-16} and 0.01, respectively) (Figs. 2,5). Insomnia and M10 remained causal risk factors for PD-AAO after multiple comparison correction with Bonferroni ($p < 1.3\times10^{-3}$, considering all the 12 traits analyzed in 3 different outcomes). Morning chronotype, OSA and insomnia were positively correlated with later PD-AAO (b = 1.07 (se = 0.37); b = 1.24 (se = 0.40) and 4.7 (se = 0.89), respectively), while M10 and sleep duration were negatively correlated with PD-AAO (b = -5.86 (se = 0.72) and -2.01 (se = 0.84), respectively). Cochran's Q and I^2 indicated heterogeneity in all 5 significant traits for PD (Table 3). The MR-PRESSO test showed presence of horizontal pleiotropy in > 50% of the instruments (Table 3). Thus, we further investigated the reliability of the results by performing additional MR tests that considered other assumptions. The MR Egger and WM were significant and consistent in terms of effect direction with the IVW results for chronotype and sleep duration. Moreover, the MBE regression was consistent in the effect direction in both traits. However, for insomnia and OSA, the WM and MR Egger, respectively, were consistent in terms of effect direction but did not reach significance (p = 0.48 and 0.14, respectively). However, as weak instruments were selected for OSA (SNV with $p<10^{-7}$ instead of SNV with $p < 10^{-8}$), we conducted MR RAPS test that showed significant causal association ($p = 6.4\times10^{-4}$, b = 1.29 (se = 0.38)). For M10 only one SNV was used as an instrument, so sensitivity analyses were not implemented. The Steiger test for all the significant traits associated with PD-AAO indicated correct causal direction (Table S3).

We performed leave-one-out analysis for the traits with a causal relationship to PD-AAO that passed the sensitivity analysis. For chronotype, we did not observe any SNV leading the causality (Fig. S1A). The leave-one-out analysis for sleep duration (Fig. S1B) showed that the entire causal effect was driven by rs113851554. Removal of that SNV resulted in the inversion of the beta values (p = 0.028; b = 4.31 (se = 1.96)). In that case, the WM was not significant (p = 0.84), thus not passing the sensitivity analysis. In the OSA's leave-one-out analysis, all the effect was guided by the rs34188544 SNV (Fig. S1C). The removal of that variant resulted in the beta inversion in the MR RAPS test (b = -1.96 and p = 0.38). As only one SNV was selected as an instrument for M10, we did not perform a leave-one-out analysis.

3.2. MR for AD risk

From the 12 traits analyzed as possible causal risk factors for AD, sleep efficiency measured with an accelerometer was the only trait that was significant (IVW p = 0.036) and showed a negative correlation (b = -10.53 (se = 5.03)) (Figs. 3,5). This result indicated that the risk of AD increased when the patient had poorer sleep efficiency. As only 2 SNV were considered valid instruments in this analysis, the sensitivity test performed when multiple instruments are used could not be conducted. The Steiger test confirmed the causal effect of sleep efficiency on AD risk (Table S3).

3.3. MR for ALS risk

We found daytime sleepiness causally associated with ALS risk (IVW p = 0.018). The correlation was positive (b = 1.17 (se 1.70)) indicating that increased daytime sleepiness was causally associated with increased risk of ALS (Figs. 4,5). The sensitivity analyses confirmed these results: neither heterogeneity (Table 3) nor single SNV driven the association (Fig. S1D) were identified. The different MR tests evaluated were consistent in effect direction despite the MR Egger was not statistically significant (p = 0.49). The Steiger test confirmed the correct causal direction (Table S3).

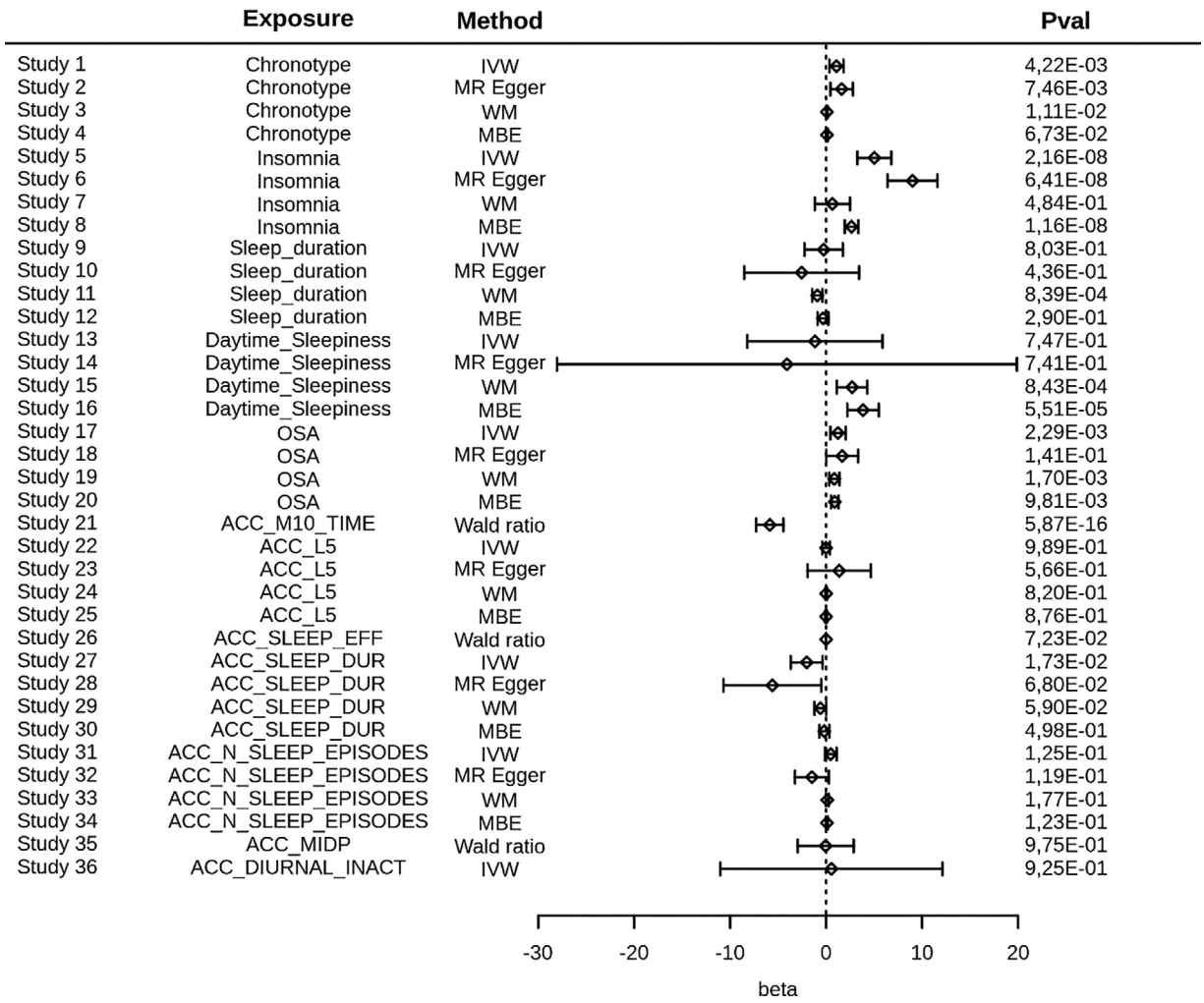

Fig. 2. Forest plot for Mendelian randomization analysis for PD-AAO outcome. The plots show the different methods used for the main (IVW) and sensitivity analyses. OSA, obstructive sleep apnea, ACC_M10, accelerometer-based measure for M10; ACC_L5, accelerometer-based measure for L5; ACC_SLEEP_EFF, accelerometer-based measure for sleep efficiency; ACC_SLEEP_DUR, accelerometer-based measure for sleep duration; ACC_N_SLEEP, accelerometer-based measure for number of sleep episodes; ACC_MIDP, accelerometer-based measure for sleep midpoint timing; ACC_DIURNAL_INACT, accelerometer-based measure for diurnal inactivity; IVW, inverse variance weighted; WM, Weighted-Median; MBE, mode-based estimate

Table 3
Heterogeneity results

Outcome	Exposure	Q_Cochran	Q_*pval*	I2	MR PRESSO	% Outliers
PD-AAO	Chronotype	36528.26	<0.001	99.6%	4.8e-03	>50%
PD-AAO	Insomnia	217216.5	<0.001	98.8%	2.19e-06	>50%
PD-AAO	OSA	6600.37	<0.001	99.9%	0.38	-
PD-AAO	Acc. Sleep Duration	4233,64	<0.001	96.0%	<2e-04	>50%
AD	Acc. Sleep Efficiency	0.09	0.76	0%	-	-
ALS	Acc. Daytime sleepiness	43.74	0.14	19.9%	-	-

Results for heterogeneity test (Q-cochran, I2 and MR-PRESSO) performed to the significant results in IVW test.
% Outliers indicated the proportion of instrumental variants considered outliers.
PD-AAO, Parkinson's disease age at onset; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; OSA, obstructive sleep apnea; Acc, Accelerometer

3.4. Reverse MR analysis

The reverse causality analysis was conducted to confirm the MR results and to assess potential new causal associations in the reverse direction. In the case of PD-AAO, the reverse MR analysis was based in only one weak instrument (Fig. S2) and has been described to lead to inconclusive results (Burgess et al., Int J Epi; 2011; Davies et al., BMJ; 2018). We found that genetically predicted risk of AD was causal for nine sleep and/or wake cycle traits: chronotype, insomnia, self-reported sleep duration, L5 measure, sleep duration measured with accelerometer, number of sleep episodes, sleep midpoint timing (MIDP) and diurnal inactivity (Fig. S3). All these traits but chronotype were negatively correlated with AD. Heterogeneity test for these traits only showed presence of heterogeneity for chronotype and number of sleep episodes. However, the MR-PRESSO test did not detect outliers (Table S3). In all

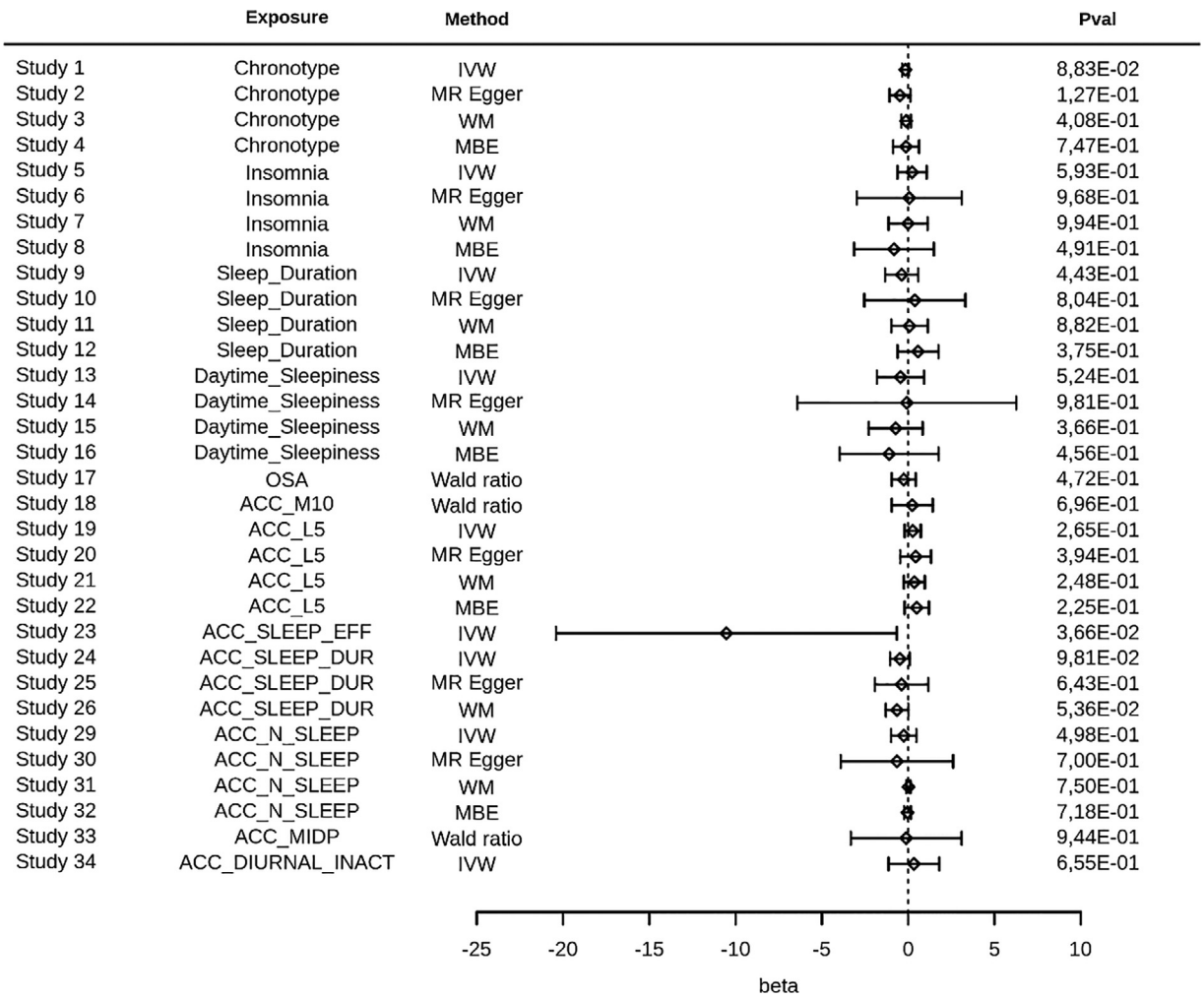

Fig. 3. Forest plot for Mendelian randomization analysis for AD outcome. The plots show the different methods used for the main (IVW) and sensitivity analyses. OSA, obstructive sleep apnea; ACC_M10, accelerometer-based measure for M10; ACC_L5, accelerometer-based measure for L5; ACC_SLEEP_EFF, accelerometer-based measure for sleep efficiency; ACC_SLEEP_DUR, accelerometer-based measure for sleep duration; ACC_N_SLEEP, accelerometer-based measure for number of sleep episodes; ACC_MIDP, accelerometer-based measure for sleep midpoint timing; ACC_DIURNAL_INACT, accelerometer-based measure for diurnal inactivity; IVW, inverse variance weighted; WM, Weighted-Median; MBE, mode-based estimate

cases, the effect direction among the different MR methods was consistent and was statistically significant with the exception of MR Egger for chronotype and number of sleep episodes (Figs. S2-S4). We did not identify any single SNV leading the causal effect (Fig. S5). The causal direction was predicted to be correct by the Steiger test (Table S5). We did not find significant causal association for sleep efficiency ($p = 0.75$), the unique trait identified to be a potential causal factor of AD.

The 5 hours with less activity (L5) measured with accelerometer was found to be causal outcome of ALS (Fig. S4). The beta for the association indicated a positive correlation (b = 0.018 (se = 0.003). The sensitivity analysis based in heterogeneity test, additional MR tests, leave-one-out and Steiger test confirmed this causal association (Table S4-S5; Figs. S4 and S5). We did not find significant causal association for daytime sleepiness ($p = 0.60$), the unique trait identified to be a potential causal factor of ALS.

3.5. Genetic correlation analysis

We studied whether apart from causal associations exists genetic correlation between ND traits and sleep and/or wake cycle traits. We did not find any significant genetic correlation (Fig. S6).

4. Discussion

The results from our MR study support a causal effect of some sleep-wake patterns with PD-AAO, AD and ALS. Specifically, we have found a potential causal effect of morning chronotype in delayed PD-AAO, which suggests protection against the onset of the disease. These results were consistent in both analyses based on self-reported and objective measures of chronotype. Our results based on GWAS using objectively obtained variables (with accelerometer devices) showed a causal relationship between M10 time and PD-AAO. M10 time is an indicative measure of circadian rhythms: the higher the M10 time value, the more of an evening person you are. These results indicated that the more of an evening person you are, the earlier the PD-AAO. Looking at both objective- and subjective-based results, these indicate that being a morning person could delay the onset of PD. Chronotype is an indicator of the circadian rhythm, an important regulator of hippocampal function, that in turn is related to neurodegeneration and cognitive deficits (Cho, 2001). Circadian rhythms are fundamental in the daily ordering of cellular metabolic cycles (Hastings and Goedert, 2013). For example, the metabolism of dopamine, a key neurotransmitter in PD, is influenced by the

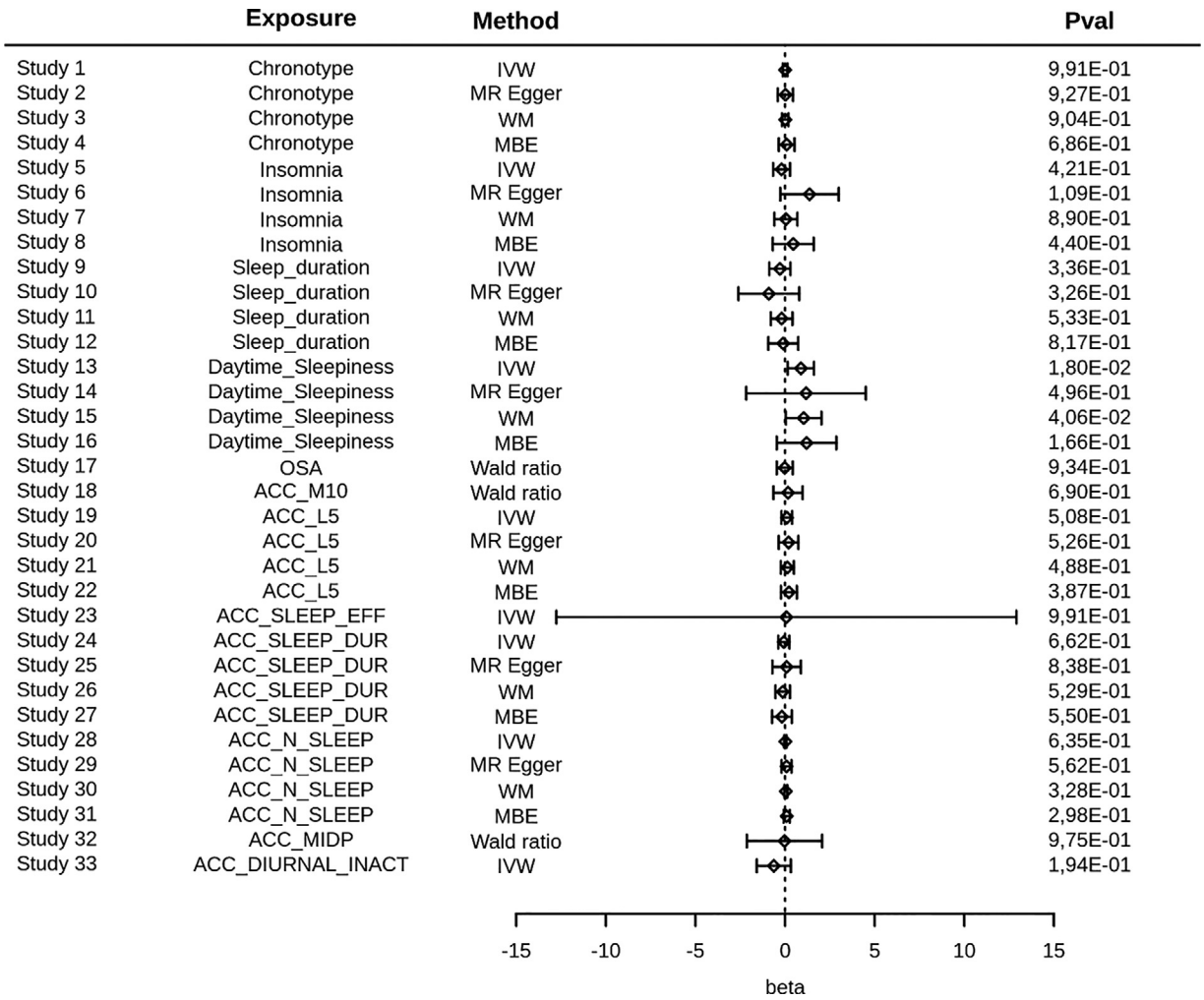

Fig. 4. Forest plot for mendelian randomization analysis for ALS outcome. The plots show the different methods used for the main (IVW) and sensitivity analyses. OSA, obstructive sleep apnea; ACC_M10, accelerometer-based measure for M10; ACC_L5, accelerometer-based measure for L5; ACC_SLEEP_EFF, accelerometer-based measure for sleep efficiency; ACC_SLEEP_DUR, accelerometer-based measure for sleep duration; ACC_N_SLEEP, accelerometer-based measure for number of sleep episodes; ACC_MIDP, accelerometer-based measure for sleep midpoint timing; ACC_DIURNAL_INACT, accelerometer-based measure for diurnal inactivity; IVW, inverse variance weighted; WM, Weighted-Median; MBE, mode-based estimate

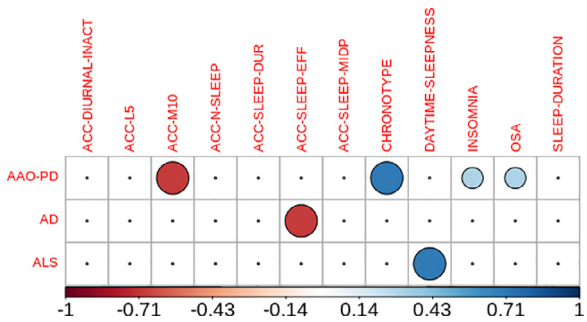

Fig. 5. Summary of the MR analyses. Summary of the results obtained from the different MR analyses. Size of the bubbles the strength of the associations: the bigger ones show significant traits in IVW results that were confirmed by sensitivity analyses. The smaller bubbles indicate significant traits in IVW results that were not confirmed by sensitivity analyses. Red color indicates positive correlation in the causal effect while blue indicate negative correlation in the causal effect (Color version of the figure is available online.)

circadian rhythm (Videnovic and Golombek, 2016). The effect of chronotype on dopamine metabolism could be a possible explanation for the results of our study.

We have identified sleep efficiency to be causally associated with a decreased risk of AD. The results indicate that the greater the sleep efficiency, the lower the risk of developing AD. The Steiger test and the reverse causality analysis confirmed the plausibility of this causal direction. As previously seen, inadequate sleep could prime the brain for neurodegeneration by promoting processes such as inflammation and synaptic damage, which exert pathogenic effects across diseases(Musiek and Holtzman, 2016). This result could reflect the importance of sleep-in metabolic homeostasis through waste removal by the glymphatic system (Xie et al., 2013).

We found daytime sleepiness to be potentially causally associated with ALS risk. The causal direction was confirmed by the reverse causality analysis and the Steiger test. Different sleep disorders have been linked with ALS. Based on a recent published systematic review, subjective sleep quality and daytime sleepiness were the sleep traits most commonly studied in relation with ALS (Lucia et al., 2020). Liu et al., identified higher frequency of excessive daytime sleepiness in patients with ALS compared with controls. It was linked with more serious frontal behavior, cognitive and physical impairment (Liu et al., 2018). In our reverse causality analysis, we found that genetically predicted increased ALS risk

was causally associated with an increase in L5 time, an objective measure of evening chronotype. Circadian alterations have been linked with ALS in a mouse model of the disease (Huang et al., 2018).

Previously, some studies in animal models and observational studies in humans indicated that sleep and/or wake cycle alterations could lead to the pathogenesis of ND (Benedict et al., 2014, Kang et al., 2009, Iliff et al., 2012). For example, some animal models of ALS and PD found that circadian disruption led to an increase in neuroinflammation that could be related to exacerbation of the neuropathology of the disease (Leng et al., 2019). Several human observational studies in older subjects showed that sleep and/or wake cycle alterations were related to an increased risk of incident all-cause dementia, including AD, vascular dementia (Musiek and Holtzman, 2016), and PD (Leng et al., 2019). However, the studies analyzing the causative risk of sleep and/or wake cycle alterations for developing ND are longitudinal or retrospective and could be biased due to causal reverse effect and confounding factors. MR overcomes these issues and could be better used with the purpose of finding causal relationships. Thus, the MR approach used in this study has allowed us to potentially identify causal relationships between sleep and/or wake cycle patterns and the risk of ND, which is important due to its potential therapeutic implications (Musiek and Holtzman, 2016).

Some previous MR studies have been published in the field of sleep and/or wake related traits and ND: 1 in PD (Noyce et al., 2019), 4 in AD (Anderson et al., 2020; Andrews et al., 2021; Henry et al., 2019; Huang et al., 2020) and 1 in ALS (Bandres-Ciga et al., 2019).

The PD MR study analyzed 5,839 GWAS as exposure traits, including sleep and/or wake cycle-related phenotypes, for their causal relationship with PD risk (Noyce et al., 2019). They developed a web-based portal to make all their results available. The available results for chronotype and risk of PD from the PD MR Portal are consistent with our results. The results were significant for morning chronotype and risk of PD in MR-Egger ($p = 0.029$), showing a negative correlation (b = -0.771). Compared with this MR study, we evaluated PD-AAO as phenotype instead of PD risk. PD-AAO has been found to be a genetically determined phenotype that shares some genetic factors with the risk of PD. However, GWAS of PD-AAO identified some additional genetic factors exclusively associated with this phenotype and not with PD risk. The genetic factors associated with this trait are also important for characterizing the pathways regulating PD (Blauwendraat et al., 2019).

Three out of the 4 MR studies in AD that we identified have analyzed the AD risk as outcome. The other one studied the reverse causal association and considered AD risk as the exposure factor. The summary statistics for the AD GWAS used as outcome in these studies differs from the one we used in our analysis. They were published before (Huang et al., 2017; Lambert et al., 2013) or they were based on the late-onset AD (Kunkle et al., 2019). In the MR study from Henry et al., 2019, the authors studied the causal association of sleep duration with cognition and AD risk. They only identified a small negative causal effect of sleep duration on reaction time, a cognitive marker. However, they did not find any association between sleep duration and all-cause dementia or AD risk using MR (Henry et al., 2019). The GWAS from Andrews et al., studied different traits previously associated with AD risk in observational studies. Among them, 2 sleep traits were included: sleep duration and insomnia. They found that longer sleep duration was causality associated with cortical thickness and shorter sleep duration with an increased risk of AD (Andrews et al., 2021). They did not reach conclusive results for insomnia because the sensitivity analyses did not confirm their observations. These results are in accordance with what we observed in our analysis of sleep duration and AD risk. We did not find significant association between these 2 traits. However, our results showed a trend toward shorter sleep duration leading to higher risk of AD ($p = 0.098$, b = -0.47 (se = 0.28)). Anderson et al., studied MR using different sleep traits as exposure. They did not show any significant causal association. Only daytime napping was potentially causally associated with AD risk (Anderson et al., 2020). None of the above articles studied the causal association of sleep efficiency and AD risk.

The MR study from Huang et al., studied the reverse causal association between AD risk and sleep traits (Huang et al., 2020). They found that the genetically predicted increase risk of AD was causally associated with increased risk of morning chronotype, earlier L5 timing and a decrease risk in insomnia, sleep duration and number of sleep episodes. Our reverse causality study for AD showed similar results. We also found a significant causal association of increased AD risk and morning chronotype, earlier L5 timing, insomnia, sleep duration and number of sleep episodes. Additionally, we also found some traits not studied by Huang et al., that were causal outcomes of AD risk: diurnal inactivity and the number of hours from the previous midnight (MIDP).

The ALS MR study (Bandres-Ciga et al., 2019) analyzed the causal association of >700 phenotypic traits from LD-hub and MR-base in ALS risk. Among these traits, they included some sleep and/or wake cycle features. None of these traits reached statistically significance in their study. However, as far as we know, the authors did not study some of the sleep traits that we did: sleep traits calculated through accelerometer devices (M10, L5, sleep efficiency, number of sleep episodes, MIDP, diurnal inactivity) and OSA. We have found daytime sleepiness to be causally associated with ALS risk. The Bandres-Ciga et al. included another summary statistic for this trait that only considered narcolepsy and thereby, it had a smaller sample size ($N = 336,082$ vs 452,071).

Our study has some limitations. Firstly, we did not have summary statistics for all sleep and/or wake cycle-related phenotypes. It is, therefore, possible that other sleep or circadian traits could be causally related to the risk of ND. Secondly, for OSA there were no valid instruments to assess causality. Despite using specific methodology to overcome this issue, the results obtained may not be totally reliable. Moreover, we were only able to consider PD, AD and ALS, as they were the only ND with complete summary statistics data.

To conclude, our study has allowed the identification of potential causal relationships between sleep and/or wake patterns and PD-AAO, AD and ALS. The causal relationships found in this study could lead to further studies investigating the therapeutic implications of sleep and/or wake cycle patterns to prevent or slow the progression of ND. Specifically, the effect of chronotype modification on PD-AAO and even on the risk of the disease, the effect of sleep efficiency on AD risk and the effect of daytime sleepiness in ALS should be evaluated in future studies.

Declaration of Competing Interest

We do not have any conflict of interest.

Credit author statement

Natalia Cullell: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft. Jara Cárcel-Márquez: Validation, Writing - Review & Editing. Cristina Gallego-Fábrega: Writing - Review & Editing. Elena Muiño: Writing - Review & Editing, Data Curation. Laia Llucià: Writing - Review & Editing. Miquel Lledós: Writing - Review & Editing. Karol Enrique Uscamaita Amaut: Writing - Review & Editing, Data Curation. Jerzy

Krupinski: Conceptualization, Supervision, Writing - Review & Editing, Project administration, Funding acquisition. Israel Fernández-Cadenas: Conceptualization, Supervision, Writing - Review & Editing, Project administration, Funding acquisition

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2021.05.008.

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