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Pathways between multiple sclerosis, sleep disorders, and cognitive function: longitudinal findings from The Nurses' Health Study

Tiffany J. Braley, MD MS[1,2], **Monica M. Shieu, PhD**[2], **Afsara Zaheed, MS**[2], **Galit Levi Dunietz, PhD**[2]

[1]Division of Multiple Sclerosis and Clinical Neuroimmunology, Department of Neurology, University of Michigan, Ann Arbor, MI, USA.

[2]Division of Sleep Medicine, Department of Neurology, University of Michigan, Ann Arbor, MI, USA.

Abstract

Background: The potential mediating and moderating effects of sleep disorders on cognitive outcomes in MS have been insufficiently studied.

Objectives: To determine direct and indirect longitudinal associations between sleep disorders and perceived cognitive dysfunction in women with MS.

Methods: The 2013 and 2017 waves of the Nurses' Health Study (n=63,866) were utilized. All diagnoses and symptoms including MS (n=524) were self-reported. Subjective cognitive function was measured using a composite score of four memory items, and three binary outcomes that assessed difficulty following instructions, conversations/plots, and street navigation. Moderating and mediating effects of diagnosed/suspected OSA, sleepiness, and insomnia between MS and cognition were estimated using the 4-way decomposition method.

Results: Prevalence of diagnosed/suspected OSA, sleepiness, and insomnia in 2013 were higher for nurses with MS (NwMS). NwMS were more likely to report cognitive difficulties in 2017. Insomnia mediated 5.4–15.1% of the total effect between MS and following instructions, conversations/plots, and memory impairment, while sleepiness mediated 8.6–12.3% of the total effect for these outcomes. In interaction analyses, OSA significantly accounted for 34% of the total effect between MS and following instructions.

Conclusion: Prevalent OSA, insomnia, and sleepiness could differentially moderate or mediate the effect of MS on cognition in women with MS.

Keywords

multiple sclerosis; sleep; sleep apnea; insomnia; cognitive impairment; sleepiness

Corresponding author: Tiffany J. Braley, MD, MS, C728 Med-Inn Building, 1500 E. Medical Center Dr., Ann Arbor, MI 48109, USA; Phone: (734) 232-1147; Fax: (734) 232-9986; tbraley@med.umich.edu.

Declaration of Conflicting Interests

The Authors declare no conflict of interest.

INTRODUCTION

Cognitive dysfunction affects up to 70% of people with multiple sclerosis (PwMS) and is considered one of the most disabling symptoms.[1] Despite its prevalence and impact, interventions to ameliorate cognitive dysfunction in MS are limited. The dearth of effective treatments has prompted the need to address modifiable risk factors for cognitive impairment.

People with MS also disproportionately experience treatable sleep disorders that are linked to cognitive dysfunction, including obstructive sleep apnea (OSA), insomnia, and excessive daytime sleepiness.[2,3,4,] Prior work suggests that PwMS are more likely to have an elevated risk for OSA,[5] based on a validated screening tool.[6,7] Further, our research suggests a link between OSA, sleep fragmentation, and impaired objective cognitive performance in MS.[8] Yet, despite observed associations between sleep disorders and cognitive dysfunction in MS, little is known about how sleep and MS interact to impact long term cognitive outcomes.

To date, much of the work on sleep and MS-related cognitive impairment has relied on objective cognitive assessments.[5,9 10] Although this approach provides necessary information, use of objective testing alone has limitations. First, administration of standardized cognitive tests that separately assess individual cognitive domains are conducted in a controlled clinical or laboratory setting, as opposed to the natural environment. Second, determination of impairment is typically based on a pre-specified threshold using normative data that can vary from the individual under study, due to cultural bias. Third, prior research has largely reported on objective cognitive performance measured at a single time-point. Although this approach has provided fundamental quantitative data, point estimates of cognitive performance based on pre-specified cutoffs do not capture qualitative information about patient experiences or account for perceived changes in cognition over time.

In contrast to objective testing, self-reported cognitive changes reflect a person's perceived change in cognitive function over time. Although discrepancies between subjective and objective assessment of cognitive impairment exist,[11] experts acknowledge the value of self-reported cognitive symptoms as a potential early indicator for cognitive decline in non-MS samples,[12,13] particularly among women.[14] Moreover, prior studies in PwMS have reported associations between sleep disturbances and self-reported cognitive decline. However, most were cross-sectional, limited by small/convenience samples, and/or restricted to subjective sleep measures.[15,16]

To address these knowledge gaps, the objective of this longitudinal study was to determine whether perceived cognitive dysfunction in MS is mediated and/or moderated by sleep disorders in women, using data from the Nurses' Health Study – one of the largest prospective investigations of risk factors for chronic diseases in women. We hypothesized that, relative to nurses with MS (NwMS) without sleep disturbances, NwMS with sleep disturbances at baseline would experience more subjective cognitive dysfunction over time, and that sleep disturbances would account for a higher percentage of the total effect of MS on cognitive changes through effect modification.

MATERIALS AND METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

This study was given "exempt and not regulated" status by the University of Michigan Institutional Review Board.

The Nurse's Health Study (NHS II Cohort)

A longitudinal cohort, the Nurse's Health Study (NHSII) began in 1989 with an enrollment of 116,429 female registered nurses. Questionnaires were administered biennially to assess lifestyle factors and health status, with a follow-up rate exceeding 90%.[17] This study included nurses who completed the long-form questionnaires in 2013 and 2017, given the detailed sleep and cognitive items included in these specific waves, respectively.

Completion of the questionnaire implied informed consent per the NHS investigators and institutional review boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health.

Study Variables

Identification of MS cases: In the 2013 wave, presence of MS diagnosis was based on response (yes/no) to: "Have you ever had any clinician-diagnosed multiple sclerosis?"

Identification of prevalent OSA, insomnia, and sleepiness: The NHSII 2013 wave included items that assessed clinical factors associated with elevated OSA risk, closely resembling items from the STOP-Bang questionnaire, a validated, 8-item instrument that assesses risk factors associated with OSA that form the acronym "STOP-Bang" (Snoring, Tiredness, Observed apneas, high blood Pressure, BMI, Age, Neck circumference, Gender).[6] Item scores are based on yes/no responses to each risk factor. The utility of the STOP-Bang has been demonstrated in a variety of populations, and validated in PwMS by our group.[7] We defined increased OSA risk based on adapted STOP-Bang items derived from the NHS II (see Table 1 for details and cutoffs). Generally, a STOP-Bang score of 3 or more signals eleavted OSA risk. To enhance specificity, suspected OSA cases were defined by either a STOP-Bang score of ≥3, in which at least two of the positive items came from the "STOP" portion of the questionnaire, plus BMI >35[18]; or a total STOP-Bang score of ≥4, in which case any combination of at least 4 positive items was permissible. Since all the participants were women, the maximum achievable STOP-Bang score was six.

Beyond risk score, we also assessed the presence of OSA *diagnosis* by a positive answer to "Have you ever had any clinician-diagnosed sleep apnea?" A variable of "known or suspected OSA" was defined presence of OSA diagnosis or high OSA risk.

The 2013 NHSII wave also included Likert-scale items related to sleep quality and sleepiness that included questions about frequency ("most of the time," "sometimes," "rarely" or "never") of trouble falling asleep, trouble staying asleep, trouble waking up too early, symptomatic sleepiness, and feeling rested upon awakening in the morning. A composite insomnia score included positive answers to these five insomnia symptoms. "Most of the time" was considered as a positive item for trouble falling asleep, trouble

staying asleep, trouble waking up too early, and symptomatic sleepiness. Conversely, a response of “rarely or never” to the rested upon awakening item was considered a positive response. The range of the insomnia composite score is from zero to five.

Symptomatic sleepiness was also evaluated as a binary variable. Participants who responded “most of the time” to the question “How often do you get so sleepy during the day or evening that you have to take a nap?” were classified positive.

Four items in the 2013 wave that resembled essential Restless Legs Syndrome diagnostic features[19] were also examined. Respondents were characterized as having RLS if all 4 diagnostic features were endorsed.

Cognitive function: In 2017, participants were asked four binary questions about *recent* situational difficulty in remembering (yes/no). We created a composite variable from these four items, with scores ranging from zero to four. Three stand-alone binary cognitive variables included: 1) difficulty in understanding or following spoken instructions; 2) recent difficulty in following a group conversation or a plot in a television program; and 3) trouble navigating familiar streets (yes/no). These three items were scored individually.

Covariates: Baseline demographic variables (age, race, smoking status, marital/cohabitation status, employment) were obtained from the 2013 survey. Race was categorized as White and non-White. Marital/cohabitation status was classified for married or cohabiting respondents versus otherwise. Current employment status was classified as current workers and other (retired, disability, etc). Self-reported depression diagnosis was assessed with a single binary item.

Statistical analysis: Descriptive statistics were calculated as proportions for categorical variables and as means and standard errors for continuous variables.

Associations between MS diagnosis and cognitive outcomes were first examined. Logistic regression was used to estimate crude and adjusted prevalence odds ratios and 95% confidence intervals for the three stand-alone binary cognitive outcomes. Linear regression was used for the memory composite outcome. Models were adjusted for age, race, smoking, marital status, and employment.

We then examined the interaction and mediation effects of known/suspected OSA, insomnia composite score, and symptomatic sleepiness in pathways between MS and four cognitive outcomes. The 4-way decomposition method, developed by VanderWeele,[20] focuses on one mediator, but decomposes the total exposure effect into 4 components due to: neither mediation nor interaction (controlled direct effect); interaction only (reference interaction); both interaction and mediation (mediated interaction); and mediation only (pure indirect effect). For the exposure-outcome models, logistic models were fitted to the three stand-alone binary cognitive outcomes, whereas linear regression models were used when memory composite was the outcome. Interaction terms (moderation) of MS*OSA, MS*insomnia, and MS*sleepiness were included in the models.

For the exposure-mediator models, logistic regression was used when known or suspected OSA or symptomatic sleepiness were treated as the mediator, while linear regression was utilized when insomnia composite score was treated as the mediator. All models included adjustment for confounders. Proportion of the total effect due to interaction between sleep variables*MS and total effects are derived from estimated parameters of the fitted models.[20] The CAUSALMED procedure in SAS 9.4 was used (Cary, NC).[21]

RESULTS

Data from 63,866 nurses (524 with MS) were utilized (Table 2).

The prevalence of known or suspected OSA was somewhat higher for NwMS (13.6%) compared to those without MS (12.2%) (Table 2). In comparison to those without MS, NwMS had higher prevalence of all insomnia symptoms, higher insomnia composite score, and higher sleepiness prevalence. Prevalence of RLS did not significantly differ between MS and non-MS respondents.

We first examined associations between MS and cognitive outcomes. In adjusted models, MS was significantly associated with difficulty in following spoken instruction (OR=2.2, CI:1.6, 3.0), difficulty in following conversations/plots (OR=1.9, CI:1.3, 2.9), difficulty in street navigation (OR=2.7, CI:1.5, 4.9), and memory difficulty (beta=0.24, CI:0.14, 0.34) (not shown).

Results of the 4-way decomposed effects of MS on cognitive outcome, due to mediation and/or interaction with sleep variables are presented in Tables 3, 4, 5 and 6.

In models with stand-alone binary cognitive outcomes (Table 3), the adjusted OR for the total effect of MS on cognitive outcomes due to mediation and/or interaction with OSA on was 2.2 (CI:1.5, 2.9) for difficulty in following spoken instruction; 1.9 (CI:1.2, 2.7) for difficulty in following conversions/plots; 2.8 (CI:1.1, 4.4) for difficulty in street navigation. For each outcome, the controlled direct effect of MS on cognition was the largest of the components (>66%). Additionally, the overall proportion of the total effect attributable to total *interaction* (driven mostly by reference interaction) was 33.5% (CI:0.1–66.9) for difficulty in following spoken instruction. The overall proportion attributable to *mediation* (pure indirect effect) was nonsignificant.

Table 4 shows the adjusted OR for the total effect of insomnia composite score as the mediator/moderator on the binary cognitive outcomes. The controlled direct effect of MS was again largest and most significant of the four decomposed components (>56%). In adjusted *mediation* analyses, the pure indirect effect of insomnia significantly accounted for 5.4% (CI:1.3, 9.5) and 8.4% (CI:5.7, 16.1) of the total effect on following spoken instructions and conversations/plots, respectively. The proportion attributable to *interaction* was nonsignificant.

Results of the adjusted OR for the total effect of symptomatic sleepiness as the mediator/moderator on the binary cognitive outcomes is presented in Table 5. The controlled direct effect of MS was the largest and most significant of the four decomposed components

(>80%). In adjusted *mediation* analysis, pure indirect effect of symptomatic sleepiness accounted for 8.6% (CI:2.2, 15.0) and 10.1% (CI:3.1, 20.2) of the total effect on difficulty in following spoken instruction and conversations/plots, respectively. The overall proportion attributable to *interaction* was small and non-significant.

Finally, we examined the four component effects of MS on the memory difficulty composite, due to mediation and/or interaction, with known/suspected OSA, insomnia composite score, and sleepiness (Table 6). The controlled direct effect of MS was the largest and most significant of the four decomposed components (>84%). There was a trend toward significance attributable to *interaction* between MS*OSA on memory (15.1%, CI:−1.7, 31.8). In adjusted *mediation* analysis, the pure indirect effect of insomnia and symptomatic sleepiness significantly accounted for 15.1% (CI: 6.2, 24.0) and 12.3% (CI: 5.1, 19.5) of the total effect on the memory difficulty composite, respectively.

Although depression was examined as a confounder in insomnia and sleepiness models, its addition was associated with negligible change in point estimates and was therefore not included in final models. As depression is more plausibly a viewed as a potential mediator rather than a confounder between MS and OSA,[22] we did not adjust for depression in OSA models since this would violate the fourth assumption of the four-way decomposition mediation analysis.

DISCUSSION

This study offers a novel approach to the deconstruction of pathways between common sleep disorders and cognitive decline in MS, on a population level, and in a longitudinal manner. Findings suggest that prevalent OSA, insomnia symptoms, and sleepiness could differentially moderate or mediate the effect of MS on perceived cognition in women with MS, highlighting distinct direct and indirect associations between these disorders.

Interventions to delay cognitive decline in MS may be of highest yield in pre-symptomatic or early symptomatic stages. Consequently, perceived decline in cognitive function, even in the absence of objective deficits, could offer a unique window of opportunity to identify treatable exacerbating factors. Sleep disorders have gained substantial recognition for their role in cognitive health. People with chronic neurological conditions may be particularly vulnerable to the impact of sleep disturbances on cognitive decline.[23] Multiple sclerosis in particular is associated with a high risk of several sleep disorders,[4] and prior work has demonstrated associations between sleep disorders, fatigue, and quality of life in MS,[24,25] highlighting the importance of understanding the scope and cognitive impact of sleep disorders in PwMS. Furthermore, treatment for some sleep disorders including OSA are associated with improved longitudinal cognitive trajectories in non-MS samples,[26] making the timely treatment of sleep disorders a potential therapeutic approach for cognitive decline.

This cohort design accounted for temporality of existing sleep diagnoses relative to recent cognitive changes, including potentially *undiagnosed* sleep disorders. This is especially germane in the context of OSA. *To date, population-based data regarding the scope and impact of sleep disorders in MS are lacking*. Despite the high prevalence of OSA

in the general population, the majority of individuals with OSA remain undiagnosed.[27] Consequently, datasets that are restricted to diagnostic or treatment codes are subject to misclassification bias, as the majority of undiagnosed cases will be missed with this approach.[28] Similarly, insomnia symptoms, experienced by up to 40% of people with MS[4], could escape formal diagnosis in claims-based queries. Despite heavier emphasis on fatigue in MS, sleepiness is also an underrecognized symptom that could impact cognitive function; however, this symptom is inconsistently captured in many cohorts.[2] Datasets such as the NHS that include more granular data regarding sleep offer a more reliable means to identify undiagnosed cases in a manner that minimizes misclassification bias.

Associations between prevalent sleep disorders and cognitive complaints in this study spanned multiple cognitive functions, including working memory, comprehension, and visuospatial function. Known or suspected OSA was most strongly associated with verbal comprehension (through moderation), while insomnia and sleepiness showed the strongest associations with working memory (through mediation), and to a lesser extent, verbal comprehension and attention. In a prior study, we identified an association between apnea severity and performance on the CVLT-II Discriminability Index—a measure of verbal memory and executive functioning (response inhibition) ability, in PwMS. Furthermore, in non-MS samples, sleepiness is associated with impaired attention and vigilance which could impact ability to follow instructions.[29] Additional research is needed to determine the neuropathological pathways underlying cognitive trajectories among PwMS in the context of different sleep disorders.

Our approach to frame recent perceived cognitive difficulties as a harbinger of objective cognitive decline is also supported by previous work in non-MS participants.[30] In a previous study, both self- and partner-reported change in cognition were associated with subsequent objective measures of clinical cognitive progression in older adults. This same study group also conducted an analysis of NHS that included a specialized set of objective telephone-based cognitive tests collected in the 2011 wave. In this analysis, the same *subjective* NHS cognitive items used in our study were associated with amyloid-β deposition in cognitively normal older individuals, that preceded changes in objective cognitive testing. Moreover, prior research has associated subjective cognitive impairment with more rapid decline to mild cognitive impairment and dementia statuses among healthy older adults.[31] These prior observations allow speculation that people with MS could experience similar patterns in cognition that may be more sensitive to the effects of disturbed sleep.

Strengths of our study included a large cohort that allowed for comparison of people with and without MS. Our ability to assess OSA risk beyond clinically confirmed diagnosis allowed for classification of undiagnosed OSA cases. The >90% NHS follow-up rate minimized non-response bias. The longitudinal survey design allowed for assessment of temporality and strengthens causal inferences.

Several limitations are acknowledged. Data on fatigue severity, which could potentially impact cognitive function, were not available. As the NHSII cohort did not include men, we cannot conclude whether men with MS experience similar associations. That said, as men are more likely to experience more severe OSA than women,[32] it is possible that lack of

male respondents could have led to more conservative estimates. Although the STOP-Bang has been validated in samples that included men and women with and without MS, women with OSA may present differently.[33] A recent study suggested that a lower STOP-Bang score may be predictive of more severe OSA in women.[34] It is therefore possible that the STOP-Bang threshold used in our study could have underestimated the full number of OSA cases, diminishing point estimates. Similarly, although the STOP-Bang has demonstrated good sensitivity to detect moderate or severe OSA in PwMS, its ability to detect mild OSA in PwMS is suboptimal. The NHS insomnia items are not sufficient to diagnose clinical insomnia per International Classification of Sleep Disorders Diagnostic Manual Third Edition (ICSD-3) criteria.[35] As data regarding sleep opportunity and perceived daytime consequences from insomnia (required for an insomnia diagnosis) were not available, insomnia could not be comprehensively characterized in this sample. It is also possible that use of a relatively short 4-year follow-up period and a highly educated sample with more cognitive reserve could have resulted in more conservative estimates. The NHS does not include data on CPAP use, which could have also blunted associations.

In conclusion, NwMS who have OSA, insomnia, or sleepiness may experience increased subjective cognitive dysfunction compared to those without these disorders. Our findings highlight sleep disorders as common potentially modifiable contributors to cognitive dysfunction in women with MS, which may work through distinct pathways.

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Table 1:

NHS and corresponding STOP-Bang questionnaire items to identify individuals at risk for obstructive sleep apnea (symptomatic sleepiness also examined as a stand-alone item)

Questions from the NHS II file	Criteria of the NHS II questions to be considered a positive result	Corresponding STOP-Bang item
How often do you snore?	Every night, most nights	Do you **S**nore loudly? (yes/no)
How often do you get so sleepy during the day or evening that you have to take a nap?	Most of the time	Do you often feel **T**ired, fatigued, or sleepy during the daytime? (yes/no)
Has anyone noticed that you stop breathing during your sleep?	Yes	Has anyone **O**bserved you stop breathing during sleep? (yes/no)
Have you ever had a high blood pressure diagnosis?	Yes	Do you have (or are you being treated for) high blood
Current usual blood pressure	Systolic categories (125 −134, 135–144, 145–154, 155–164, 165–174, 175+ mmHg), or diastolic categories (75 −84, 85–89, 90–94, 95–104, 105+mmHg)	**P**ressure? (yes/no)
BMI	>35 kg/m2	**B**MI>35 (yes/no)
Year born	>50 years	**A**ge>50 (yes/no)
N/A	N/A	**N**eck circumference > 40 cm (yes/no)
Sex	Men	**G**ender male (yes/no)

Table 2:

Summary statistics—mean (standard deviation) and prevalence (%) of selected variables and sleep disorders, at baseline in 2013

	Total (n=63,866)	Multiple sclerosis diagnosis (n=524)	No multiple sclerosis diagnosis (n=63,342)
Age (years)	58.7 (4.6)	59.0 (4.3)	58.7 (4.6)
Race/ethnicity			
White (%)	95.3	95.4	95.3
Black (%)	1.2	1.4	1.2
Hispanic (%)	1.6	1.9	1.6
Other (%)	1.9	1.3	1.9
Smoking (%)	4.3	6.7	4.3
Married or cohabitated (%)	77.6	76.1	77.6
Currently working (%)	68.3	42.0	68.6
BMI (kg/m^2)	27.5 (6.3)	27.3 (6.2)	27.5 (6.3)
Hypertension (%)	60.1	60.5	60.1
Obstructive Sleep Apnea (OSA)			
OSA diagnosis (%)	7.3	8.6	7.3
Elevated OSA risk[a] (%)	8.3	8.6	8.3
Known or suspected OSA[b] (%)	12.2	13.6	12.2
STOP-Bang score (mean)	2.0 (1.0)	2.1 (1.0)	2.0 (1.0)
Insomnia			
Difficulty falling asleep (%)	13.2	17.8	13.2
Trouble waking up during the night (%)	28.4	33.3	28.4
Waking too early (%)	12.4	12.6	12.4
Symptomatic sleepiness (%)	7.4	14.9	7.0
Not feel rested in the morning (%)	13.2	19.5	13.1
Insomnia composite score[c] (mean)	0.74 (1.1)	0.97 (1.2)	0.74 (1.1)

[a]Defined by surrogate STOP-Bang score items Elevated-risk cases were defined by the presence of either 1) a STOP-Bang score of ≥3, in which at least two of the positive items came from the “STOP” portion of the questionnaire, plus a positive score for male gender or BMI >35; or 2) a total STOP-Bang score of ≥4, in which case any combination of at least 4 positive items was permissible

[b]Defined by either having a OSA diagnosis or elevated OSA risk by surrogate STOP-Bang score.

[c]Summary score that included included positive answers from trouble falling asleep, trouble staying asleep, trouble waking up too early, trouble with excessive sleepiness to the point of requiring daily naps, and lack of feeling rested upon awakening in the morning.

Table 3:

Adjusted[a] odds ratios (OR; 95% CI) for the 4 component effects of multiple sclerosis (vs. no multiple sclerosis) on cognitive outcomes, due to mediation and/or interaction with known or suspected obstructive sleep apnea (OSA)[b]: results of the 4-way decomposition method with logistic regression

Component effect of multiple sclerosis	OR (95%CI)	Percentage of total effect (95% CI)	
Difficulty in following spoken instruction			
Controlled direct[c]	1.9 (1.2, 2.6)	66.2 (32.5, 99.9)	
Reference interaction[d]	1.4 (0.96, 1.8)	32.3 (0.19, 64.4)	33.5 (0.1, 66.9)[g]
Mediated interaction[e]	1.0 (0.92, 1.1)	1.2 (−6.3, 8.7)	
Pure indirect[f]	1.0 (0.98, 1.0)	0.32 (−1.7, 2.3)	
Total	2.2 (1.5, 2.9)	100	---
Difficulty in following conversions or a plot			
Controlled direct[c]	2.1 (1.1, 3.0)	98.3 (62.3, 134.3)	
Reference interaction[d]	1.0 (0.68, 1.3)	1.2 (−33.5, 36.0)	1.3 (−23.7, 3.2)[g]
Mediated interaction[e]	1.0 (0.99, 1.0)	0.04 (−1.2, 1.3)	
Pure indirect[f]	1.0 (0.98, 1.0)	0.42 (−2.5, 3.3)	
Total	1.9 (1.2, 2.7)	100	---
Difficulty in navigatingfamiliar streets			
Controlled direct[c]	2.8 (0.90, 4.6)	86.3 (42.0, 130.5)	
Reference interaction[d]	1.2 (0.45, 2.0)	13.0 (−29.5, 55.0)	13.5 (−30.7, 57.6)[g]
Mediated interaction[e]	1.0 (0.94, 1. 1)	0.50 (−2.9, 3.9)	
Pure indirect[f]	1.0 (0.97, 1.0)	0.29 (−1.5, 2.1)	
Total	2.8 (1.1, 4.4)	100	---

[a]All effects are adjusted for baseline confounders: age, race (White and non-White), smoking, marital status, employment.

[b]Defined by either having a OSA diagnosis or elevated OSA risk by STOP-Bang score.

[c]Neither mediation nor interaction (MS→cognition)

[d]Interaction only (MS*OSA)

[e]Both interaction and mediation (MS*OSA and MS→OSA→cognition)

[f]Mediation only (MS→OSA→cognition)

[g]Reflects the proportion due to interaction.

Table 4:

Adjusted[a] odds ratios (OR; 95% CI) for the 4 component effects of multiple sclerosis (vs. no multiple sclerosis) on cognitive outcomes, due to mediation and/or interaction with insomnia composite score[b]: results of the 4-way decomposition method with logistic regression

Component effect of multiple sclerosis	OR (95%CI)	Percentage of total effect (95% CI)	
Difficulty in following spoken instruction			
Controlled direct[c]	2.3 (1.5, 3.0)	100.9 (86.9, 114.9)	
Reference interaction[d]	0.95 (0.90, 1.1)	−3.8 (−8.7, 1.1)	−6.3 (−21.0, 8.4)[g]
Mediated interaction[e]	0.97 (0.85, 1.1)	−2.5 (−12.5, 7.5)	
Pure indirect[f]	1.1 (1.0, 1.1)	5.4 (1.3, 9.5)	
Total	2.2 (1.5, 2.9)	100	---
Difficulty in following conversions or a plot			
Controlled direct[c]	1.2 (0.96, 2.6)	77.0 (42.6, 111.5)	
Reference interaction[d]	1.1 (0.86, 1.3)	7.5 (−14.3, 29.2)	14.6 (−18.3, 47.4)[g]
Mediated interaction[e]	1.1 (0.95, 1.2)	7.1 (−4.3, 18.5)	
Pure indirect[f]	1.1 (1.0, 1.1)	8.4 (5.7, 16.1)	
Total	1.9 (1.2, 2.7)	100	---
Difficulty in finding your way around familiar streets			
Controlled direct[c]	2.6 (0.59, 4.5)	56.6 (−31.6, 144.8)	
Reference interaction[d]	2.9 (0.60, 5.2)	72.0 (46.1, 194.0)	40.0 (−50.7, 130.6)[g]
Mediated interaction[e]	0.81 (0.40, 1.2)	−36.0 (−70.8, −1.1)	
Pure indirect[f]	1.1 (1.0, 1.1)	0.34 (−0.92, 7.7)	
Total	3.5 (0.72, 6.3)	100	---

[a] All effects are adjusted for baseline confounders: age, race (White and non-White), smoking, marital status, employment.

[b] Summary score that included included positive answers from difficulty falling asleep, trouble with waking up during night, waking up too early, feeling sleepy during the day or evening, not feeling rested in the morning.

[c] Neither mediation nor interaction (MS→cognition)

[d] Interaction only (MS*insomnia)

[e] Both interaction and mediation (MS*insomnia and MS→insomnia→cognition)

[f] Mediation only (MS→insomnia→cognition)

[g] Reflects the proportion due to interaction.

Table 5:

Adjusted[a] odds ratios (OR; 95% CI) for the 4 component effects of multiple sclerosis (vs. no multiple sclerosis) on cognitive outcomes, due to mediation and/or interaction with symptomatic sleepiness: results of the 4-way decomposition method with logistic regression

Component effect of multiple sclerosis	OR (95%CI)	Percentage of total effect (95% CI)	
Difficulty in following spoken instruction			
Controlled direct[b]	1.9 (1.6, 2.6)	82.2 (51.1, 113.4)	
Reference interaction[c]	1.1 (0.87, 1.2)	4.7 (−11.1, 20.4)	9.2 (−21.9, 40.2)[f]
Mediated interaction[d]	1.1 (0.87, 1.1)	4.5 (−10.8, 19.8)	
Pure indirect[e]	1.1 (1.1, 1.1)	8.6 (2.2, 15.0)	
Total	2.1 (1.4, 1.8)	100	---
Difficulty in following conversions or a plot			
Controlled direct[b]	1.7 (0.94, 2.5)	80.8 (37.6, 124.0)	
Reference interaction[c]	1.0 (0.84, 1.2)	4.6 (−17.2, 26.5)	9.1 (−33.7, 51.9)[f]
Mediated interaction[d]	1.0 (0.85, 1.2)	4.4 (−16.5, 25.4)	
Pure indirect[e]	1.1 (1.0, 1.1)	10.1 (3.1, 20.0)	
Total	1.9 (1.1, 2.7)	100	---
Difficulty in finding your way around familiar streets			
Controlled direct[b]	2.9 (1.1, 4.7)	118.0 (88.5, 147.0)	
Reference interaction[c]	0.79 (0.55, 1.0)	−12.8 (−29.4, 3.8)	−25.2 (−58.4, 8.2)[f]
Mediated interaction[d]	0.80 (0.55, 1.0)	−12.4 (−29.4, 4.6)	
Pure indirect[e]	1.1 (1.1, 1.2)	7.2 (−0.87, 15.3)	
Total	2.6 (1.0, 4.2)	100	---

[a] All effects are adjusted for baseline confounders: age, race (White and non-White), smoking, marital status, employment.

[b] Neither mediation nor interaction (MS→cognition)

[c] Interaction only (MS*symptomatic sleepiness)

[d] Both interaction and mediation (MS*symptomatic sleepiness and MS→ symptomatic sleepiness→cognition)

[e] Mediation only (MS→ symptomatic sleepiness→cognition)

[f] Reflects the proportion due to interaction.

Table 6:

Adjusted[a] estimate for the 4 component effects of multiple sclerosis (vs. no multiple sclerosis) on the memory composite due to mediation and/or interaction with insomnia composite score[b] and known or suspected obstructive sleep apnea (OSA)[c] and symptomatic sleepiness: results of the 4-way decomposition method with linear regression

Component effect of multiple sclerosis	OR (95%CI)	Percentage of total effect (95% CI)	
Insomnia composite score[b]			
Controlled direct[d]	0.22 (0.12, 0.32)	90.0 (80.8, 99.1)	
Reference interaction[e]	0.0001 (−0.0004, 0.0006)	0.04 (−0.18, 0.27)	−5.1 (−12.5, 2.4)[h]
Mediated interaction[f]	−0.01 (−0.03, 0.005)	−5.1 (−12.6, 2.4)	
Pure indirect[g]	0.04 (0.02, 0.05)	15.1 (6.2, 24.0)	
Total	0.24 (0.14, 0.34)	100	---
Known or suspected obstructive sleep apnea[c]			
Controlled direct[d]	0.20 (0.09, 0.31)	84.5 (66.96, 102.2)	
Reference interaction[e]	0.04 (−0.0001, 0.07)	14.7 (−1.5, 30.8)	15.1 (−1.7, 31.8)[h]
Mediated interaction[f]	0.0009 (−0.007, 0.009)	0.38 (−3.0, 3.8)	
Pure indirect[g]	0.001 (−0.008, 0.01)	0.42 (−3.3, 4.1)	
Total	0.24 (0.14, 0.34)	100	---
Symptomatic sleepiness			
Controlled direct[d]	0.22 (0.11, 0.33)	92.9 (76.4, 109.4)	
Reference interaction[e]	−0.060 (−0.03, 0.01)	−2.7 (−10.8, 5.4)	−5.2 (−2.1, 10.5)[h]
Mediated interaction[f]	−0.060 (−0.02, 0.01)	−2.5 (−10.2, 5.2)	
Pure indirect[g]	0.029 (0.016, 0.042)	12.3 (5.1, 19.5)	
Total	0.24 (0.14, 0.34)	100	---

[a] All effects are adjusted for baseline confounders: age, race (White and non-White), smoking, marital status, employment.

[b] Summary score that included included positive answers from difficulty falling asleep, trouble with waking up during night, waking up too early, feeling sleepy during the day or evening, not feeling rested in the morning.

[c] Defined by either having a OSA diagnosis or high OSA risk by STOP-Bang score.

[d] Neither mediation nor interaction (MS→memory)

[e] Interaction only (MS*sleep variables)

[f] Both interaction and mediation (MS*sleep variables and MS→sleep variables→ memory)

[g] Mediation only (MS→sleep variables→ memory)

[h] Reflects the proportion due to interaction.