International Psychogeriatrics: page 1 of 14
doi:10.1017/S1041610224000590

The effect of study partner characteristics on the reporting of neuropsychiatric symptoms across the neurocognitive spectrum

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ABSTRACT

Objectives: We explored the influence of study partner (SP) characteristics on SP-reported neuropsychiatric symptoms (NPS) presence across the neurocognitive spectrum and on the prognostic utility of mild behavioral impairment (MBI).

Design, setting, and participants: We performed cross-sectional ($n = 26{,}748$) and longitudinal ($n = 12{,}794$) analyses using participant-SP dyad data from the National Alzheimer's Coordinating Center. Participants were cognitively normal (CN; $n = 11{,}951$) or had mild cognitive impairment (MCI; $n = 5686$) or dementia ($n = 9111$).

Measurements: SPs rated NPS using the Neuropsychiatric Inventory Questionnaire. We used multivariable logistic regression to model the association between SP characteristics (age, sex, and relationship to participant [spouse, child, and other]) and NPS status (outcome). Cox regressions assessed SP characteristics as moderators of MBI associations with incident dementia or as predictors of incident dementia in MBI + participants only.

Results: Among CN persons, younger, female, and spouse SPs reported NPS more frequently. In MCI, younger SPs and those who were spouses or children of participants reported higher NPS odds. For dementia participants, NPS odds were higher in female and spouse SPs. MBI associations with incident dementia were slightly weaker when SPs were older but did not depend on SP sex or relationship to participant. Among MBI + participants with spouse or child SPs, hazard for dementia was higher when compared to MBI + participants with other SPs.

Conclusions: SP age, sex, and relationship to participant influence NPS reporting across the neurocognitive spectrum, with potential implications for MBI prognosis. Considering SP characteristics may enhance the accuracy of NPS assessments, which may facilitate therapy planning and prognosis.

Key words: neuropsychiatric symptoms, mild behavioral impairment, informant, study partner, dementia

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Received 10 Feb 2024; revision requested 10 Apr 2024; revised version received 05 Apr 2024; accepted 14 Apr 2024.
Dylan X. Guan and Dinithi Mudalige have equal contribution to the writing of this manuscript.

Introduction

Neuropsychiatric symptoms (NPS), such as apathy, depression, anxiety, agitation, aggression, social disinhibition, and psychosis, are prevalent in over 80% of older persons living with dementia (Lyketsos

et al., 2002). These symptoms are linked to diminished quality of life, greater functional decline, financial burden, caregiver distress, and elevated rates of institutionalization and mortality (Gonzalez-Salvador *et al.*, 2000; Murman *et al.*, 2002; Peters *et al.*, 2015; Sheikh *et al.*, 2018; Steele *et al.*, 1990). NPS can also emerge in advance of severe cognitive and functional impairment, with the onset of mild behavioral impairment (MBI) in older persons serving as an indicator of elevated dementia risk (Creese and Ismail, 2022; Ismail *et al.*, 2016). MBI, characterized by later-life emergent and persistent NPS, has been observed in 37% of subjective cognitive decline and 54% of mild cognitive impairment (MCI) memory clinic patients (Hu *et al.*, 2023). MBI is linked to poorer cognition and accelerated cognitive decline (Creese *et al.*, 2019; Kassam *et al.*, 2023), a lower rate of reversion from MCI to normal cognition (McGirr *et al.*, 2022), and higher dementia risk (Ismail *et al.*, 2021; Kan *et al.*, 2022; Rouse *et al.*, 2024; Ruthirakuhan *et al.*, 2022). Additionally, MBI is associated with several fluid and imaging biomarkers of neurodegeneration, including amyloid-β, tau, neurofilament light, white matter hyperintensities, medial temporal lobe atrophy, and changes in functional connectivity (Creese *et al.*, 2021; Ghahremani *et al.*, 2023a; Gill *et al.*, 2021; Ismail *et al.*, 2023; Johansson *et al.*, 2021; Lussier *et al.*, 2020; Matuskova *et al.*, 2021; Miao *et al.*, 2022; Miao *et al.*, 2021; Naude *et al.*, 2020). Greater impairments in gait, hearing, and frailty have also been observed in older persons with MBI (Gosselin *et al.*, 2022; Gosselin *et al.*, 2023; Guan *et al.*, 2022a; Guan *et al.*, 2022b). Together, these findings underscore the importance of addressing NPS as a therapeutic target and as a disease marker, which requires accurate detection and assessment of NPS in older adults across the neurocognitive spectrum (Soto *et al.*, 2024).

Study partners (SPs), or informants, are essential for detecting and assessing NPS in older persons. The Neuropsychiatric Inventory (NPI) was designed to be completed by an informed caregiver (Cummings, 2020), and the Mild Behavioral Impairment Checklist (MBI-C) was developed primarily with SP input in mind (Ismail *et al.*, 2017). In many cases, SP insight complements, or even substitutes, self-reported data, especially when cognitive decline may compromise participant insight into their own symptoms (anosognosia) (Cacciamani *et al.*, 2021). Moreover, SPs play a critical role in facilitating study enrollment and engagement by participating in the informed consent process, ensuring adherence to study protocols, and providing critical information about several cognitive, behavioral, and functional outcomes (Largent *et al.*, 2018; Watson *et al.*, 2014).

Several investigations indicate that the reliability of SP-reported information can vary depending on the characteristics of the SP. Spouses, for instances, have been reported to more accurately provide information about participant cognitive performance than other SPs (Cacchione *et al.*, 2003; Ready *et al.*, 2004). Another study found that spouse SPs rated participants as more impaired in several cognitive domains than SPs who were the participants' children (Stites *et al.*, 2022). In some cases, SPs have also been shown to predict cognitive trajectories with greater accuracy than participants themselves (Nuño *et al.*, 2019). While these findings highlight the influence of SP characteristics on cognitive assessments, the relationship between SP characteristics and behavioral assessments in older persons across the neurocognitive spectrum still needs to be explored.

This study had two primary objectives. Our first objective was to investigate the effect of SP attributes – specifically their age, sex, and relationship to the participant – on the probability of SP-reported NPS. Our second objective was to explore the influence of SP characteristics on the prognostic ability of MBI. We addressed the second objective in two ways: first, by examining if SP attributes moderated the relationship between MBI and subsequent dementia, and second, by assessing how the hazard of dementia among participants with MBI differed according to the attributes of the SP who reported the MBI. The latter approach differed from the former by focusing on the impact of SP characteristics among participants with MBI only, rather than comparing participants with MBI to those without MBI.

Methods

Study design

Data for this study were obtained from the National Alzheimer's Coordinating Center Uniform Dataset (NACC-UDS), which consisted of data gathered from 45 Alzheimer's Disease Research Centers (ADRCs) funded by the National Institute on Aging in the United States. These ADRCs recruited participants, both with and without dementia, who were evaluated approximately annually between 2005 and 2022 using standardized data collection forms, including those for participant demographic, neurological examination, and cognitive information. At each ADRC, informed consent was obtained from participants and ethics approval was obtained from their local institutions before data were submitted to National Alzheimer's Coordinating Center (NACC). NACC recruitment and data collection procedures can be found elsewhere (Beekly *et al.*, 2004; Besser *et al.*, 2018; Morris *et al.*, 2006).

https://doi.org/10.1017/S1041610224000590 Published online by Cambridge University Press

Participants

The NACC-UDS for the May 2022 data release contains longitudinal data for 45,100 participants. Participants <50 years of age at baseline ($n = 1069$) or who had psychiatric and neurological conditions that precluded MBI diagnosis ($n = 14{,}556$) were excluded from the study. The excluded psychiatric/neurological conditions included post-traumatic stress disorder, bipolar disorder, schizophrenia, obsessive-compulsive disorder, remote history of anxiety or depression, Down syndrome, and Huntington's disease.(McGirr *et al.*, 2022) In addition, participants who were missing data on relevant demographic ($n = 244$), Neuropsychiatric Inventory Questionnaire (NPI-Q; $n = 991$), or SP characteristics ($n = 1492$) were excluded. The final sample consisted of 26,748 participants, including 11,951 CN participants, 5686 participants with MCI, and 9111 with dementia, as illustrated in Figure 1. As the second study objective was analyzed incident dementia as the outcome, the 9111 participants with dementia at baseline and 4843 participants without follow-up data were excluded from the longitudinal analysis.

Measures

NPS were assessed using the NPI-Q (Cummings, 2020), which asks SPs to report on the presence of NPS over the previous month based on 12 items that cover different NPS domains. These items include apathy, depression, anxiety, elation, agitation, irritability, aberrant motor behavior, social inappropriateness, disinhibition, delusions, hallucinations, sleep behavior, and appetite. If NPS were reported as present (i.e., endorsed by SPs), then SPs were asked to rate the severity of the NPS on a scale from 1 to 3, with higher scores indicating greater severity.

For this study, NPS were grouped into seven domains: apathy, mood/anxiety (depression, anxiety, elation), agitation/aggression (agitation, irritability, aberrant motor behavior), social disinhibition, and psychosis (hallucinations, delusions), sleep, and appetite. A cumulative severity score of ≥ 1 indicated the presence of an NPS domain. NPS were considered persistent if they were present for two consecutive study visits, which enabled operationalization of the MBI symptom persistence criterion in dementia-free participants (Guan *et al.*, 2023; McGirr *et al.*, 2022). This persistence criterion was also applied to dementia participants to enable meaningful comparisons across cognitive groups (CN, MCI, and dementia) by ensuring that differences in NPS prevalence and SP effects on NPS reporting could not be attributed to differences in how NPS status was operationalized.

Data on SP age, sex, and relationship to participant, which were identified *a priori* as SP attributes of interest based on existing literature, were analyzed in this study (Cacchione *et al.*, 2003; Ready *et al.*, 2004; Stites *et al.*, 2022). SP relationships were categorized into three groups: spouse, child, and other. The other SP category included less frequently observed relationships, including siblings, other relatives, friends, paid caregivers, and health care providers.

Statistical analysis

The demographic and clinical characteristics of both participants and their SPs were summarized with descriptive statistics, including means, standard deviations (SDs), ranges, and percentages. To compare the characteristics of included participant-SP dyads versus those excluded for missing NPI-Q or relevant SP data, we employed independent samples t-tests for continuous variables or chi-square tests for categorical variables. Bootstrapping was used to generate 95% confidence intervals (CIs) for each NPS prevalence estimate.

The first study objective was addressed by modeling cross-sectional associations between SP characteristics (i.e., SP age, sex, and relationship to participant; exposure) and SP endorsement of participant NPS (outcome) using logistic regression. These analyses were conducted separately for the CN, MCI, and dementia groups. Neurovegetative symptoms were not assessed for MBI-related analysis, as they are not included in the MBI construct (Ismail *et al.*, 2016). To assess whether the effect of SP sex on NPS endorsement varied based on their relationship to the participant, we subsequently included an SP sex-relationship multiplicative interaction term, in addition to the main effects, to the logistic regression models. All cross-sectional models controlled for participant age, sex, and education, to ensure that any observed SP associations with NPS could not be explained by correlated participant demographics.

The second study objective was addressed using two models. Consistent with the cross-sectional analyses, SP attributes of interest were SP age, sex, and relationship to participant. First, we used a Cox proportional hazards regression model incorporating MBI × SP characteristic interaction terms to investigate if the relationship between MBI and incident dementia depended on SP characteristics. This model included all participants who were dementia-free at baseline (CN and MCI; $n = 12{,}794$) with follow-up data, regardless of MBI status. It served to compare between MBI participants, with varying SPs, to those without MBI (e.g., if hazard for dementia was higher for spouse SPs compared

https://doi.org/10.1017/S1041610224000590 Published online by Cambridge University Press

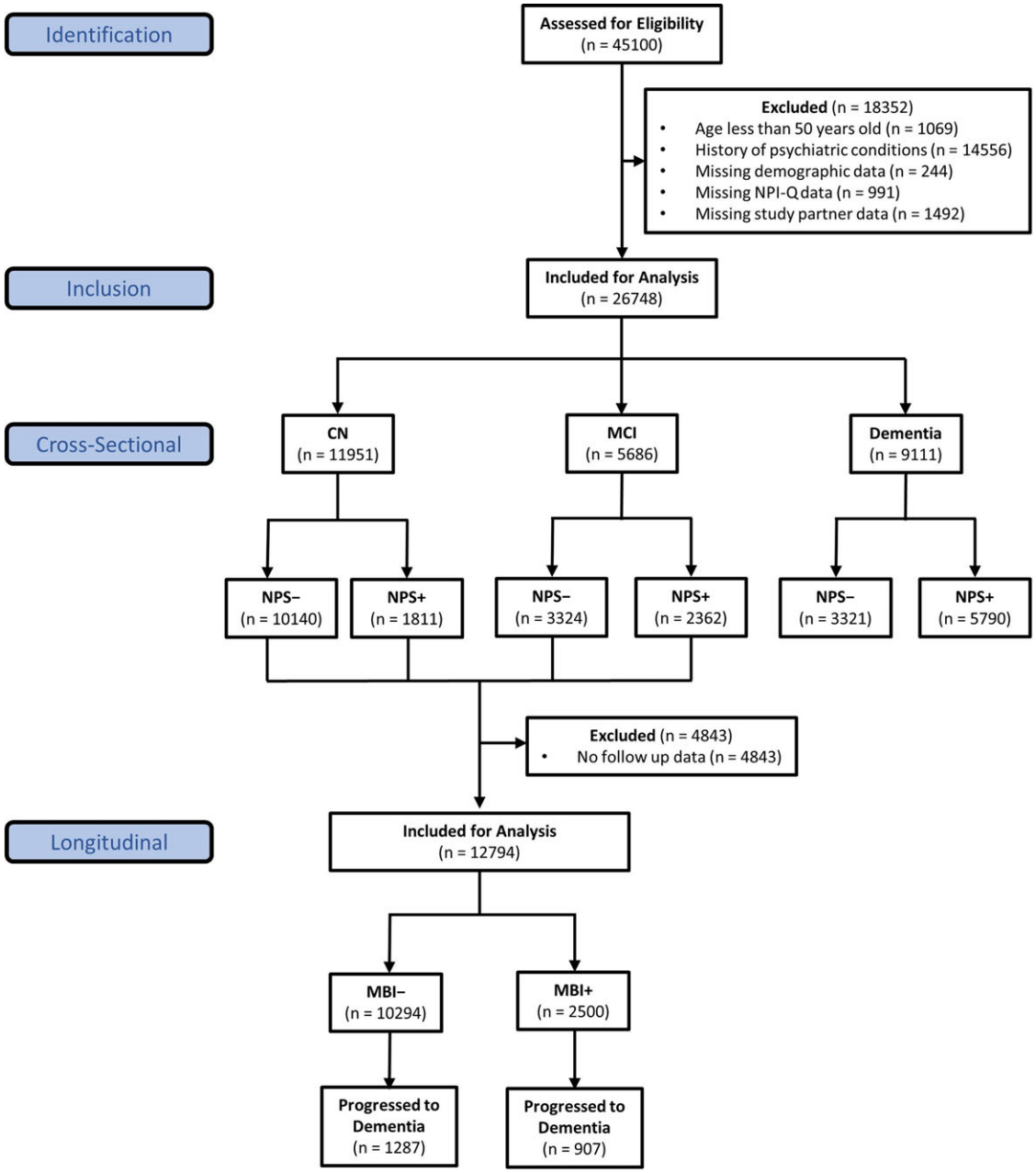

Figure 1. Participant flow diagram. Abbreviations: NPI-Q = Neuropsychiatric Inventory Questionnaire; MBI = mild behavioral impairment; NPS = neuropsychiatric symptoms; CN = cognitively normal; MCI = mild cognitive impairment.

to no MBI, and if this differed when MBI was reported by other SPs). Subsequently, a separate Cox proportional hazards regression model was applied to solely participants with MBI at baseline ($n = 2504$) to assess how SP characteristics influenced progression to dementia within this group (e.g., if hazard for dementia was higher for MBI reported by spouse SPs compared to MBI reported by other SPs).

For each Cox proportional hazards model, Schoenfeld and Martingale residuals were evaluated to ensure that the assumptions of proportional hazards or linearity were satisfied for each exposure variable, as appropriate. The Cox regression models controlled for participant age, sex, years of education, and baseline cognitive function (CN or MCI). As several statistical comparisons were performed ($k = 20$; 12 to investigate SP age, sex, spouse/child statuses associations with NPS odds; 8 to investigate SP age, sex, spouse/child interactions with MBI or as predictors of dementia in MBI), we adjusted the relevant p-values for multiple comparisons using the Benjamini-Hochberg procedure based on false discovery rate. The statistical significance threshold was set to $q < .05$. The correct p-values (i.e., q-values) are presented alongside the unadjusted

https://doi.org/10.1017/S1041610224000590 Published online by Cambridge University Press

p-values. All analyses were performed using R version 4.2.2.

Results

Sample characteristics

Baseline participant and SP characteristics stratified by cognitive diagnosis are summarized in Table 1. The full study cohort consisting of CN, MCI, and dementia participants (55.7% female) was on average 72.9 years old (SD = 9.3, range = 50–104) and had completed 15.1 years of education (SD = 3.4, range = 0–30). Forty-four percent of participants were classified as CN (44.7%; $n = 11{,}951$), 21.3% as MCI (n = 5686), and 34.0% as dementia ($n = 9111$). Participants excluded for missing NPI-Q or relevant SP data tended to be slightly older (74.8 vs 72.8 years), completed fewer years of education (14.5 vs 15.1 years), and were more likely to be diagnosed with dementia (36.2% vs 33.6%) than participants included for analysis (Table 2). Participants with longitudinal data had a mean follow-up time of 4.4 years (SD = 3.0, range = 0.4–15.5).

SPs (66.4% female) were 64.1 years old (SD = 13.4, range = 18–108) and were most often spouses (58.3%; of whom 59.9% were female) or children (24.1%; of whom 71.7% were female) of participants; other SPs (i.e., non-spouse and non-child; of whom 80.6% were female) made up the remaining 17.8% of SPs across the entire cohort. Male participants tended to have more female (90.4%) than male (9.6%) SPs, and more spouse (78.8%) than child (12.0%) SPs. Female participants tended to have a similar proportion of male (52.7%) and female (47.3%) SPs, as well as more spouse (41.8%) than child (33.6%) SPs.

Prevalence of NPS

Across the entire pooled cohort including CN, MCI, and dementia, we found that NPS meeting the persistence criterion were present in 37.2% of participants, with an average severity of 2.1 (SD = 3.4, range = 0–30). Agitation and aggression were the most commonly reported NPS (17.7%), followed by mood and anxiety (16.1%), apathy (8.6%), sleep (6.3%), appetite (4.5%), social disinhibition (3.9%), and psychosis (2.6%). Among CN participants, NPS were endorsed in 15.2%, and mood and anxiety symptoms were the most prevalent (5.6%), followed closely by agitation and aggression (5.2%). Sleep (2.6%), apathy (1.0%), appetite (0.8%), social disinhibition (0.6%) and psychosis (0.2%) were less common in CN participants. NPS were endorsed in 41.5% of MCI participants, with agitation and aggression being the most frequent (19.3%), followed by mood and anxiety (17.5%), sleep (7.2%), apathy (6.8%), appetite (3.8%), social disinhibition (3.3%), and psychosis (1.3%). Finally, the prevalence of NPS was greatest among participants with dementia (63.5%), with agitation and aggression being the most common (33.1%), followed by mood and anxiety (28.9%), apathy (19.6%), sleep (10.7%), appetite (9.9%), social disinhibition (8.7%), and psychosis (6.6%).

SP characteristics and SP endorsement of NPS

Table 3 summarizes the influence of SP characteristics on the odds of SP-endorsed NPS separately across CN, MCI, and dementia groups, all controlling for participant demographics. Among CN participants, the odds of SP-endorsed NPS were 14% lower (aOR = 0.86, 95%CI: 0.80–0.91, $p < 0.001$, $q < .001$) for every decade increase in SP age, 16% greater (aOR = 1.16, 95%CI: 1.02–1.32, $p = 0.02$, $q = .05$) when the SP was a female as opposed to a male, and 62% greater (aOR = 1.62, 95%CI: 1.39–1.89, $p < 0.001$, $q < .001$) when the SP was a spouse of the participant as opposed to Other SPs (i.e., non-spouse and non-child). However, the odds of endorsing participant NPS were not statistically different between SPs who were children of CN participants and Other SPs (aOR = 1.07, 95%CI: 0.88–1.31, $p = 0.51$, $q = .56$).

In MCI, SP age and relationship to participant were linked to NPS endorsement, but not SP sex. Specifically, the odds of SP-endorsed NPS were 9% lower (aOR = 0.90, 95%CI: 0.84–0.96, $p = 0.003$, $q = .01$) for every decade increase in SP age. Relative to other SPs, the odds of SP-endorsed NPS were 104% higher (aOR = 2.01, 95%CI: 1.66–2.42, $p < 0.001$, $q < .001$) for spouse SPs, and 40% higher (aOR = 1.40, 95%CI: 1.11–1.76, $p = 0.004$, $q = .01$) for child SPs. However, endorsement of NPS in MCI was comparable in female and male SPs (aOR = 0.96, 95%CI: 0.83–1.12, $p = 0.62$, $q = .62$).

Finally, only SP sex and SP relationship to participant were associated with SP-endorsed NPS in participants with dementia. Female SPs endorsed NPS with 18% greater odds (aOR = 1.18, 95%CI: 1.05–1.33, $p = 0.005$, $q = .02$) than male SPs, and spouse SPs endorsed NPS with 23% greater odds (aOR = 1.23, 95%CI: 1.02–1.47, $p = 0.03$, $q = .05$) than Other SPs. However, the odds of SP-endorsed NPS did not change significantly as a function of SP age (aOR = 0.98, 95%CI: 0.93–1.04, $p = 0.50$, $q = .56$), or if the SP was a child of the participant (aOR = 1.13, 95%CI: 0.94–1.36, $p = 0.18$, $q = .30$).

In each cognitive sample, we did not find that the effect of SP sex on the odds of SP-endorsed NPS

https://doi.org/10.1017/S1041610224000590 Published online by Cambridge University Press

Table 1. Participant and study partner characteristics stratified by participant cognitive status

VARIABLE	TOTAL	CN	MCI	DEMENTIA
n	26,748	11,951	5686	9111
Participant Age (years)	72.9 (9.3), 50–104	71.9 (9.0), 50–101	74.0 (8.7), 50–101	73.6 (9.9), 50–107
Participant Sex (female)	14,891 (55.7)	7488 (62.7)	2742 (48.2)	4661 (51.2)
Participant Education (years)	15.1 (3.4), 0–30	15.7 (3.1), 0–29	15.2 (3.4), 0–30	14.4 (3.7), 0–30
SP Age (years)	64.1 (13.4), 18–108	63.9 (13.7), 18–108	65.5 (13.2), 18–100	63.6 (13.1), 18–104
SP Sex (female)	17,759 (66.4)	7600 (63.6)	4016 (70.6)	6143 (67.4)
SP Relationship				
Spouse	15,600 (58.3)	6210 (51.9)	3542 (62.3)	5848 (64.2)
Child	6437 (24.1)	2745 (23.0)	1202 (21.1)	2490 (27.3)
Other	4711 (17.6)	2996 (25.1)	942 (16.6)	773 (8.5)
NPS Prevalence				
Any NPS	9963 (37.2)	1811 (15.2)	2362 (41.5)	5790 (63.5)
Apathy	2295 (8.6)	122 (1.0)	389 (6.8)	1784 (19.6)
Mood/Anxiety	4299 (16.1)	666 (5.6)	997 (17.5)	2636 (28.9)
Agitation/Aggression	4735 (17.7)	619 (5.2)	1097 (19.3)	3019 (33.1)
Social Disinhibition	1045 (3.9)	66 (0.6)	185 (3.3)	794 (8.7)
Psychosis	689 (2.6)	18 (0.2)	73 (1.3)	598 (6.6)
Sleep	1688 (6.3)	306 (2.6)	409 (7.2)	973 (10.7)
Appetite	1212 (4.5)	99 (0.8)	215 (3.8)	898 (9.9)
NPS Severity				
All NPS	2.1 (3.4), 0–30	0.6 (1.5), 0–22	1.7 (2.6), 0–23	4.4 (4.2), 0–30
Apathy	0.3 (0.7), 0–3	0.1 (0.3), 0–3	0.2 (0.6), 0–3	0.8 (1.0), 0–3
Mood/Anxiety	0.6 (1.2), 0–9	0.2 (0.7), 0–8	0.6 (1.1), 0–7	1.2 (1.4), 0–9
Agitation/Aggression	0.8 (1.5), 0–9	0.2 (0.7), 0–9	0.7 (1.2), 0–9	1.6 (1.9), 0–9
Social Disinhibition	0.2 (0.5), 0–3	0.0 (0.2), 0–3	0.1 (0.4), 0–3	0.4 (0.8), 0–3
Psychosis	0.2 (0.6), 0–6	0.0 (0.2), 0–6	0.1 (0.4), 0–6	0.4 (1.0), 0–6
Sleep	0.3 (0.7), 0–3	0.1 (0.4), 0–3	0.3 (0.7), 0–3	0.5 (0.9), 0–3
Appetite	0.2 (0.6), 0–3	0.1 (0.3), 0–3	0.2 (0.5), 0–3	0.5 (0.8), 0–3

Note. All values have been rounded to one decimal place as appropriate, except for p-values which have been rounded to three decimal places. Continuous variables are shown in mean (standard deviation), range. Categorical variables are shown in n (%). Study partners with a relationship to participant designated as "other" included siblings, other relatives, friends, neighbors, caregivers, or healthcare providers. Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; NPS, neuropsychiatric symptoms.

Table 2. Demographic comparison between included participants and participants excluded for missing NPI-Q or relevant study partner data

VARIABLE	TOTAL	INCLUDED	MISSING	*P*
n	29,231	26,748	2483	
Participant Age (years)	72.9 (9.3), 50–106	72.8 (9.3), 50–104	74.8 (10.0), 50-106	< 0.001
Participant Sex (female)	16,289 (55.7)	14,891 (55.7)	1398 (56.3)	0.55
Participant Education (years)	15.1 (3.5), 0–30	15.1 (3.4), 0–30	14.5 (3.9), 0–26	< 0.001
Diagnosis				0.007
CN	13,056 (44.7)	11,997 (44.9)	1059 (42.7)	
MCI	6281 (21.5)	5755 (21.5)	526 (21.2)	
Dementia	9894 (33.8)	8996 (33.6)	898 (36.2)	

Note. Relevant SP data consisted of SP age, sex, and relationship to participant. All values have been rounded to one decimal place as appropriate, except for p-values which have been rounded to three decimal places. Continuous variables are shown in mean (standard deviation), range. Categorical variables are shown in n (). Comparisons between included participants and participants excluded for missing NPI-Q or SP data were tested using independent samples t-tests or Mann-Whitney U tests for continuous variables and chi-square or Fisher's exact test for categorical variables, as appropriate. Abbreviations: SP, study partner; NPI-Q, Neuropsychiatric Inventory Questionnaire; CN, cognitively normal; MCI, mild cognitive impairment; NPS, neuropsychiatric symptoms.

https://doi.org/10.1017/S1041610224000590 Published online by Cambridge University Press

Table 3. Associations between study partner characteristics and study partner endorsement of NPS or incident

MODEL SAMPLE PREDICTOR	OUTCOME	*N*	EFFECT SIZE	95% CI	*P*/*Q*
Cross-Sectional Logistic Regression	SP-reported NPS		**aOR**		
CN		11,951			
SP Age			0.86	0.80–0.91	<.001/ <.001
SP Sex (Female)			1.16	1.02–1.32	.02/.05
SP Relationship (Spouse)			1.62	1.39–1.89	<.001/ <.001
SP Relationship (Child)			1.07	0.88–1.31	.51/.56
MCI		5686			
SP Age			0.90	0.84–0.96	.003/.01
SP Sex (Female)			0.96	0.83–1.12	.62/.62
SP Relationship (Spouse)			2.01	1.68–2.42	<.001/ <.001
SP Relationship (Child)			1.40	1.11–1.76	.004/.01
Dementia		9111			
SP Age			0.98	0.93–1.04	.50/.56
SP Sex (Female)			1.18	1.05–1.33	.005/.02
SP Relationship (Spouse)			1.23	1.02–1.47	.03/.05
SP Relationship (Child)			1.13	0.94–1.36	.18/.30
Longitudinal Cox Regression	Incident dementia		**aHR**		
CN/MCI with or without MBI		12,794			
MBI × SP Age			0.92	0.86–0.98	.01/.03
MBI × SP Sex (Female)			0.89	0.74–1.07	.21/.32
MBI × SP Relationship (Spouse)			0.88	0.67–1.17	.38/.50
MBI × SP Relationship (Child)			0.90	0.66–1.24	.53/.56
CN/MCI with MBI		2504			
SP Age			0.96	0.87–1.06	.40/.50
SP Sex (Female)			0.92	0.76–1.10	.37/.50
SP Relationship (Spouse)			1.70	1.28–2.27	<.001/.001
SP Relationship (Child)			1.51	1.08–2.12	.02/.04

Note. The outcome variable for the cross-sectional logistic regression models is whether SPs endorsed participant NPS, and its coefficients are in adjusted odds ratios (aOR). The outcome variable for the longitudinal Cox regression model incident dementia, and its coefficients are in adjusted hazards ratios (aHR). SP age was coded so that each coefficient corresponds to the change in aOR or aHR per decade increase in SP age. The reference group for SP sex was male sex. The reference group for SP relationship were those who were not a spouse and not a child of the participant. q-values indicate p-values that have been corrected for multiple comparisons using the Benjamini-Hochberg procedure based on false discovery rate. Abbreviations: SP, study partner; NPS, neuropsychiatric symptoms; MBI, mild behavioral impairment; 95% CI, 95 confidence interval; FDR, false rate discovery.

depended on SP relationship to participants (CN $p = 0.57$, MCI $p = 0.42$, dementia $p = .54$). Although Figure 2 shows a potential interaction between SP sex and relationship to participant in the MCI group, this moderation effect was eliminated when controlling for participant sex.

SP characteristics and MBI associations with incident dementia

In the sample of 12,794 participants without dementia at baseline, the association between MBI and incident dementia (aHR = 2.41, 95%CI: 2.21–2.64, $p < .001$) was found to depend on SP age: for every decade increase in SP age, the MBI aHR for incident dementia was 0.08 lower (aHR = 0.92, 95%CI: 0.86–0.98, $p = 0.01$, $q = .03$). In contrast, SP sex (aHR = 0.89, 95%CI: 0.74–1.07, $p = 0.21$, $q = .32$), spouse SP status (aHR = 0.88, 95%CI: 0.67–1.17, $p = 0.38$, $q = .50$), and child SP status (aHR = 0.90, 95%CI: 0.66–1.24, $p = 0.53$, $q = .56$) did not moderate the association between MBI and incident dementia. The vast majority of dementia cases ($n = 2297$ events) were attributed to Alzheimer's disease (82.5%), 4.8% to frontotemporal lobar degeneration, 3.0% to Lewy body disease, and 10.0% to other causes recorded in the NACC-UDS.

Among MBI participants only, progression to dementia was found to be higher for some participants when MBI was reported by certain SP attributes. Specifically, when MBI was endorsed by a spouse SP, these participants developed dementia at a rate 70% (aHR = 1.70, 95%CI:

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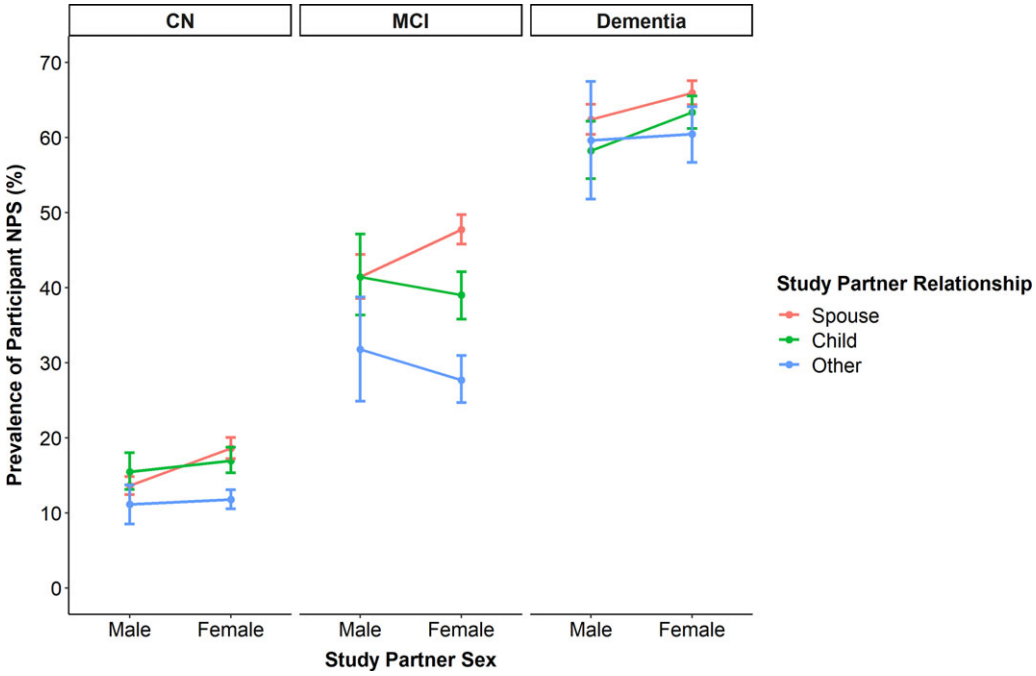

Figure 2. Prevalence of study partner endorsed neuropsychiatric symptoms stratified by study partner characteristics and participant cognitive status. Vertical error bars represent bootstrapped 95% confidence intervals for each prevalence estimate. Abbreviations: CN = cognitively normal; MCI = mild cognitive impairment.

1.28–2.27, $p < 0.001$, $q = .001$) higher than those with MBI that was endorsed by other SPs. A similar direction and magnitude of effect was observed in participants whose MBI was endorsed by child SPs (aHR = 1.51, 95%CI: 1.08–2.12, $p = 0.02$, $q = .04$). The rate of MBI participants developing dementia did not change as a function of whether MBI was endorsed by older SPs (aHR = 0.96, 95%CI: 0.87–1.06, $p = 0.40$, $q = .50$) or female SPs (aHR = 0.92, 95%CI: 0.76–1.10, $p = 0.37$, $q = .50$). Furthermore, none of the relationships between SP relationship to participant, age, or sex and incident dementia in MBI participants were moderated by baseline cognitive status (i.e., whether participants were CN or MCI; all $p > .20$)

Discussion

Our study revealed that several SP characteristics were associated with a change in the odds of SP-endorsed NPS across the neurocognitive spectrum. In CN participants, younger, female, and spouse SPs were all more likely to endorse participant NPS compared to other SPs. This pattern was similar in MCI, where younger, spouse, and child SPs all endorsed NPS with greater odds than their counterparts, except for female SPs who endorsed NPS similarly to male SPs. In dementia participants, the most cognitively impaired group, only female and spouse SPs had greater odds of SP-endorsed NPS. Generally, the effects of SP age, sex, and relationship to participant on the odds of SP-endorsed NPS were weakest in the dementia group compared to the CN and MCI groups. Across all cognitive groups, we did not find that the effects of SP sex depended on SP relationship to participant.

Among dementia-free participants at baseline, MBI associations with incident dementia were slightly weaker when identified by older SPs, but otherwise did not depend on SP sex or relationship to participant. However, MBI participants with spouse and child SPs progressed to dementia more rapidly than MBI participants with other SPs. Together, these findings suggest that SP characteristics influence the reporting of NPS across the neurocognitive spectrum. Yet, MBI remains a robust indicator of elevated dementia risk when compared to older persons without MBI, regardless of SP attributes. Nevertheless, persons with MBI may be further stratified into risk groups based on whether their MBI was identified by a spouse or child SP.

Our findings are novel in that they demonstrate several effects of SP characteristics on the SP-endorsed participant NPS, though they are still generally consistent with patterns observed within the existing literature on cognitive and functional outcomes, particularly regarding SP relationship to participants. When assessing the memory, judgment, and organizational skills of 730 older

https://doi.org/10.1017/S1041610224000590 Published online by Cambridge University Press

adult participants ranging from CN to dementia, spouse SPs tended to indicate greater participant cognitive impairment than non-spouse SPs including, but not limited to, children of participants (Stites *et al.*, 2022). In another study of 4284 older adult participants with MCI, SPs who were spouses or children of the participant rated participants as being more functionally impaired on average than other SPs (Hackett *et al.*, 2020). Together with our findings, these studies suggest that SPs who are spouses of participants tend to report greater cognitive, functional, and behavioral impairment compared to non-spouses across the neurocognitive spectrum (CN, MCI, and dementia).

Whether spouse and child SPs are overestimating NPS or, alternatively, providing more accurate assessments of NPS still needs to be fully understood. However, early observations in this line of research suggest that spouse and child SPs are more sensitive to objective changes in cognition and behavior than other SPs. For example, SPs who were spouses or children of participants and cohabitated with them generally reported information about the cognitive abilities of participants that was more consistent with neuropsychological test performance (Cacchione *et al.*, 2003; Ready *et al.*, 2004). A more recent study also reported that SP-reported cognitive decline and objective measures of participant cognition were more concordant when the SP was a spouse of the participant and had known the participant for longer (Nosheny *et al.*, 2018). Indeed, SPs who interact more frequently with participants and over a longer period of time, as in the case of spouse or child SPs, may be best suited to detect changes in participant behavior that represent differences from longstanding patterns. This pattern may be the case, especially in populations of older adults without dementia, where changes in behavior that suggest MBI tend to be more subtle. Our longitudinal findings support this hypothesis, as older adults with MBI that was endorsed by spouse or child SPs progressed to dementia at higher rates than older adults with MBI that was endorsed by SPs who were neither spouses nor children of participants. In addition, we found the effect of SP relationship to participant on the odds of SP-endorsed NPS to be weakest in dementia participants, likely because NPS tend to be more frequent and severe, and therefore generally easier to detect and recognize at more advanced stages of cognitive and functional impairment regardless of SP characteristics.

How other SP characteristics beyond relationship to participant, such as SP sex or age, affect SP-reported cognitive, behavioral, and functional outcomes has been explored less extensively. In one study of MCI participants, SP sex had no impact on SP ratings of functional impairment (Hackett *et al.*, 2020), consistent with our finding that SP sex had no effect on SP-endorsed NPS in MCI. However, we did find SP sex effects in CN and dementia, with female SPs having greater odds of endorsing participant NPS than male SPs in both cognitive groups, which suggests that SP sex effects may vary according to the baseline cognitive status of participants. These findings on SP sex and SP-endorsed NPS provide some insight into previously observed sex differences in the prevalence of NPS across the neurocognitive spectrum. That is, in older adults without dementia, MBI symptoms tend to be more prevalent in male than in female participants (Guan *et al.*, 2022a; Wolfova *et al.*, 2022), possibly because male participants tend to have spouse SPs who are female and more likely to endorse participant NPS. However, this hypothesis does conflict with observations of NPS prevalence in populations of older adults with dementia, who are more cognitively and functionally impaired than pre-dementia populations, where NPS are generally more prevalent in female than in male participants (Eikelboom *et al.*, 2021). Although more research is needed, one explanation for this contradiction is that as female participants get older, they are less likely to have male spouse SPs, thereby reducing the effect of SP sex on the overall reported prevalence of NPS in females with dementia. It is also likely that SP characteristics only contribute partially to, and therefore cannot fully explain, sex differences in NPS prevalence across the neurocognitive spectrum.

The mechanism by which SP sex impacts the likelihood of SPs to detect and report on participant NPS is poorly understood and should be the target of future investigations. It is possible that the effect of SP sex on SP endorsement of NPS may arise from sociocultural differences and may be more strongly attributed to differences in factors pertaining to gender than biology. Studies investigating how SP endorsements vary by SP gender, rather than sex, are therefore needed. A similar mechanism may underlie our findings surrounding the effect of SP age on SP-endorsed NPS, where the odds of endorsing participant NPS generally declined as participants got older. This may reflect a generational gap, where younger populations are more aware of, and sensitive to, changes related to mental health in others, compared to older populations. If sociocultural differences underlie the effects of SP sex and age on the SP endorsement of NPS, future studies should also investigate the effect of SP ethnocultural groups among a diverse cohort of participants. A recent study showed that Black/African American SPs generally rated participants as less functionally impaired when compared to SPs from other racial/ethnic backgrounds (Hackett *et al.*,

https://doi.org/10.1017/S1041610224000590 Published online by Cambridge University Press

2020). Still, the effect of SP ethnicity on reports of NPS has yet to be extensively explored.

An investigation comparing spousal and child SPs assessments of NPS to self-reported measures is warranted. The emergence of novel tools for evaluating NPS, such as the MBI-C (Ismail *et al.*, 2017), which has also been validated for self-administration (Creese *et al.*, 2020), allows for this type of analysis. Furthermore, suggestions to remove SP requirements for study participation have been raised, given that the disadvantages of enrolling dyads may outweigh the advantages in preclinical and prodromal ADRD stages (Grill *et al.*, 2016; Largent *et al.*, 2018). Preliminary evidence in apathy shows that CN older adults tended to report more severe apathy compared to reports by SPs and clinicians, but MCI older adults tended to report less severe apathy (Guercio *et al.*, 2015). Furthermore, there have been several studies that have highlighted differences in participant and SP reports of cognitive decline across the ADRD continuum (Amariglio *et al.*, 2015; Nuño *et al.*, 2019; Ryan *et al.*, 2019; Truong *et al.*, 2022; Vannini *et al.*, 2017). During preclinical stages of ADRD (i.e., CN), participant-reported subjective cognitive complaints appear to better predict incident cognitive decline relative to SP reports (Nosheny *et al.*, 2019; Nuño *et al.*, 2019). However, at later stages of the ADRD continuum, such as in MCI, SP reports of participant cognition grow increasingly more valuable and correlate more strongly with incident cognitive decline and biomarker burden than participant self-reports (Munro *et al.*, 2021; Nosheny *et al.*, 2022). Whether these differences in self- and SP-report also exist for NPS as an outcome should be the target of future investigations.

Two primary implications for clinical and research practice can be derived from our study. First, because NPS remain a high-priority therapeutic target, clinical trials for NPS interventions may benefit from enrolling SPs that are most likely to provide accurate and reliable information regarding behavioral outcome measures. Our study suggests that SPs who are spouses or children of participants may be desirable for these purposes. Second, the identification of older adults at risk of ADRD is necessary to facilitate the study and targeted administration of disease-modifying or preventative treatments. A growing body of evidence suggests that identifying older adults with MBI is an effective method to enrich samples for biomarker positivity for AD clinical trials (Ghahremani *et al.*, 2023b; Ismail *et al.*, 2023), improving screening efficiency for early-stage disease, allowing earlier administration of potential therapies (Creese and Ismail, 2022; McGirr *et al.*, 2022). MBI, within research contexts, may provide the greatest utility as a dementia marker when it is detected by spouse or child SPs. Although SP-rated instruments for measuring NPS, as well as cognition and function, are common in research settings, these tools also may have utility in routine clinical care (Choudhury *et al.*, 2022).

This study possesses a number of strengths. Several observed effects were not only statistically significant even after adjusting for multiple comparisons, in part due to the considerable statistical power of our study, but also had clinically significant effect sizes. For instance, the odds of endorsing participant NPS was more than twice as high when the SP was a spouse of participants with MCI compared to a non-spouse, and there was a 62% increase in the hazard of MBI participants developing dementia when MBI was endorsed by a spouse, even after adjusting for other SP and participant characteristics. Furthermore, our study evaluated several different SP characteristics, as well as the interaction between SP sex and SP spousal status, allowing for a more complete understanding of the effect of SP characteristics on the reporting of participant NPS. However, this study also possesses some limitations. The NPI-Q was used to measure NPS in our study consisting of CN, MCI, and dementia participants, but it was initially designed for use and validated only in ADRD (Cummings, 2020). Furthermore, we did not study the effect of informant characteristics on the severity of participant NPS, only its presence or absence. This may be the target of future studies aiming to inform ADRD clinical trials that use SP-reported quantitative measures of NPS severity as an outcome. Finally, we only assessed the relationship between global NPS status and all-cause dementia. There may be specific associations between certain NPS and dementia subtypes that may be influenced differently by study partner characteristics, which warrants additional research.

Conclusion

NPS are prevalent and act as both priority therapeutic targets and markers of dementia across the ADRD continuum. SPs play a vital role in the assessment of NPS, which is typically performed through SP-rated instruments. We demonstrate that SP age, sex, and relationship to participant (spouse, child, or other) are associated with the odds of reporting NPS across the neurocognitive spectrum. Furthermore, we reveal that the prognostic value of MBI is largely independent of SP attributes, although persons with MBI may be at greater risk for dementia when MBI is identified by spouse or child SPs compared to other SPs.

https://doi.org/10.1017/S1041610224000590 Published online by Cambridge University Press

Conflicts of interest

The authors declare that there are no conflicts of interest.

Description of author(s)' roles

D. X. Guan and Z. Ismail formulated the research questions. D. X. Guan planned and carried out the statistical analysis and wrote and revised the manuscript. D. Mudalige wrote and revised the manuscript. Z. Ismail, R. Nosheny, C. E. Munro, and E. E. Smith revised the manuscript.

Acknowledgements

DXG is supported by the Hotchkiss Brain Institute, Killam Trust, and Alzheimer Society of Canada. ZI is supported by the Canadian Institutes of Health Research (BCA2633) and the UK National Institute for Health and Care Research Exeter Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADCs: P50 AG005131 (PI James Brewer, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG005138 (PI Mary Sano, PhD), P50 AG005142 (PI Helena Chui, MD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005681 (PI John Morris, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG008051 (PI Thomas Wisniewski, MD), P50 AG008702 (PI Scott Small, MD), P30 AG010124 (PI John Trojanowski, MD, PhD), P30 AG010129 (PI Charles DeCarli, MD), P30 AG010133 (PI Andrew Saykin, PsyD), P30 AG010161 (PI David Bennett, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG013846 (PI Neil Kowall, MD), P30 AG013854 (PI Robert Vassar, PhD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P30 AG019610 (PI Eric Reiman, MD), P50 AG023501 (PI Bruce Miller, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P30 AG028383 (PI Linda Van Eldik, PhD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P30 AG035982 (PI Russell Swerdlow, MD), P50 AG047266 (PI Todd Golde, MD, PhD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG049638 (PI Suzanne Craft, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD), P20 AG068024 (PI Erik Roberson, MD, PhD), P20 AG068053 (PI Marwan Sabbagh, MD), P20 AG068077 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), P30 AG072959 (PI James Leverenz, MD). NACC funding sources were not involved in the formulation of the research question, in the analysis and interpretation of the data, in the writing of the report, or in the decision to submit the article for publication.

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https://doi.org/10.1017/S1041610224000590 Published online by Cambridge University Press

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