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Neuropsychiatric Symptoms and Incident Cognitive Decline and Dementia in Cognitively Normal Older Adults: A Systematic Review and Meta-Analysis

Elbayoumi, Heba

UNIVERSITY OF CALGARY

Neuropsychiatric Symptoms and Incident Cognitive Decline and Dementia in Cognitively Normal Older Adults: A Systematic Review and Meta-Analysis

by

Heba Elbayoumi

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Abstract

Objective: To determine risks of cognitive decline or dementia in cognitively normal cohorts with neuropsychiatric symptoms (NPS), stratified by mild behavioral impairment (MBI) domains.

Methods: A systematic search (MEDLINE, EMBASE, and PSYCINFO) was completed up to January 2022. Pooled hazard ratios (HR) with Standard Error (SE), I^2, and tau^2 were determined utilizing DerSimonian-Laird random-effects models. Heterogeneity and publication bias were investigated. PRISMA and MOOSE checklists were followed.

Results: Of 12,674 screened abstracts, 36 prospective studies representing 326,739 participants were included. Risks (HR) for incident cognitive decline or dementia by MBI domain were: 1) apathy 2.00 (95%CI:1.57-2.57); 2) affect 1.61 (95%CI:1.45-1.80; adjusted 1.44, 95%CI:1.30-1.61); 3) agitation 3.07 (95%CI: 2.15-4.38); 4) social inappropriateness 3.84 (95%CI:1.54-9.55); and 5) psychosis 3.99 (95%CI:3.05-5.23). Heterogeneity was most evident in affect (I^2=86.56%, tau^2=0.04), with time and NPS ascertainment as the main contributors.

Conclusion: Cognitively normal older adults with NPS are at greater risk for mild cognitive impairment and dementia than those without NPS. Risks differ between the 5 MBI domains.

Preface

This thesis includes one manuscript. The manuscript will be submitted for publication; the journal is going to be the Neuroscience & Biobehavioral Reviews. The first author on the manuscript (HE) was responsible for the data analysis, interpreting the results and the writing of the manuscripts, with input and approval from the senior author and co-authors. All the authors participated in the review of the work. Permission from co-authors will be attained to include this manuscript in this thesis and, when possible, from the publisher.

Elbayoumi H, Patten S, Bulloch A, Pringsheim T M, Goodarzi Z, Ismail Z, Neuropsychiatric Symptoms and Incident Cognitive Decline and Dementia in Cognitively Normal Older Adults: A Systematic Review and Meta-Analysis.

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Dedication

At first, dedicating this work to Almighty ALLAH, without his mercy and sympathy we were not able to accomplish this work. To my parents, Wendy Mitchell, and my husband Khaled.

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Symbol Definition

AD	Alzheimer's disease
CADTH	Canadian Agency for Drugs and Technologies in Health
CANTAB	The Cambridge Neuropsychological Test Automated Battery
CI	Confidence Interval
CIND	Cognitive Impairment no Dementia
CSF	Cerebrospinal fluid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th edition
FDA	US Food and Drug Administration
FTD	Frontotemporal Dementia
GAD	Generalized Anxiety Disorder
HR	Hazard Ratio
ISTAART-AA	Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment
MBI	Mild Behavioral Impairment
MCI	Mild cognitive Impairment
MMSE	Mini-Mental State Exam
NC	Normal Cognition
NOS	Newcastle Ottawa Scale
NPI	Neuropsychiatric Inventory
NPS	Neuropsychiatric Symptoms
RR	Relative Risk
SCD	Subjective Cognitive Decline
SE	Standard Error
SMC	Subjective Memory Complaints
SR	Systematic review
SRMA	Systematic Review and Meta-analysis
STAART	International Society to Advance Alzheimer's Research and Treatment

Chapter One: Introduction

Overview and Objectives

This thesis evaluates the association between neuropsychiatric symptoms (NPS) in cognitively normal older adults, framed in the context of mild behavioural impairment (MBI), with incident cognitive decline and dementia. The thesis document contains a review of the background literature (Chapter 1), a manuscript ready for submission (Chapter 2), and a discussion of the results, most significant findings, and considerations for future research (Chapter 3).

1.1 Aims

This dissertation aimed to examine the association between NPS, incident cognitive decline and dementia in cognitively normal older adults. This overall aim was accomplished by: (1) conducting a systematic review of the literature; (2) quantifying the association between NPS and incident cognitive decline and dementia utilizing a meta-analysis; (3) critically examining the results of the meta-analysis and completing meta-regressions to explain heterogeneity; and (4) exploring the relevance and future directions for clinical care and research.

1.2 Dementia Background

Dementia is a worldwide public health concern, expected to affect 150 million people by 2050 (Nichols et al., 2022). According to recent data, more than 402,000 seniors aged 65 years and older are diagnosed with dementia in Canada. These data translate to a point prevalence of 7.1%. Two-thirds of Canadian seniors diagnosed with dementia are women (Canada.ca, 2017). The Canadian annual incidence rate is 14.3 new cases for every 1,000 persons aged 65 and older. This incidence rate means about 76,000 new Canadians receive a diagnosis of dementia every year (Canada.ca, 2017). Dementia is an important public health matter, affecting a person's

physical, psychological, social, and financial well-being. Dementia's impact also extends to families and society. As of 2016, according to the National Population Health Study of Neurological Conditions, the estimated monetary cost of dementia is 10.4 billion. That estimation includes the estimated costs to the Canadian healthcare system and out-of-pocket caregiver costs. This cost is estimated to rise to 16.6 billion by 2031with the current estimated incidence rates (Canada, 2016).

Clinically, dementia is a syndrome marked by an acquired and gradually progressive decline in cognition (e.g., short-term memory, executive function) and/or behaviour (e.g., mood, motivation, impulse control), which impairs function and independent living (Tang-Wai et al., 2020). Dementia profoundly impacts autonomy, self-care, and quality of life and is associated with institutional placement (Gauthier et al., 2021). An often-forgotten group affected by dementia are caregivers, who may suffer from burnout and stress from managing the cognitive, behavioural, and functional impairments experienced by their loved ones with dementia (Kim and Park, 2019).

Clinical diagnosis of dementia depends on fulfilling clinical criteria, the most common of which are the National Institute of Aging Alzheimer's Association (NIA-AA) criteria for dementia: 1) interference with the ability to work and/or function as per usual in daily activities; 2) evident decline in functioning or performance compared to previous levels; 3) changes are not due to delirium or other psychiatric disorders; 4) diagnosis of cognitive impairment is performed by two means: history taking from the patient or informant and an objective cognitive assessment tool; 5) cognitive or behavioural impairment involves at least two of the five following domains:

i) short term memory; ii) impaired reasoning and judgement, iii) impaired visuospatial abilities, iv) impaired language, v) changes in personality or behaviour (McKhann et al., 2011). The Diagnostic and Statistical Manual (DSM-5) also has criteria for dementia, classified as Major Neurocognitive Disorder: A) evidence of significant cognitive decline in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition); B) cognitive deficits interfere with independence in everyday activities; C) cognitive deficits do not occur exclusively in the context of a delirium; and D) not better explained by another mental disorder (APA, 2013). Other causes of dementia include cerebrovascular vascular disease, which can co-occur with AD and other dementias. Less common dementias include Dementia with Lewy Bodies and Frontotemporal Dementia (Gauthier et al., 2021).

Cognitive impairment can manifest in many ways. Impaired memory and attention can present with forgetfulness of events, losing personal items and repetitive questions or conversations. Impaired language can be presented with difficulty recalling common words, finishing sentences, or errors in speech, spelling, or writing. Impaired recognition visuospatial abilities could involve impairment in recognizing common objects or faces, the inability to operate simple implements, or orient clothing to the body. Executive dysfunction can present with poor judgment, failure to manage finances, or properly assess safety and risk. Additionally, other neurological and non-neurological conditions, and medications can affect cognition, all of which need to be ruled out before considering a dementia diagnosis (McKhann et al., 2011).

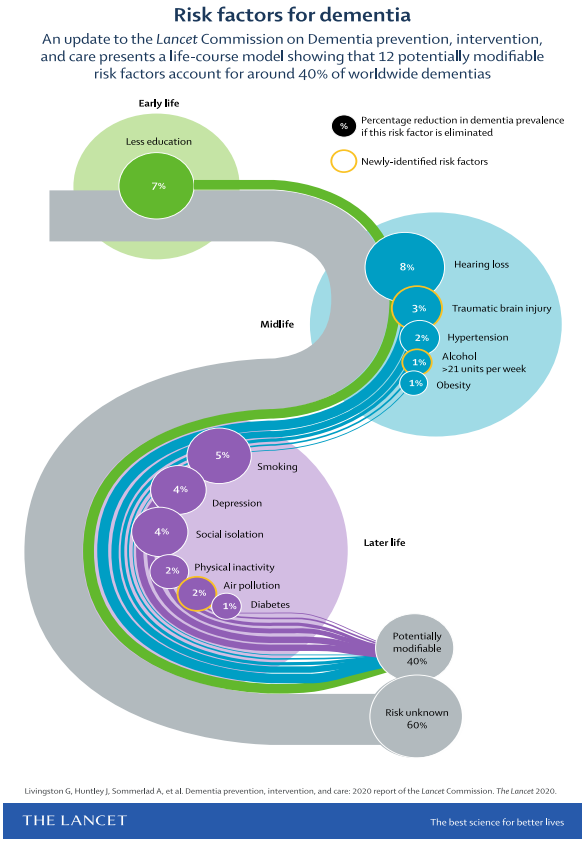
In clinical care and research, the measurement of cognitive performance is essential to diagnosis. Cognitive testing ranges from brief global screening measures to detailed neuropsychological testing (Ismail et al., 2010). Examples of these tests include the Mini Mental State Exam (Folstein et al., 1975), which is historically the most frequently used cognitive screening tool or the Montreal Cognitive Assessment, which is now widely used (Nasreddine et al., 2005). The recommendation to clinicians is to use short assessment tools for cognitive screening in a clinical setting for ease of applicability, less burden on patients, and efficiency in gathering clinical information, but to identify the need for further detailed neuropsychological testing when necessary (Tang-Wai et al., 2020).

Biologically, underlying diseases cause dementia, the most common of which is Alzheimer's disease (AD). AD is marked by β-amyloid plaques and tau tangles (McKhann et al., 2011). These plaques and tangles accumulate over decades, causing brain dysfunction and cerebral atrophy, resulting in clinical symptoms. Indeed, the NIA-AA published in 2018 a biological definition of AD based on the presence of β-amyloid and tau. In this framework, AD is staged clinically based on cognitive performance as Stages 1-2 (preclinical AD - objectively normal cognition), Stage 3 (prodromal AD - mild cognitive changes absent functional decline), and Stages 3-6 (AD dementia - cognitive and functional impairment) (Jack Jr et al., 2018). The biological definition of AD is an important step forward for drug development, although detection of early-stage AD remains challenging.

Risk factors for dementia are an area of great study as some may represent modifiable targets for dementia prevention. Recently, the Lancet Commission published a life course model

of dementia, highlighting 12 modifiable risk factors across the lifespan. These risks include limited education, obesity, midlife hypertension, traumatic brain injury, alcohol consumption, hearing loss, smoking, depression, physical inactivity, social isolation, air pollution, and diabetes (Livingston et al., 2020)(Figure A).

I Figure A. Risk Factors for Dementia



Note: This figure is copied from (Livingston et al., 2020).

In addition to using risk factors to determine dementia risk and identify preventative treatment targets, there has also been great interest in identifying early markers of disease to facilitate the detection of neurodegenerative disease in advance of dementia. Broad screening

using neuroimaging and biomarkers is infeasible at a primary care screening level, let alone at a population health level, and thus the prevailing approach has been to explore changes in cognition emerging in advance of dementia to predict prodromal disease better.

1.3 Mild Cognitive Impairment

Mild cognitive impairment (MCI) was initially described as an intermediate stage between normal aging and dementia, which captures an at-risk group for incident dementia (Ganguli, 2006), and represents prodromal dementia for some (Ganguli, 2014). Although described in many previous contexts, MCI is most commonly operationalized in the Petersen or Mayo criteria with 5 components: 1) memory complaint; 2) memory deficit; 3) normal mental status; 4) absence of functional impairment; 5) absence of dementia. Revisions of the criteria incorporated non-memory domains, with categorization into amnestic (single- and multi-domain) and non-amnestic (single- and multi-domain) subtypes (Petersen, 2016). The MCI equivalent in DSM-5 is Mild Neurocognitive Disorder: A) evidence of modest cognitive decline in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition); B) cognitive deficits do not interfere with independence in everyday activities; C) cognitive deficits do not occur exclusively in the context of a delirium; and D) not better explained by another mental disorder (APA, 2013).

According to a meta-analysis of 41 studies, the annual rate of progression of MCI to dementia is 5-10%, with over 50% of participants not progressing to dementia even after 10 years of follow up (Mitchell et al., 2014). There is significant heterogeneity in this mild cognitive syndrome, as evidenced by the high rate of reversion to normal cognition. A meta-analysis of 25

studies found a 24% reversion rate, greater in community (31%) versus clinical (14%) samples (Malek-Ahmadi, 2016). Nonetheless, MCI remains the most prominent risk syndrome proximal to dementia. However, greater specificity in the diagnosis is required to predict dementia better and better identify those with AD in advance of dementia (McGirr et al., 2022).

1.4 Subjective Cognitive Decline and Normal Cognition

Recent efforts have explored dementia risk even earlier in the cognitive continuum, in the absence of objective cognitive deficits. This is a challenging and somewhat speculative task, given that impaired cognition is the predominant clinical marker of risk. Subjective cognitive decline (SCD) was originally hypothesized as an early stage of dementia but subsequently operationalized in the Jessen criteria (Jessen et al., 2020). These criteria are: 1) subjective decline in memory; 2) onset of SCD within the last 5 years; 3) onset of SCD identified at the age of 60 and older; 4) expression of worries associated with SCD; 5) persistence of SCD over time; 6) seeking medical help; and 7) confirmation of cognitive decline by an observer (Jessen et al., 2020).

Epidemiological research has determined that SCD is associated with a greater risk for incident MCI and dementia (Mitchell et al., 2014). A meta-analysis of 28 studies and found the risk of dementia doubled in older adults with subjective memory complaints (SMC) with no objective deficits compared to those without SMC. The estimated annual conversion rate (ACR) from SMC to MCI was 6.6% and to dementia was 2.3%. Data from 11 long-term studies >5 years in the meta-analysis found that 26.6% of persons with SMC progressed to MCI and 14.1% to dementia (Mitchell et al., 2014). Biomarker research has determined that SCD can identify a

group with early AD, however, as with MCI, markers to improve specificity are required (Jessen et al., 2020).

The issues with SCD are amplified in normal cognition, where no cognitive symptoms are present to identify a risk group. Historically, the approach to capture this preclinical disease group has included identifying those with a family history of autosomal dominant dementia AD or risk genes like ApoE4. However, these are subgroups not representative of the larger population, and screening for these participants is not feasible from a public health perspective. Leveraging non-cognitive markers such as NPS may offer an opportunity for better prognostication and early detection.

1.5 NPS in dementia

Neuropsychiatric symptoms are non-cognitive features of dementia, including disturbances in mood, affect, behaviour and perception (Lanctôt et al., 2017b). NPS are almost ubiquitous in dementia. A report from the Cache County study measured NPS prevalence over ~5 years in incident cases of dementia, finding a point prevalence for any symptom of 56% at baseline and 97% experiencing at least one symptom in the first 5 years after dementia diagnosis (Steinberg et al., 2008). Further, NPS are associated with faster functional decline, poorer quality of life, more rapid progression to severe dementia, greater likelihood of institutionalization, increased use of psychiatric medications, higher mortality, amplified caregiver burden, and substantial costs to health systems (Fischer et al., 2012a, Lanctôt et al., 2017b, Fischer et al., 2012b). Thus, it has become clear that NPS are an inherent part of the neurodegenerative process, representing a more severe phenotype of dementia compared to the absence of NPS.

In response, in 2011 the NIA-AA included NPS ("changes in personality, behavior, or comportment") as a core clinical criterion for AD with the following descriptor: "symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors" (McKhann et al., 2011). The inclusion of NPS was overdue given that Auguste D., the first patient described by Alois Alzheimer, presented to hospital not due to cognitive impairment but rather affective symptoms and suspiciousness, ultimately demonstrating agitation, anxiety, delusions, and negativity over the course of her illness (Maurer et al., 2006). Ironically, in DSM-5, NPS are poorly represented, incorporated only as a specifier ("with behavioural disturbance"), with the following descriptor: "if the cognitive disturbance is accompanied by a clinically significant behavioural disturbance (e.g., psychotic symptoms, mood disturbance, agitation, apathy, or other behavioural symptoms)" (Sachdev et al., 2014).

Given the significance of NPS in dementia, a burgeoning body of literature has described the prevalence of NPS. A recent meta-analysis on the prevalence of NPS in dementia reported that apathy to be the most common NPS with an overall prevalence of 49%, followed by depression at 43%, aggression at 40%, anxiety at 39%, delusions at 31%, disinhibition at 17%, and hallucinations 16% and (Zhao et al., 2016). An even more recent meta-analysis explored sex differences in prevalence of NPS in AD, finding that females had higher prevalence of depression and psychosis, and males had higher prevalence of apathy, highlighting the importance of sex in assessing NPS (Eikelboom et al., 2022).

1.6 NPS in MCI

Given that NPS can be present at baseline dementia diagnosis, it stands to reason that NPS can present in advance of dementia at the MCI phase. Studies have demonstrated this to be the case. Systematic reviews and meta-analyses have reported prevalences ranging from 12-85%, with lower NPS prevalence in community versus clinical samples (Monastero et al., 2009, Martin and Velayudhan, 2020, Apostolova and Cummings, 2008). Narrative, scoping and systematic reviews as well as meta-analyses have determined the prevalence of specific NPS in MCI. Based on these studies apathy prevalence ranges from 15-39% (Lanctôt et al., 2017a); depression pooled prevalence is 32%, higher in clinical versus community samples (Ismail et al., 2017b); anxiety pooled prevalence is 21% (Chen et al., 2018); agitation prevalence ranges from 5-25% in population studies and up to 45% in clinical studies (Bateman et al., 2020); and psychotic symptoms range in prevalence from 1.3-10.5%, with delusions more common than hallucinations (Ismail et al., 2022).

In parallel with dementia, NPS in MCI represent a worse phenotype of MCI, associated with caregiver burden (Lyketsos et al., 1997, Fischer et al., 2012b). In a study of vascular MCI, NPS were associated with a greater risk of institutionalization, mortality, and cognitive decline (Sep et al., 2022). A number of studies have determined that global NPS burden in MCI is associated with incident dementia (Mallo et al., 2020, McGirr et al., 2022), highlighting the importance of these symptoms even in advance of dementia. Further, studies have reported associated risk of cognitive decline and dementia associated with isolated NPS or defined clusters of NPS. A recent meta-analysis investigating apathy in dementia-free participants, primarily with MCI, found a pooled HR of incident dementia of 2.39 (van Dalen et al., 2018b).

For depression, a recent meta-analysis of community-based MCI studies found depression to have a pooled Risk Ratio for dementia of 1.69 (Tan et al., 2019). For anxiety, a meta-analysis determined anxiety to predict cognitive decline and dementia with RRs of 1.77 and 1.57, respectively (Gulpers et al., 2016). Another recent meta-analysis investigating the impact of anxiety on progression from MCI to dementia estimated a pooled HR of 1.18 (Li and Li, 2018). For agitation symptoms, several longitudinal studies in patients with MCI have associated agitation/aggression with incident dementia, with HRs ranging from 1.6–4.4 (Dietlin et al., 2019). For disinhibition, the incidence of dementia in a mixed MCI and NC Mexican-based population sample estimated relative risk of 1.5 for dementia (Acosta et al., 2018). Although infrequent in MCI, psychosis was found to carry an 8-11-fold increased risk of developing dementia (Martin and Velayudhan, 2020). Thus, based on the current evidence, the presence of NPS in MCI patients is associated with a greater risk of dementia.

1.7 NPS in normal cognition

Relatively little literature has explored NPS at the normal end of the cognitive continuum. One of the challenges in this literature is that in cognitively normal older adults, the neurodegenerative disease may not be on top of mind for a clinician, and the presence of NPS may result in the provision of a psychiatric diagnosis (Tang-Wai et al., 2020). Retrospective studies and case series of specialty clinic patients has determined that about ~28% initially received psychiatric diagnoses, especially depression, which in some cases represented unidentified apathy (Woolley et al., 2011, Cieslak et al., 2018). Further, the most commonly used tool to measure NPS, the Neuropsychiatric Inventory (Cummings, 1997), was developed to measure NPS severity in dementia patients. The NPI, which is clinician-rated after informant

interview, assesses the following NPS: aberrant motor behavior, anxiety, apathy/indifference, agitation/aggression, depression/dysphoria, delusions, disinhibition, elation/euphoria, hallucinations, irritability/lability, nighttime behaviors, and the neurovegetative symptoms of sleep and appetite disturbances.

While the NPI has been used extensively in MCI, its use in cognitively normal cohorts has been less frequent. Nonetheless, some cohorts of cognitively normal older adults have reported the prevalence of NPS using the NPI or its derivatives, but without systematic review and meta-analytical data informing the field. The longitudinal population-based Mayo Clinic Study of Aging described the baseline sample CN older adults with NPS measures, reporting on apathy (4.0%), depression (10.9%), anxiety (4.7%), agitation (2.3%), and irritability (6.8%) as the most common symptoms (Geda et al., 2014). In the National Alzheimer Coordinating Center dataset, which included community dwelling participants referred to a dementia study, prevalences of the same NPS in NC were higher and reported as apathy (4.6%), depression (13.1%), anxiety (8.9%), agitation (5.9%), irritability (11.3%). Additionally, less frequent NPS were also reported including disinhibition (2.6%), delusions (0.8%) and hallucinations (0.3%) (Liew, 2020a). In a cross-sectional analysis of a memory clinic sample, NPS prevalence in patients with objectively normal cognition was higher still reported as apathy (32.8%), depression (47.9%), anxiety (34.5%), agitation (33.6%), irritability (46.2%), disinhibition (21.8%), delusions (1.7%), and hallucinations (2.5%) (Sheikh et al., 2018). Thus, consistent with the MCI literature, NPS were overrepresented in clinical vs community samples, with population studies having the lowest prevalence.

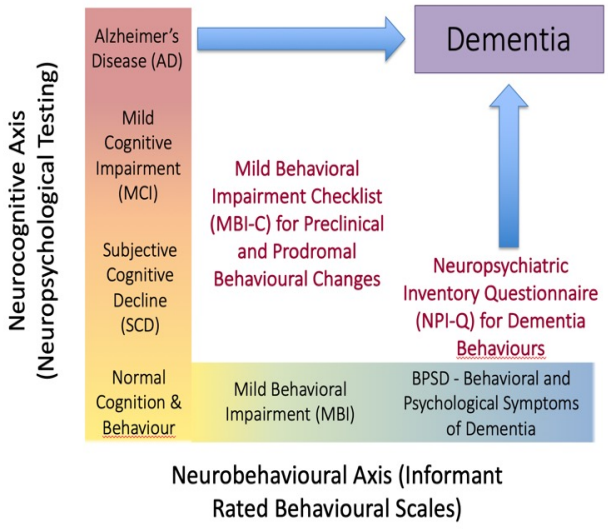
1.8 Mild Behavioural Impairment (MBI)

In contrast to MCI as a cognitive prodrome to AD, MBI was originally described by Taragano in 2003 as a behavioural prodrome to FTD with the following criteria: 1) persistent behavioural changes and mild psychiatric symptoms, especially disinhibition; 2) no serious memory complaints; 3) normal activities of daily living; and 4) not demented (Taragano and Allegri, 2003). The subsequent 5-year longitudinal study (Taragano et al., 2009) comparing MCI and MBI demonstrated that the risk of dementia was greater for MBI than MCI (HR=1.43, 95% CI 1.01- 2.03), with 34% of patients with MCI and 70% of patients with MBI developing dementia. Of the MBI group, 44.5% developed FTD (versus 6.3% of the MCI group). Of the MCI group, 27% developed AD (versus 22.7% of the MBI group). Importantly, progression to AD was comparable in both groups. Further, despite the absence of memory symptoms at study entry, 49.6% of the MBI group had cognitive symptoms on testing, and 35.5% of the MCI group had psychiatric symptoms. The MBI+cognitive symptom group and the MCI+behavioural symptom group had a comparable risk of progression to dementia (Taragano et al., 2009). Thus, while MBI was a simple and appealing model, the dichotomization of risk into cognitive and behavioural phenotypes was not successful in identifying distinct groups for dementia prognostication. Additionally, detailed cognitive testing would be required for proper case definitions, which would not be suitable for scaling up or for broader screening purposes (Ismail et al., 2016).

In response to these surprising findings and logistical issues, a working group was convened in 2012 under the rubric of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART-AA) NPS Professional Interest Area.

The main goal of the working group was to reformulate the approach to the identification of dementia prodromes. Specifically, the aims were to: 1) describe later onset NPS as preclinical/prodromal syndromes of all dementias (and not just FTD), with clear operationalized criteria; 2) define explicitly the relationship between MBI and MCI (and not as competing constructs); and 3) standardize the assessment to help define and identify early the target population (Ismail et al., 2016). Ultimately, the MBI name was retained in order to present MBI as a complement rather than a contrast to MCI, the former representing the neurobehavioural axis of pre-dementia risk and the latter representing the neurocognitive axis of pre-dementia risk (Ismail et al., 2021) (Figure B).

II Figure B. Cognitive and behavioral pre-dementia risk axes



Note: This figure is copied from (Ismail et al., 2021).

The MBI criteria were published in 2016, consistent with the a priori aims. Completely novel in these new criteria was the incorporation of 5 behavioural domains, identified from epidemiological and neurobiological evidence and clinical expertise: 1) decreased motivation

(apathy); 2) affective dysregulation (mood and anxiety symptoms); 3) impulse dyscontrol (agitation, aggression, impulsivity); 4) social inappropriateness (impaired social cognition); and 5) abnormal perception or thought content (psychotic symptoms, i.e., hallucinations and delusions) (Ismail et al., 2016). (Figure C). The MBI core criteria stipulate that NPS emerge *de novo* in later-life and persist for ≥6 months (Ismail et al., 2016). These stipulations increase the likelihood that MBI symptoms represent early markers of neurodegenerative disease rather than transient NPS associated with medical, psychosocial or socioeconomic stressors, or other life events independent of the neurodegenerative process. In fact, MBI is represented in Stages 2 and 3 of the NIA-AA framework as "mild, recent onset behavioral symptoms…which persist and cannot be explained by life events" (Jack Jr et al., 2018).

III Figure C. ISTAART Research Diagnostic Criteria for MBI

ISTAART research diagnostic criteria for MBI

1. Changes in behavior or personality observed by patient, informant, or clinician, starting later in life (age ≥50 years) and persisting at least intermittently for ≥6 months. These represent clear change from the person's usual behavior or personality as evidenced by at least one of the following:
   a. Decreased motivation (e.g., apathy, aspontaneity, indifference)
   b. Affective dysregulation (e.g., anxiety, dysphoria, changeability, euphoria, irritability)
   c. Impulse dyscontrol (e.g., agitation, disinhibition, gambling, obsessiveness, behavioral perseveration, stimulus bind)
   d. Social inappropriateness (e.g., lack of empathy, loss of insight, loss of social graces or tact, rigidity, exaggeration of previous personality traits)
   e. Abnormal perception or thought content (e.g., delusions, hallucinations)
2. Behaviors are of sufficient severity to produce at least minimal impairment in at least one of the following areas:
   a. Interpersonal relationships
   b. Other aspects of social functioning
   c. Ability to perform in the workplace
   The patient should generally maintain his/her independence of function in daily life, with minimal aids or assistance.
3. Although comorbid conditions may be present, the behavioral or personality changes are not attributable to another current psychiatric disorder (e.g., generalized anxiety disorder, major depression, manic or psychotic disorders), traumatic or general medical causes, or the physiological effects of a substance or medication.
4. The patient does not meet criteria for a dementia syndrome (e.g., Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, other dementia). MCI can be concurrently diagnosed with MBI.

Legend: ISTAART, International Society to Advance Alzheimer's Research and Treatment; MBI, mild behavioral impairment; MCI, mild cognitive impairment.
Note: This figure is copied from (Ismail et al., 2016).

A substantial body of literature now supports the utility of the MBI construct. MBI has demonstrated associations with cognitive impairment (Kassam et al., 2022, Rouse et al., 2021,

Sun et al., 2021b), incident cognitive decline and dementia (Ismail et al., 2021, Kan et al., 2022, McGirr et al., 2022, Creese et al., 2019, Wolfova et al., 2022, Matsuoka et al., 2019, Taragano et al., 2018, Tsunoda et al., 2021), greater dementia risk than later life psychiatric syndromes (Matsuoka et al., 2019, Taragano et al., 2018), amyloid-β (Lussier et al., 2020, Miao et al., 2021c), tau (Johansson et al., 2021), neurodegeneration (Naude et al., 2020, Gill et al., 2020, Gill et al., 2021, Matuskova et al., 2021, Shu et al., 2021), white matter hyperintensities (Miao et al., 2021b), neuropathological confirmation of clinically diagnosed AD (Ruthirakuhan et al., 2022), and AD risk genes (Creese et al., 2021, Andrews et al., 2018). A relevant and recent study highlights the improved prognostic specificity of stratification of MCI samples by MBI status compared to traditional NPS assessment approaches. The MCI+MBI group not only associated with greater 3-year dementia risk and annual progression rate to dementia, but a *lower* risk of reversion to normal cognition. A contrasting traditionally measured NPS group did not differ from the no NPS group for reversion. However, much of the nascent MBI literature has described MCI samples, with relatively little in normal cognition, and the utility of each of the MBI domains has not yet been fully explored.

1.9 Knowledge gaps

The existing knowledge suggests that NPS could be a powerful predictor of incident cognitive dementia, although more research in cognitively normal older adults is required. As NPS measurement is often not considered in cognitively normal cohorts, the literature is scant and dispersed. A systematic review and meta-analysis of MBI prevalence has been published, although relatively few studies included cognitively normal samples (Pan et al., 2022). Further, very little research has explored the MBI domains, especially in normal cognition. A systematic

review and meta-analysis have determined estimates of MBI domain prevalence, influenced extensively by MCI samples (Pan et al., 2022). Longitudinal data are sparser still, and thus a systematic review and meta-analysis of available studies in normal cognition is required, in advance of the newer studies based on the MBI criteria, which will take time to materialize. Moreover, pooled estimates of risk for each MBI domain do not exist and would be valuable to inform future research.

The unique aspect of this systematic review and meta-analysis is that it investigates the MBI-domain associated risk of cognitive decline, MCI, or dementia in cognitively normal older adults. We aim to summarize and quantify this neurobehavioural risk, in a group in whom cognitive risk cannot be measured easily. To our knowledge, no other published studies have reported this risk. We aim to shed some light on the magnitude and direction of association by estimating pooled hazard ratios for incident cognitive decline, MCI, and dementia.

Chapter Two: Neuropsychiatric Symptoms and Incident Cognitive Decline and Dementia in Cognitively Normal Older Adults: A Systematic Review and Meta-Analysis

Neuropsychiatric Symptoms and Incident Cognitive Decline and Dementia in Cognitively Normal Older Adults: A Systematic Review and Meta-Analysis

Heba Elbayoumi, Scott B. Patten, Tamara Pringsheim, Andrew Bulloch, Zahra Goodarzi, Zahinoor Ismail*

Affiliations:
Hotchkiss Brain Institute, University of Calgary, 3280 Hospital Dr. NW, Calgary, AB T2N 4Z6, Canada
Department of Community Health Sciences
Department of Psychiatry, University of Calgary, 2500 University Dr. NW, Calgary, AB T2N 1N4, Canada
Department of Clinical Neurosciences, University of Calgary, 2500 University Dr. NW, Calgary, AB T2N 1N4, Canada
Mathison Centre for Mental Health Research & Education, 3280 Hospital Dr. NW, Calgary, AB T2N 4Z6, Canada

Corresponding author:
Zahinoor Ismail MD FRCPC
3280 Hospital Dr. NW
Calgary AB, T2N 4Z6, Canada.

Email: ismailz@ucalgary.ca.
Tel.: +1 403 210 6900; Fax: 000-000-0000

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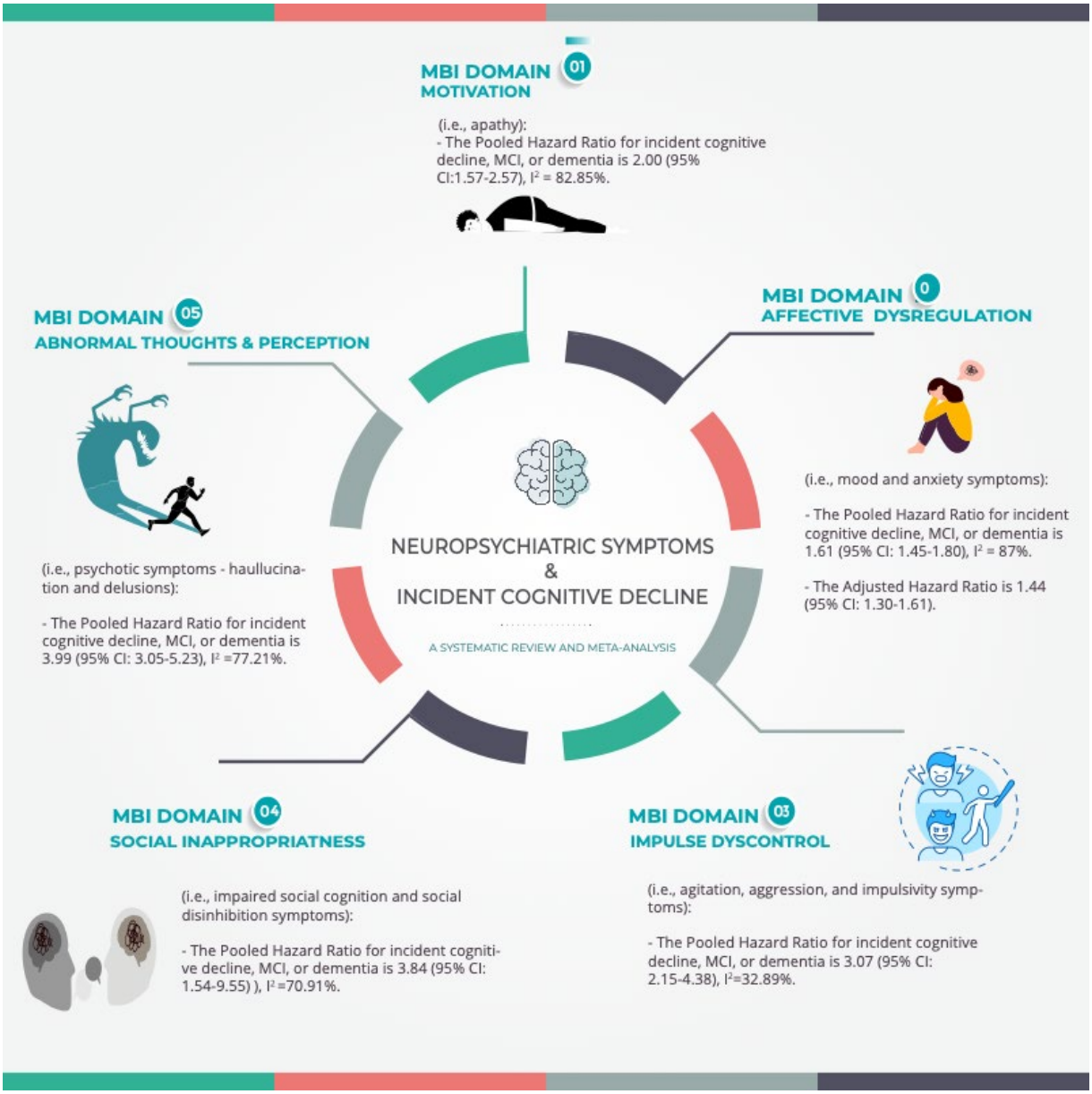
Highlights:

- To understand the risk of incident cognitive decline and dementia associated with the presence of neuropsychiatric symptoms (NPS) in cognitively normal older adults, a systematic review and meta-analysis of longitudinal studies was completed
- NPS were grouped into 5 domains consistent with the ISTAART-AA Mild Behavioral Impairment (MBI) criteria, which describe later life NPS as an at-risk group for incident cognitive decline and dementia
- All 5 Mild behavioral impairment (MBI) domains were found to be associated with significant risk. Psychotic symptoms were associated with the greatest risk, followed by social inappropriateness, impulse dyscontrol, apathy, and affective dysregulation.
- Heterogeneity was common with NPS assessment approach and follow-up time being common contributors
- Future research should consider more standardized protocols for risk assessment in dementia-free older adults, potentially using the MBI checklist, which was developed explicitly for dementia risk assessment

1. **Figure 1. Graphical abstract (required by Ageing Research Reviews)**



Abstract: (168/170)

Objective: To determine risks of cognitive decline or dementia in cognitively normal cohorts with neuropsychiatric symptoms (NPS), stratified by mild behavioral impairment (MBI) domains.

Methods: A systematic search (MEDLINE, EMBASE, and PSYCINFO) was completed up to January 2022. Pooled hazard ratios (HR) with Standard Error (SE), I^2, and tau^2 were determined utilizing DerSimonian-Laird random-effects models. Heterogeneity and publication bias were investigated. PRISMA and MOOSE checklists were followed.

Results: Of 12,674 screened abstracts, 36 prospective studies representing 326,739 participants were included. Risks (HR) for incident cognitive decline or dementia by MBI domain were: 1) apathy 2.00 (95%CI:1.57-2.57); 2) affect 1.61 (95%CI:1.45-1.80; adjusted 1.44, 95%CI:1.30-1.61); 3) agitation 3.07 (95%CI: 2.15-4.38); 4) social inappropriateness 3.84 (95%CI:1.54-9.55); and 5) psychosis 3.99 (95%CI:3.05-5.23). Heterogeneity was most evident in affect (I^2=86.56%, tau^2=0.04), with time and NPS ascertainment as the main contributors.

Conclusion: Cognitively normal older adults with NPS are at greater risk for mild cognitive impairment and dementia than those without NPS. Risks differ between the 5 MBI domains.

Keywords:

Neuropsychiatric Symptoms; Mild Behavioral Impairment; Normal Cognition; Mild Cognitive Impairment; Dementia

Main Text:

1. Introduction

Neuropsychiatric Symptoms (NPS) are core to the dementia process and almost ubiquitous during the course of disease (Steinberg et al., 2008). NPS often emerge in older adults prior to dementia, at the mild cognitive impairment (MCI) stage, where NPS are associated with faster progression to dementia (Peters et al., 2013, Rosenberg et al., 2013). However, NPS can also emerge in older adults with normal cognition, potentially representing an early manifestation or marker of neurodegenerative disease. Indeed, 59% of all-cause dementia, and 30% of cases of Alzheimer's disease dementia (AD) present with NPS prior to a cognitive diagnosis (Wise et al., 2019). A better understanding of the relationship between later-life NPS and dementia risk is of paramount importance.

Behavioral prodromes are well-established in frontotemporal dementia, and in that context, mild behavioral impairment (MBI) was originally described (Taragano and Allegri, 2003). As a competing construct to MCI (the well-known cognitive prodrome to AD), MBI was characterized by prominent behavioral change in the absence of cognitive decline. In 2016 the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART-AA) Neuropsychiatric Syndromes Professional Interest Area revised the construct and published novel MBI criteria (Ismail et al., 2016). The ISTAART-AA criteria describe later life *de novo* emergence and persistence of NPS, representing a shift from longstanding behavioral patterns, as an at-risk state for incident cognitive decline and all-cause dementia (including AD). Most importantly, MBI was not defined as an alternative or contrast to MCI, but rather as a complement or behavioral analogue. Just as late life decline in cognition could

represent neurodegenerative disease, so could late life behavioral change, with both demanding clinical attention (Ismail et al., 2016, Ismail et al., 2020). Thus, MBI could emerge at any stage along the cognitive continuum, i.e., in normal cognition or MCI.

MBI consists of symptoms in 5 domains: 1) decreased drive and motivation (apathy) (Sherman et al., 2018); 2) affective dysregulation (mood and anxiety symptoms) (Ismail et al., 2018); 3) impulse dyscontrol (agitation, aggression, impulsivity, response inhibition) (Bateman et al., 2020, Saari et al., 2021); 4) social inappropriateness (impaired social cognition, social disinhibition) (Desmarais et al., 2018); and 5) abnormal thoughts and perception (psychotic symptoms, i.e., hallucinations and delusions) (Fischer and Agüera-Ortiz, 2018). Given the explicit requirements for later life symptom emergence, and persistence for ≥6 months, the Mild Behavioral Impairment Checklist (MBI-C) was developed to identify MBI following the ISTAART-AA criteria (Ismail et al., 2017a). Since then, both the MBI syndrome and the MBI-C rating scale have been validated (Creese et al., 2020, Mallo et al., 2018, Cui et al., 2019, Hu et al., 2022), demonstrating associations with cognitive impairment (Rouse et al., 2021, Kassam et al., 2022), incident cognitive decline and dementia (Creese et al., 2019, Ismail et al., 2021, Tsunoda et al., 2021, Matsuoka et al., 2019, McGirr et al., 2022, Kan et al., 2022), geriatric conditions such as hearing impairment, dual-task-gait cost, frailty and others (Fan et al., 2020, Gosselin et al., 2019, Soo et al., 2021, Gosselin et al., 2022, Guan et al., 2022a, Guan et al., 2022b), genetic risk for AD (Andrews et al., 2018, Creese et al., 2021), biomarkers for amyloid, tau and neurodegeneration (Miao et al., 2021a, Gill et al., 2020, Gill et al., 2021, Johansson et al., 2021, Naude et al., 2020, Matuskova et al., 2021, Lussier et al., 2020), and clinico-pathological confirmation of AD (Ruthirakuhan et al., 2021). Summarizing this emerging literature is

important for a better understanding of the nature of risk with later-life related behavioral symptoms.

Although studies have explored the association between NPS and cognitive decline in cognitively impaired individuals, the literature in normal cognition is scant and inconsistent. There exists a need to conduct a systematic review to summarize the current body of findings and a meta-analysis to assess the strength of the association by providing a single summary estimate of effect. This work can additionally identify any knowledge gaps and recommend future research. There has been no systematic review assessing the risk of incident cognitive decline, MCI, and/or dementia within cognitively normal cohorts at baseline, stratified by the five MBI domains as exposures. Therefore, this study aimed to determine domain-level risk, utilizing samples from longitudinal studies and population cohorts.

2. Methods

This study included longitudinal studies of older adults reporting baseline NPS and longitudinal cognitive outcomes. The protocol was registered on PROSPERO (CRD42019049529) and followed MOOSE (Stroup et al., 2000) and PRISMA (Moher et al., 2009) checklists.

2.1 Literature Search

The literature search included terms related to NPS (Supplementary Table A), cognition, and incidence. Terms were identified with the aid of a librarian and by expert knowledge. Terms within each cluster were combined with the Boolean operator OR and between clusters with the

AND operator. The search included MEDLINE, PsycINFO, and EMBASE literature repositories up to January 2022. In order to increase the sensitivity and specificity of retrieving all related studies the search included multiple keywords (Weingarten et al., 2004, Wilczynski and Haynes, 2007). No restrictions were placed upon the year of the study, though only English-language studies were included for feasibility. References of included studies and grey literature were also searched, including the Canadian Agency for Drugs and Technologies in Health (CADTH) and Google Scholar. Reference manager software Endnote (Endnote, Version 20.0.1, 2021) was employed for organizing references, removing duplicate references, and conducting the initial screening phase.

2.2 Research Questions

The PICO framework (Richardson et al., 1995) was utilized to formulate the primary research question as follows: Patient - cognitively normal older adult; Intervention/Exposure - NPS; Comparison - no NPS; Outcome - cognitive decline, MCI or dementia, with reported hazard ratio (HR) or odds ratio (OR).

2.3 Study Selection

Inclusion criteria (at initial abstract screening stage) were: 1) studies in cognitively normal participants reporting baseline prevalence of any NPS and subsequent incidence of MCI or dementia, or cognitive decline measured by a rating scale, comparing baseline to endpoint; 2) original research (i.e., not review, commentary, letter, or editorial articles); and 3) published in English. All full-text articles were retrieved and reviewed in duplicate.

2.4 Abstract review

Endnote libraries including all extracted reference lists were independently reviewed in duplicate (HE and ZI), based on inclusion criteria. Libraries were sorted into three groups: 1) Yes (reviewer-selected studies, meeting inclusion criteria); 2) No (not meeting inclusion criteria); 3) Reviews (systematic/narrative reviews published in relation to the search). Selected references were transferred into the final library for full-text retrieval and data abstraction.

2.5 Data Abstraction

The full-text review was completed in duplicate (HE and ZI), and discrepancies were resolved by consensus. Relevant data were extracted to Excel spreadsheets by HE with support from ZI, including study information (author, year of publication, country, and continent), study characteristics (mean age of participants, location, duration of data collection), condition information (data source, condition definition, total number of participants), and the reported measure of effect (HR, OR).

2.6 Risk of Bias Assessment

An adapted version of the Newcastle-Ottawa Quality Assessment scale was utilized to assess the methodological quality of the included observational/cohort studies. The scale consists of 3 main categories, with a maximum score of 9. The categories are: 1) selection (4 points); 2) comparability (2 points); and 3) outcome (3 points), which are used to classify studies as good, fair, and poor.

2.7 Statistical Analysis

A random-effects model was used, based on the assumption of possible clinical and methodological heterogeneities between the included studies. Since the I^2 was ≥ 50% within most domains, a Dersimonian-Laird random-effects model was used, based on the assumption that observed variance stemmed from study heterogeneity due to population and methodology variations, and not due to sampling variability. Pooled log HRs were generated by the inverse variance-weighted method, to account for precision regarding measure of effect. HRs and other included measures of effects were log-transformed to approximate normality. Adjusted measures of effect and standard error were included, if reported by the study. All domains were sub-grouped by the cognitive outcome (i.e., change in cognitive score, MCI, dementia). In addition, I^2 and tau^2 were utilized to quantify the magnitude of heterogeneity between the included studies. I^2 is the percentage of the total variation in study estimates due to heterogeneity and tau^2 is an estimated variance of the underlying effects across studies. Stata (Version 17.0 for Mac, 2021) was employed for data synthesis.

To explore heterogeneity, a list of possible variables based on the literature and expert knowledge was created. The identified variables were assessed for effect modification or confounding, utilizing meta-regression and stratification. Meta-regression incorporated the following variables: 1) continent; 2) sex; 3) mean participant age; 4) cognitive outcome (change in cognitive score, incident MCI/CIND (cognitive impairment no dementia), or incident dementia); 5) approach used to capture the cognitive outcome (rating scale, diagnosis by trained personnel, diagnostic criteria); 6) specific symptom within the domain (for domains populated by more than one NPS); 7) method of NPS ascertainment (self-, informant-, or clinician-rated); 8)

quality of included studies (risk of bias score or rating level); 9) sample type (community vs. clinical); and 10) length of follow-up (years, continuous and dichotomized at ≤3 vs. >3 years).

Publication bias was assessed by visual inspection of funnel plot symmetries, Begg and Egger tests, and a nonparametric trim-and-fill method in each domain used even when publication bias was not evident. Individual study influences were investigated by leave-one-out sensitivity analyses and visual inspection of Galbraith plots. Additional sensitivity analyses were explored in each domain dependent on the particulars of the included studies to ascertain the robustness of meta-analysis and the conclusions. All p-values were from 2-tailed tests, deemed statistically significant at $p < 0.05$.

3. Results

3.1. Literature Search

A total of 12,674 references were screened for eligibility, with 346 studies identified for full-text review, and 36 included in the final meta-analysis (Almeida et al., 2019, Almeida et al., 2017, Bae et al., 2015, Brodaty et al., 2012, Caracciolo et al., 2011, Dufouil et al., 1996, Gallacher et al., 2009, Geda et al., 2014, Johansson et al., 2019, Johnson et al., 2016, Kassem et al., 2017, Kida et al., 2016, Lee et al., 2019, Lee et al., 2020, Palmer et al., 2007, Panza et al., 2008, Pietrzak et al., 2012, Ravaglia et al., 2008, Richard et al., 2013, Santabárbara et al., 2019, Singh-Manoux et al., 2017, Spira et al., 2012, Verdelho et al., 2013, Wilson et al., 2007, Burke et al., 2016, Grande et al., 2020, Bock et al., 2020, Ceïde et al., 2020, Han et al., 2021, Gerritsen et al., 2022, Kørner et al., 2009, van Dalen et al., 2018b, Thakur et al., 2021, Liew, 2020a, Stafford et al., 2021, Sun et al., 2021a). Some studies were excluded because they shared datasets

(Donovan et al., 2014, Liew, 2020b, Geda et al., 2006, Roberts et al., 2015, Pankratz et al., 2015), or reported global risk of NPS/MBI without domain estimates (Creese et al., 2019, Matsuoka et al., 2019, Taragano et al., 2009, Ismail et al., 2021, Wadsworth et al., 2012, Grande et al., 2020). The PRISMA flowchart is presented in Figure 2.

3.2. Characteristics of included studies

A total of 326,739 participants were enrolled, with a weighted mean age by sample size of 71.94 years. In addition, 19,7274 participants were female, comprising 60.4% of the total sample. The weighted mean duration of follow-up was 6.63 years, ranging from 1-17.7 years. Publication years ranged from 1996-2022. North America accounted for 11 studies, with 15 European studies, 4 Australian, 5 Asian, and 1 South American. Key characteristics of all included studies were reported based on the MOOSE guidelines (Stroup et al., 2000) and are shown in Table 1.

3.3. Risk of bias

Of the 36 included studies, 25 were rated as good, 9 were identified as fair, and 2 received a poor rating (Table 2). The risk of bias variable in the regression models was not significant for the 5 MBI domains.

3.4. Meta-analyses results

Meta-analysis results with HRs for incident cognitive decline and dementia for each domain are shown in Table 3.

3.4.1 MBI Domain 1 - Impaired Drive and Motivation (Apathy)

Meta-analysis included 11 studies with 12 measures of interest (Table 4a) with an overall sample size of 17,454 participants, weighted mean age of 74.2 and SD 4.64 years. Publication dates ranged between 2007 and 2022. The pooled HR for incident cognitive decline, MCI, or dementia was 2.00 (95% CI:1.57-2.57) with I^2=82.85% and tau^2=0.10. Forest plots are presented in Figure 3a. Meta-regression showed that NPS ascertainment approach was a significant contributor to heterogeneity (β= -0.479 SE (0.22); p =0.032). Stratum-specific estimates were generated with HRs for the different NPS ascertainment approaches (Figure 4a). Informant-reported apathy symptoms had substantially higher risk of cognitive decline and dementia relative to self- and clinician-rated (HR 2.53 vs 1.51). Publication bias was not found and neither Begg nor Egger tests were significant. Funnel plots are shown in Figure 5a.

3.4.2 MBI Domain 2 Affective Dysregulation (Mood and Anxiety Symptoms)

Meta-analysis included 27 studies having 33 measures of interest (Table 4b) with an overall sample size of 309,277 participants, weighted mean age of 67.83 and SD 6.9 years. In addition, 56.8% of study participants were female. Publication dates ranged between 1996 and 2022. The pooled HR for incident cognitive decline, MCI, or dementia was 1.61 (95% CI:1.45-1.80) with I^2=87% and tau^2=0.04. Forest plots are presented in Figure 3b. Meta-regression showed that the follow up time (β=-0.45; SE (0.19); p=0.021) and NPS ascertainment approach (β=0.34; SE (0.12); p=0.004) were contributors to heterogeneity (Table 5, Figure 4b). Stratum-specific estimates were generated. For studies with follow up time ≤3 years, HR was 2.36 (95% CI:1.40-3.96; I^2=57.79%), for studies >3 years, HR was 1.55 (95% CI:1.39-1.72; I^2=87.64%) (Figure 4c). For NPS ascertainment approach, self-reported or clinician-rated tools had a HR of

1.55 (95% CI:1.39-1.72; I^2=87.06%) for incident cognitive decline and dementia; the HR for informant-rated NPS tools was 3.06 (95% CI:1.95-4.80; I^2=22.85%) potentially indicating misclassification bias. Publication bias was found. While the Begg test was not significant, the Egger test was (p<0.001). Trim-and-fill methods imputed 10 studies resulting in an adjusted HR of 1.44 (95% CI: 1.30-1.61) (Figure 5b, Table 6).

3.4.3 MBI Domain 3 - Impulse Dyscontrol (Agitation, Aggression, and Impulsivity Symptoms)

Meta-analysis included 5 studies having 5 measures of interest (Table 4c) with an overall sample size of 24,152 participants, weighted mean age of 67.2 and SD 7.79 years. In addition, 61.31% of study participants were female. Publication dates ranged between 2012 and 2021. The pooled HR was 3.07 (95% CI 2.15-4.38); with I^2=32.89% and tau^2=0.05 (Figure 3c). With less than 40% heterogeneity, meta-regression models were not utilized. Publication bias was not found and neither Begg nor Egger tests were significant (Figure 5c).

3.4.4 MBI Domain 4 – Social Inappropriateness (Impaired Social Cognition and Social Disinhibition Symptoms)

Meta-analysis included 3 studies having 3 measures of interest (Table 4d) with an overall sample size of 3,784 participants, weighted mean age of 75.76 and SD 4.4 years. In addition, 54.75% of study participants were female. Publication dates ranged between 2012 and 2016. The pooled HR for incident cognitive decline, MCI, or dementia was 3.84 (95% CI:1.54-9.55) with an I^2=70.91% and tau^2=0.44 (Figure 3d). Publication bias was not found and neither Begg nor Egger tests were significant (Figure 5d).

3.4.5 MBI Domain 5 - Abnormal Thoughts and Perception (Psychotic Symptoms, i.e., Hallucinations and Delusions)

Meta-analysis included 6 studies having 7 measures of interest (Table 4e) with an overall sample size of 30,531 total participants, weighted mean age of 70.63 and SD 7.9 years. Publication dates ranged from 2008 to 2021. In addition, 60.4% of study participants were females. The pooled HR for incident cognitive decline, MCI, or dementia was 3.99 (95% CI:3.05-5.23), with an I^2=77.21% and tau^2=0.08 (Figure 3e and Table 3). Meta-regression demonstrated that study quality was a significant contributor to heterogeneity (Table 5). Stratum-specific estimates were not attempted due to the small number of included studies. Publication bias was not found and neither Begg nor Egger tests were significant (Figure 5e).

4. Discussion

This systematic review and meta-analysis of cognitively normal older adults determined that symptoms in all 5 MBI domains were associated with a greater risk of incident cognitive decline and dementia, compared to those without symptoms. Psychotic symptoms were associated with the greatest risk, followed by social inappropriateness, impulse dyscontrol, apathy, and affective dysregulation, which had the lowest estimated risk, but the greatest heterogeneity. Previous studies and meta-analyses in participants with MCI have found NPS to have a higher risk of incident dementia (Palmer et al., 2007, Acosta et al., 2018, Martin and Velayudhan, 2020, Tan et al., 2019, Apostolova and Cummings, 2008, Chen et al., 2018, Mallo et al., 2020, Mourao et al., 2016, McGirr et al., 2022, Liew, 2019), consistent with our findings in normal cognition. However, given the novelty of MBI, no previous studies had explored risk at an MBI domain level. These differences between domains regarding risk support the utility of the 5 MBI domains in research and clinical care.

4.1. Main Findings:

4.1.1 Impaired Drive and Motivation (Apathy)

Domain 1, Apathy, was associated with a HR of incident cognitive decline and dementia of 2.0. Longitudinal studies in mixed non-dementia samples have found apathy to be associated with incident dementia with an OR of 1.65 and HR of 1.9 (Bock et al., 2020, Clarke et al., 2010). A recent meta-analysis investigating apathy in dementia-free participants, primarily with MCI, found a pooled HR of incident dementia of 2.39 (van Dalen et al., 2018b). In a very recent prospective study with a short follow up time, apathy was found to be associated with incident motoric-cognitive-risk syndrome, which is an at-risk state for incident dementia (Ceïde et al., 2020). Thus, our findings extend the current literature to cognitively normal elderly, suggesting apathy is associated with risk of cognitive decline and dementia.

NPS ascertainment approach was a source of heterogeneity in this domain. Informant-reported apathy symptoms had a substantially higher risk of cognitive decline and dementia, relative to self- and clinician-rated symptoms (HR 2.53 vs 1.51). These findings suggest apathy is vulnerable to misclassification bias. Further research on clinical and epidemiological differences based on rater is required.

4.1.2 Affective Dysregulation (Mood and Anxiety Symptoms)

Domain 2, Affective Dysregulation, was associated with an adjusted HR for incident cognitive decline and dementia of 1.45. Two previous systematic reviews and meta-analyses of case-control and cohort studies in non-dementia populations found depression to be associated with a 2-fold increase in risk of dementia (Jorm, 2001, Ownby et al., 2006). Similarly another recent meta-analysis of community-based MCI studies found depression to have a pooled Risk

Ratio for dementia of 1.69 (Tan et al., 2019). Meta-analysis has also determined anxiety to be a predictor of cognitive decline and dementia with Relative Risks of 1.77 and 1.57 respectively (Gulpers et al., 2016). A recent meta-analysis investigating the impact of anxiety on progression from MCI to dementia estimated a pooled HR of 1.18 (Li and Li, 2018). Thus, our findings for risk associated with affective dysregulation are also consistent with the published literature.

Affective dysregulation had the greatest heterogeneity of the 5 domains, with an I^2 of 87.0%. Both follow up time (continuous variable) and NPS ascertainment approach were significant contributors to heterogeneity. Previous meta-analyses have similarly reported heterogeneity due to the duration of follow-up (Chen et al., 2018, Ownby et al., 2006, Gulpers et al., 2016). Included studies had follow-up times ranging from 1-17 years. We used a continuous and dichotomized ($\leq$3 years vs > 3 years) variable to classify follow up time. For dichotomization, 3 years was chosen as the cut-off based on previous longitudinal studies in cognitively normal older adults (Ismail et al., 2021). The rationale was that 3 years is an acceptable wait-time to capture cognitive change, without being so long that participants might be lost to attrition and other age-related diseases. This dichotomization revealed that shorter studies were associated with greater risk than longer studies, with estimated HRs of 2.36 vs 1.55 respectively. This finding might seem counterintuitive. However, one might speculate that in longer studies, the non-exposed group may have enough time for other dementia risk factors to take effect. For example, in an included study with 14 years of follow up data, the association between depression and incident dementia was only apparent in the first 5 years of exposure, after which the association disappeared. The authors interpreted this finding as support for emergent depression in older adults as a prodromal feature of dementia (Almeida et al., 2017). The Whitehall Study reported a similar finding with an 11-year risk period (Singh-Manoux et al.,

2017). The findings from these studies support later life onset of depression as a potential prodromal feature of dementia, consistent with the core MBI criterion of symptom emergence in later life.

NPS assessment approaches were also contributors to heterogeneity in this domain, consistent with previous findings (Cacciamani et al., 2017, Sánchez-Benavides et al., 2018, Verhülsdonk et al., 2013). Study publication dates ranged from 1996 to 2022, and therefore included variable approaches to assessing NPS. For example, NPS ascertainment tools included different versions of the Geriatric Depression Rating Scale (e.g., GDS-15; GDS-30), two versions of the Neuropsychiatric Inventory (NPI; NPI-Q), and DSM criteria, amongst others. These approaches fundamentally differed by the source of information on affective symptoms (i.e., informant-, self-, or clinician-rated/diagnosed). Interestingly, stratification revealed informant-reported affective symptoms to have a substantially higher risk of cognitive decline and dementia, relative to self- and clinician-rated symptoms (HR 3.06 vs 1.55). This difference may possibly reflect misclassification bias. One reason for this bias may be anosognosia, a symptom whereby the patient is unaware of their cognitive or behavioral symptoms. Affective anosognosia has been described in dementia (Verhülsdonk et al., 2013). Indeed, in cogntively normal older adults, anosognosia for cognitive deficits, better reported by informants, was considered a robust marker of preclinical disease, associated with AD biomarkers and (Cacciamani et al., 2017). Similarly, our findings suggest that even in cognitively normal older adults, NPS reported by informants may be better dementia prognosticators than self-reported symptoms. Accordingly, a recent meta-analysis has found that the NPI and NPI-Q (in which symptom information is obtained from an informant) predict progression from MCI to dementia (Mallo et al., 2020). Similarly, clinician-rated measures (usually based on an interview with a

patient who reports the presence or absence of symptoms) may also be susceptible to anosognosia, thus providing less prognostic utility than informant reports.

It is also important to address clinician-rating in prospective cohort studies, which may be associated with misclassification bias in outcome. This type of bias is related to the principle that raters have increased suspicion of the disease, which leads to greater sensitivity and lower specificity. In our study, the HRs were stratified using a dichotomous variable; (i.e., informant- vs self- or clinician-rated/diagnosed) based on the findings from the meta-regression models. Our findings associated the clinician-rated and self-rated NPS with lower HR than informant-rated, which could be explained by the fact that the majority of the studies utilized a self-rated tool and only 6 studies utilized a clinician-based assessment of NPS. There is an identified need for future studies investigating the association using different informant-based methods and clinician-based methods to assess the degree of impact on classification methods implemented, and to minimize the observed heterogeneity when attempts are made to conduct meta-analyses. An MBI-C validation highlights this issue in which factor analysis revealed different factor structures for self- and informant-reports, with slightly different prevalences of MBI domains (Creese et al., 2020).

Publication bias was evident in this domain, consistent with 2 previous meta-analyses of depression and dementia risk (Ownby et al., 2006, Mourao et al., 2016). Publication bias can overestimate the HRs due to selective publication of only significant studies, leaving non-significant findings unpublished (and thus not represented meta-analyses). The trim and fill method was used to adjust for this bias, and the measure of interest remained in the same direction and significant after study imputation. This finding implies that the association in

question is substantial, but as this is a simulation technique, replication in the future will be important.

4.1.3 Impulse Dyscontrol (Agitation, Aggression, and Impulsivity Symptoms)

Domain 3, Impulse Dyscontrol, was associated with a HR of incident cognitive decline and dementia of 3.07. Several longitudinal studies in MCI have associated agitation and/or aggression with incident dementia, with HRs ranging from 1.6–4.4 (Dietlin et al., 2019, Forrester et al., 2016). In older adults with normal cognition, agitation, aggression, and impulsivity might be attributed to aging, and not routinely considered in dementia prognostication. Our findings suggest that these clusters of NPS are of concern due to the high risk of dementia, suggesting more routine measurement of NPS in older adults with suspected behavioral changes. Interestingly, there was no significant heterogeneity in this domain with I^2 =32.89%, as similar agitation measures (NPI/NPI-Q) were used in all studies, and all studies included community-based populations where follow up time did not vary significantly (2 - 5 years). Thus, meta-regression models were not fitted.

4.1.4 Social Inappropriateness (Impaired Social Cognition and Social Disinhibition Symptoms)

Domain 4, Social Inappropriateness, was associated with a HR of incident cognitive decline and dementia of 3.84. A longitudinal study analyzing the incidence of dementia in a mixed MCI and NC Mexican-based population reported a relative risk of 1.5 for dementia in those with disinhibition (Acosta et al., 2018). Thus, while disinhibition is not common in older adults, when present, the associated risk for cognitive decline is elevated.

This domain had substantial heterogeneity (I^2= 70.91%), with the cognitive outcome variable a significant contributor. Meta-regression was not attempted due to the lack of statistical power given the number of the included studies. More studies are recommended exploring the association of disinhibition and the risk of cognitive decline in the cognitively normal target population.

4.1.5 Thoughts and Perception (Psychotic Symptoms, i.e., Hallucinations and Delusions)

MBI domain 5, Thoughts and Perception, was associated with an HR of incident cognitive decline and dementia of 3.99, the highest estimated risk in our study. Longitudinal studies in mixed non-dementia samples have found psychosis to be associated with a high risk of incident cognitive decline, evaluated by the Mini Mental State Examination (MMSE), with an OR of 5.66 (Soares et al., 2017). Two more studies estimated delusions to be associated with a HR of incident dementia of 2.8 in a mixed group of MCI and CN and 1.7 in a CIND (i.e., MCI) group (Acosta et al., 2018, Peters et al., 2013). Psychosis is also a low frequency NPS, much less common in MCI than dementia. Although infrequent in MCI, psychosis carries an 8-11-fold increased risk of developing dementia (Martin and Velayudhan, 2020). Thus, psychotic symptoms are felt to have greater prognostic value than other NPS (Dillon et al., 2013, Fischer and Agüera-Ortiz, 2018, Ismail et al., 2022).

In our study, this domain had substantial heterogeneity with I^2=77.21%; regression models revealed study quality to be a contributor. These findings align with previously published literature investigating psychotic symptoms in dementia-free older adults (Lyketsos et al., 2002, Apostolova and Cummings, 2008, Köhler et al., 2013, Kørner et al., 2009).

4.2. Limitations

Several limitations need consideration for interpretation of findings, including: 1) the number of identified studies in each domain; 2) heterogeneity; 3) publication bias; and 4) study quality.

4.2.1 Identified Studies

Compared to MCI, fewer published studies have investigated the exposure of interest in cognitively normal populations, which led to three domains with <10 studies included in the final meta-analysis. It is commonly recommended to have at least 10 studies per variable of interest when attempting meta-regression, otherwise, reliability may be in question (Schmidt and Hunter, 2015). The novelty of MBI and the study of NPS in cognitively normal older adults may be a contributor to the dearth of studies in some of the domains. Most dementia risk studies have been completed in MCI populations or in mixed non-dementia populations of normal cognition and MCI; neither of these populations could be included in this meta-analysis. Further, this study could not include several of the identified studies in the meta-analysis since the reported estimates did not apply to our methodology. For example, studies were not included if the outcome was reported as a z-test (Burhanullah et al., 2020), or if Cohen's d was used to report effects (Gulpers et al., 2019). Finally, most of the identified studies were community-based populations with the exception of (Verdelho et al., 2013) which is an issue of generalizability, as the estimates might differ in clinic-based populations.

4.2.2 NPS Ascertainment Approach

Not all studies had similar tools to capture NPS of interest, although most of the informant-based studies used the NPI/NPI-Q. However, these scales were primarily developed to measure

NPS in dementia patients (Ismail et al., 2021). The Mild Behavioral Impairment Checklist (MBI-C) was developed specifically to capture later life emergent and persistent NPS in functionally independent community-dwelling older adults (Ismail et al., 2017a). MBI criteria stipulate that NPS must persist for ≥6 months, resulting in greater specificity and signal-to-noise ratio for detecting symptoms that may be sequelae of underlying neurodegenerative disease, as opposed to symptoms that manifest due to social, economic, interpersonal, or medical concerns. Future studies using this validated tool may provide even more precise estimates of risk, although more studies are required.

4.2.3 Study Quality

Study quality was found to be significant in the meta-regression models in the psychosis domain, suggesting that quality of some of the included studies was not ideal. Included studies were missing information on non-respondents, utilized a wide range of approaches to capture psychosis, and incorporated various methods to quantify cognitive decline, MCI, and dementia. While the extent of these variations on each study level was not considerable (with only minor influence on the final reported measures of effects), variability in methodology likely did contribute to the observed heterogeneity found in this present meta-analysis.

5. Implications

To our knowledge, this meta-analysis is the first to comprehensively quantify the association between NPS in cognitively normal older adults and the risk of incident cognitive decline and dementia, classified by the MBI domains described in the recent ISTAART-AA MBI criteria. Notwithstanding the limitations, our study provides valuable information on the utility of assessing NPS in cognitively normal older adults for dementia risk assessment, when

neurodegenerative disease may not be on the differential diagnosis, consistent with some clinical guidelines (Ismail et al., 2020, Montero-Odasso et al., 2020). This meta-analysis provides clinicians with pooled HRs for each specific MBI domain. Quantifying the risk provides clinicians concrete estimates, to assist in clinical decision making. This quantification also provides researchers estimates that can help inform future studies and estimate power and sample size for investigations. Further studies are required, using more rigorous and consistent methodology, incorporating NPS measures developed for dementia prognostication, and linking with biomarkers of neurodegenerative disease. This study provides a launching point for future research, which can explore use of predictive methods (e.g., machine learning) to confirm the validity of the implied risk stratification.

Competing Interests:

ZI has received funds from Otsuka/Lundbeck. His institution has received funds from Acadia, Biogen, and Roche. The remaining authors declare no competing interests.

Chapter Three: Discussion

3.1 Summary of main findings:

This dissertation has investigated the association between NPS and cognitive decline in cognitively normal older adults. A systematic review and meta-analysis of relevant longitudinal studies was completed to quantify the risk of incident cognitive decline, mild cognitive impairment (MCI), and dementia in cognitively normal cohorts with NPS (Chapter 2). To our knowledge, this systematic review and meta-analysis is the first to collectively assess each MBI domain in cognitively normal older adults and quantify the risk.

Although studies have explored the association between later-life NPS and cognitive decline (van Dalen et al., 2018a, Geda et al., 2013, Gulpers et al., 2019, Li and Li, 2018, Martin and Velayudhan, 2020), this review was motivated by the publication of the ISTAART-AA MBI criteria in 2016 (Ismail et al., 2016). These criteria recognized that new-onset NPS in later life could signify dementia risk, with the risk for behavioural symptoms (NPS) serving as a complement to the risk represented by cognitive symptoms. That cognitive (MCI) and behavioural (MBI) risk states could co-occur signified a change from the original construct of the behavioural prodrome to dementia (in which cognition and behaviour were competing constructs) (Taragano and Allegri, 2003). Further, the ISTAART-AA MBI criteria organized NPS into 5 domains to be assessed for dementia prognostication. These domains are impaired drive and motivation (apathy), affective dysregulation (mood and anxiety symptoms), impulse dyscontrol (agitation, aggression, impulsivity), social inappropriateness (impaired social cognition, social disinhibition), and abnormal thoughts and perception (psychotic symptoms, i.e., delusions and hallucinations). However, given that behavioural symptoms can precede cognitive

symptoms in many, and most studies were conducted in MCI or unspecified non-dementia samples, there existed a need to determine risk from behavioural symptoms alone (i.e., in cognitively normal cohorts) as an approach to earlier assessment of dementia risk. Thus, this systematic review and meta-analysis was completed to summarize the literature and generate a single measure of effect for each domain.

With adherence to PRISMA and MOOSE guidelines, 12,674 abstracts were screened, 346 full text articles reviewed, and ultimately, 36 studies representing 326,739 participants were selected for inclusion in the meta-analysis (Manuscript Table 1 and Figure 2). Risks (HR) for incident cognitive decline or dementia by MBI domain were: 1) apathy 2.00 (95% CI: 1.57-2.57); affective dysregulation 1.61 (95% CI: 1.45-1.80; adjusted HR 1.44, 95% CI :1.30-1.61); 3) agitation 3.07 (95% CI: 2.15-4.38); 4) social inappropriateness 3.84 (95%CI: 1.54-9.55); and 5) psychosis 3.99 (95% CI: 3.05-5.23) (Chapter 2, Figure 1 Graphical abstract).

Heterogeneity was observed (Chapter 2, Table 3) in apathy I^2=82.85% and tau^2=0.10, affective dysregulation (I^2=86.60%, tau^2=0.04), social inappropriateness (I^2=70.91% and tau^2=0.44), and psychosis (I^2=77.21% and tau^2=0.08). For apathy, NPS ascertainment approach contributed to heterogeneity, with informant-reported apathy symptoms having a substantially higher risk of cognitive decline and dementia relative to self-and clinician-rated symptoms (HR 2.53 vs 1.51). For affective dysregulation, follow-up time and NPS ascertainment approach were the main contributors to heterogeneity, with shorter studies associated with greater risk than longer studies (HR 2.36 vs 1.54), and informant-reported affective symptoms having greater risk than self- and clinician-rated (HR 3.06 vs 1.54). For psychosis, study quality contributed to

heterogeneity, although stratum-specific estimates were not determined due to the small number of studies.

Publication bias was found in the affective dysregulation domain, as evidenced by the Egger test and funnel plots (Chapter 2, Table 6, and Figure 5b). The trim-and-fill method was implemented to impute theoretically missing studies, and with the addition of 10 studies, the adjusted HR declined to 1.44 from 1.60 (Chapter 2, Table 6, and Figure 5b).

3.2 Strengths of the Study

Registration of the systematic review protocol on PROSPERO was a strength. Having the protocol published first helps to ensure study quality and integrity and allows for comparisons between the reported review methods and the initially planned design. Additionally, registration at the early stages of the review helps avoid duplication of effort from other research groups. This study established predetermined inclusion and exclusion criteria for study selection at the screening phases of the study. The inclusion criteria were guided the PICO framework, which helped formulate a focused primary research question (Richardson et al., 1995). A well-formulated research question is a crucial step in synthesizing evidence-based decisions, as was done in this study.

Adherence to PRISMA and MOOSE was another strength. PRISMA stands for Preferred Reporting Items for Systematic Reviews and Meta-Analysis and is an evidence-based set of items utilized for reporting this type of study. MOOSE stands for Meta-analysis of Observational Studies. PRISMA is comprised of a 27 item checklist and a 4-phase flow diagram (Moher et al.,

2009). The MOOSE checklist focuses on reporting the conducted synthesis and utilization of data from observational studies (Stroup et al., 2000). Making PRISMA and MOOSE checklists available for review (Appendix B) promotes transparency in reporting methods and findings and ensures that the systematic review and meta-analysis meets the standards of quality evidence synthesis. This also enables other reviewers and authors to critique the quality of the completed work.

3.3 Challenges and Limitations

3.3.1 Dearth of studies in normal cognition

This meta-analysis was based on a limited number of longitudinal studies in 3 out of the 5 MBI domains investigated, which is a limitation. In conducting the database search, we made sure to utilize general search MeSH terms identified by the librarian and the tree of MeSH terms specifically for each database to establish a comprehensive search. We identified previously published systematic reviews in each specific NPS domain and used them as a reference to identify any possibly missed studies. Additionally, we hand-searched the reference lists of the included studies to identify relevant studies, utilized expert knowledge (ZI) to explore any recently published studies or those in press, and searched the grey literature to locate any unpublished or missing from our systematic search. Our search was updated; the most recent search was completed in January 2022 to capture the most current literature. Unfortunately, most dementia risk studies have been completed in MCI populations or mixed non-dementia populations of NC and MCI; neither of these populations could be included in this meta-analysis due to the focus on normal cognition (but are important and worthy of consideration in subsequent meta-analyses). The novelty of the published MBI criteria and the previously limited

interest in NPS in cognitively normal older adults may have also contributed to the dearth of studies in some domains. However, this is anticipated to change. There has been a recent surge in papers and editorials on MBI, given the global uptake of the construct, expansion into other clinical areas, and relevance to low and middle-income country public health (Sweeder et al., 2021, Leon, 2022, Gatchel, 2021, Leppla et al., 2021, Mortby, 2021, Sultzer, 2019, Yoo et al., 2020). Future studies can be informed by this one.

3.3.2 The impact of heterogeneity

Detecting and identifying the sources of heterogeneity in meta-analyses is an important step. Heterogeneity is a measure of the variability between the included studies. It can arise from: 1) methodological heterogeneity, from studies using different design methods (e.g., type of outcome measure or follow-up time); 2) clinical heterogeneity, due to different participant clinical features (e.g., medical comorbidities, age, setting); and 3) statistical heterogeneity, from different analytical approaches used to quantify the outcome measure (e.g., time-to-event analyses, logistic regressions). In this study, both methodological heterogeneity and statistical heterogeneity were evident.

Methodological heterogeneity in apathy and affective dysregulation, was, in fact, an exciting finding from our study. Our meta-regression analysis revealed that the source of information on the reported symptoms (i.e., informant-, self-, or clinician-rated/ diagnosed) was found to be a contributor to heterogeneity. These findings might suggest a non-differential misclassification bias which biases the estimates towards the null - as we can see, the HR was lower in the self-rated/clinician-rated stratum. Thus, further research based on rater is required to explore misclassification bias and clinical and epidemiological differences between groups.

Additionally, meta-regression models showed length of follow-up time was a methodological difference that contributed to heterogeneity. While it is challenging to harmonize studies by follow-up time when the number of studies are limited, this is a consideration for future research.

Regarding statistical heterogeneity, we included only HRs and ORs as measures of effect; some studies were excluded due to the use of other measures of effect, which would be difficult to harmonize and pool into one meta-analysis. For example, the (Burhanullah et al., 2020) study was excluded as the reported measure of effect was a z-test. Nonetheless, it is important to measure statistical heterogeneity (or between-study heterogeneity). This can be accomplished with the following tests: 1) Cochran's Q statistic; 2) Higgins' and Thompson's I^2 ;3) the between-study variance t^2; 4) H^2, derived from Cochran's Q; and 5) R^2, similar to H^2 and calculated from t^2 (Rücker et al., 2008). While I^2 is the most used method to report statistical heterogeneity in meta-analyses, it is not the best measure of heterogeneity. I^2 is commonly used given its ease of interpretation by clinicians as the percentage of variability between studies, not due to sampling error (Rücker et al., 2008). Additionally, the Cochrane Handbook for Systematic Reviews of Interventions provides arbitrary cutoffs of thresholds for I^2 of heterogeneity which could be misleading since this test can be affected by other factors like the number of patients included in a meta-analysis (Rücker et al., 2008, Higgins et al., 2019). The decision to pool studies in a meta-analysis should not be based only on the percentage of I^2 but rather the clinical relevance (Rücker et al., 2008).

In this dissertation, we reported statistical heterogeneity using I^2 and t^2 statistics. The t^2 is not measured by an absolute scale like the rest; it is measured on a scale but reported as an

outcome quantifying between-study variability. The advantage of this estimate is that it is not affected by the number or size of the studies (Rücker et al., 2008). Statistical heterogeneity was significantly evident in 4 MBI domains: apathy, affective dysregulation, social inappropriateness, and psychosis, utilizing I^2 statistics. I^2 was more than 70% in these 4 domains. According to ranges for interpretation of I^2 following the Cochrane Handbook for Systematic Reviews of Interventions, I^2 between 75% to 100% implies considerable heterogeneity. Given the clinical importance of pooling the measures of effects in question, we continued with the meta-analyses by utilizing the between-study variance t^2 as an expression of heterogeneity. We did not count solely on the arbitrary thresholds of I^2, which would have suggested against pooling those studies together.

3.3.3 Publication bias and missing studies

Publication bias poses a severe threat to the validity of pooled measures of effect in meta-analysis studies. Publication bias is a systematic error that can lead to inflated benefit or overestimation of the effect size in question. Publication bias arises from unpublished literature due to non-significant findings or publishing journal biases. In the last 3 decades, it has been evident that publication bias is more common than we would like, especially in psychiatry/psychology (Rosenthal, 1979). A study investigating publication bias in 91 meta-analysis studies in the field of psychological sciences found that 20% to 40% of the studies reported publication bias (Ferguson and Brannick, 2012). A recent meta-meta-analysis of 582 systematic reviews and meta-analyses from Psychological Bulletin and the Cochrane Database of Systematic Reviews found evidence for mild publication bias in psychology and medicine (Van Aert et al., 2019). In our study, publication bias was found in the affective dysregulation domain.

We used several methods to assess for publication bias in this study. One method was to visualize the symmetry of the funnel plots generated. The funnel plot is a graphical representation of the effect size and its precision. The objective of the funnel plots is to illustrate the presence of small-study effects. The x-axis represents the effect size, the y-axis represents the standard error, and the circle dots represent each study. In the event of no publication bias, the funnel plot should be symmetrical. The presence of a gap in the funnel or asymmetry implies small-study effects. Small-study effects can be due to publication bias (Egger et al., 1997). We also utilized Begg's and Egger's tests (Begg and Mazumdar, 1994) to assess for publication bias. Begg's test computes the rank correlating (Kendall's t) while Egger's uses linear regression to determine the small-studies effect. In our study, the funnel plots showed asymmetry, and Egger's test was significant for the affective dysregulation domain.

We corrected for publication bias in this SRMA study using a trim-and-fill approach. We utilized the Duval and Tweedie method, which is a nonparametric (rank-based) data augmentation technique to help with the symmetry of the observed included studies. This method imputes additional studies, allowing for estimate adjustment based on the hypothetically missing studies from publication bias (Duval and Tweedie, 2000). If the adjusted effect remains substantial, in the same direction, and consistent with clinical presentation in clinical practice, the trim-and-fill method can be applied despite heterogeneity. Although we understand that trim-and-fill doesn't fix the systemic error, it helps to observe the adjusted estimates and see if they have significantly shifted from the pooled estimate. The agreement in regards to the direction of the estimated and corrected effect is of more importance to researchers (Van Aert et al., 2019). It

is also vital that the resulting estimate is consistent with established estimates published in the literature and consistent with the observed clinical picture in practice.

3.3.4 Study Quality [Risk of Bias]

Bias risk assessment is a crucial step in producing a high-quality meta-analysis study. Bias risk assessment is a mandatory requirement of the PRISMA (Moher et al., 2009). This step helps identify and categorize the individual study's methodologies, which enables the identification of studies with a high risk of bias. The inclusion of biased or poor-quality studies can compromise the meta-analysis results, jeopardize the quality of work, and produce overestimated or underestimated measures of effect. Therefore, assessing a study's quality and risk of bias is crucial before conducting the meta-analysis to flag potentially problematic studies and guarantee the quality of the produced work (Chan and Harky, 2020).

This study utilized the Newcastle-Ottawa Quality Assessment Scale (NOS) (Wells et al., 2000). We used an adapted version of the Newcastle-Ottawa Quality Assessment Scale to assess the methodological quality of the included observational/cohort studies. The selection of this tool was based on its widespread use in this field of literature. The scale consists of 3 main categories: 1) selection (4 points); 2) comparability (2 points); and 3) outcome (3 points), which are used to classify studies as good, fair, or poor.

Study quality was significant in the meta-regression models for the psychosis domain. Few of the included studies were missing information on the non-respondents' question under the selection category, also known as attrition bias. It is important to mention that there were only 6 included studies and 7 measures of effects in this domain, which is not statistically ideal

when running meta-regression models. It is recommended to have at least 10 studies to run meta-regression models to obtain statistical power and draw inferences with more confidence (Higgins et al., 2019). Future research exploring the association of psychosis and incident cognitive decline and dementia is urged to enable meta-regression models with better statistical power.

3.4 Public Health, Clinical, and Research Implications

Epidemiology is the foundation of public health. Epidemiology studies disease distribution and health determinants in populations (Patten, 2015). The natural stages of disease are classified based on disease progression over time and into 5 stages: underlying, susceptibility, sub-clinical, clinical presentation, and disease outcome (Kisling and J, 2022). Public health activities focus on population-based disease prevention and promotion of health by programs and policies. There are four main types of interventions established for disease prevention, grouped based on the identified stages of the disease: primordial, primary, secondary, and tertiary (Kisling and J, 2022, Patten, 2015). Given the course of dementia disease and the lack of clear knowledge around exact pathological pathways that leads to its development, we focus on secondary prevention in this dissertation.

It is vital to understand impact of dementia on an individual's family and on society. Dementia places a high burden on caregivers. In 2019, it was found that informal caregivers (i.e., family members) spend an average of 5 hours daily providing care to their dementia suffering family members (WHO, 2021), which can also lead to emotional, physical, and financial stress on the family. Patients with neurocognitive disorders affect the health economic system in the form of multiple doctor visits, emergency room visits, hospitalization, and requirement for support services and supportive living in long-term care facilities. As of 2016, according to the

National Population Health Study of Neurological Conditions, the estimated monetary cost of dementia in Canada is $10.4 billion annually. This estimated cost includes the estimated costs to the Canadian healthcare system and out-of-pocket caregiver costs. This cost is estimated to rise to $16.6 billion by 2031with the current estimated incidence rates (Canada, 2016). Globally, the estimated societal cost in 2019 was US$ 1.3 trillion, and it is expected to reach and exceed US$ 2.8 trillion due to increased incidence rates and care costs (WHO, 2021).

Dementia is incurable. Current medications treat symptoms without changing the course of disease. Nonetheless, early detection of cognitive impairment offers a wide range of possible benefits for the patient, like access to resources to facilitate functioning in the community, introduction of cholinesterase inhibitors medications when necessary, and harm reduction by identifying unsafe driving and other safety issues (Tang-Wai et al., 2020). For development of disease modifying drugs, detection also needs to be earlier, to intervene before disease has progressed too far to make a difference. However, early detection has been challenging.

We found associations between MBI domains and subsequent cognitive decline. But does this mean MBI domains cause cognitive decline? Hill's criteria for causality in a nutshell are as follows: 1) strength; 2) consistency; 3) specificity; 4) temporality; 5) biologic gradient; 6) plausibility; 7) coherence; 8) experimental evidence; and 9) analogy. Our study focused on temporal sequence. Studying the temporal relationship of risk factors and disease is important for early detection, but it can be difficult to distinguish between associations vs true causality (Ganguli and Kukull, 2010). Temporal sequence is accomplished when the exposure of interest was evident in the study sample prior to developing the outcome of interest like prospective

studies (Hill, 1965). One can argue that it is obvious from the pooled HRs that there is an association between NPS and incident cognitive decline. But, we don't know if, in these samples, the brain changes that cause dementia also produce late-onset NPS (Robert van Reekum et al., 2001). Prospective studies can provide hypotheses around associations but can't confirm causality, and more extensive research is required to do so.

Overall, this notion of temporality applies to NPS. It is essential to distinguish between NPS as *disease marker* and NPS as *disease risk factor*. Professor Mary Ganguli has proposed the general term "predictor" to act as an umbrella harboring any factors associated with the disease incidence (Ganguli and Kukull, 2010). Subsequently, predictors are subcategorized into 2 subsets: 1) evident markers or manifestations that occur before the onset of the disease itself; 2) independent risk factors that can alter disease incidence (Ganguli and Kukull, 2010). The unique position of MBI is that it better serves as disease marker than conventionally measured NPS. This difference is due to the ISTAART-AA core criteria of symptom emergence in later life, representing a shift from longstanding behavioral patterns, and the persistence of these symptoms for at least 6 months. These criteria select a subgroup from the broader group with conventionally measured NPS, in whom NPS are more likely a sequelae of underlying neurodegenerative disease. In the broader NPS group, a larger proportion have symptoms that might present transiently or reactively to life events or psychosocial stressors. While not all with MBI have disease, as a tool for early detection in cognitively normal older adults, it outperforms the alternatives. In contrast, there is a well-established literature describing psychiatric symptoms (especially depression) as a risk factor for disease. Not accounting for temporality and natural

history of symptoms can result in confusion and mixing of NPS as marker and psychiatric syndrome as risk factor. MBI takes this into account. However, more research is required.

Knowledge dissemination and communication of the findings in this study to stakeholders and policymakers is crucial. The pooled estimates of the associated risk of cognitive decline with NPS in the cognitively healthy population are indicators to help policymakers understand the magnitude of the associated risk and the potential economic and social benefits from early detection. Subsequently, it can lead to better allocation of resources to help benefit the public. Lastly, the translation of this body of knowledge to the public and media is important to facilitate learning and understanding more about the disease.

3.5 Directions for Future Research

There is an identified need to conduct more prospective epidemiological studies assessing NPS as potential markers and predictors of incident dementia. Studies are required to help define each stage of the neurodegenerative disease and generate hypotheses to shape clinical and biomarker studies. Exploring the available literature was an attempt to understand the temporal sequence of NPS and cognitive decline. This revealed a lack of sufficient studies investigating the risk of cognitive decline associated with NPS in cognitively normal older adults, and even fewer invoking MBI criteria. Although we generated pooled estimates for risk associated with the 5 MBI domains, i.e., 5 clusters of symptoms in MBI, it is unclear if and how many of the participants in the studies met MBI criteria. As ongoing studies consistent with these criteria are published, a future systematic review and meta-analysis can be completed, to compare risk when expectations are explicit for symptom persistence and later life emergence.

Relatedly, future research needs to utilize a more uniform and consistent methodology to ascertain NPS (exposure of interest). The established methodological heterogeneity between the identified studies in the affective dysregulation domain is a clear example of how the different tools and sources of information can contribute to significant heterogeneity, potentially leading to a non-differential misclassification bias causing the estimates to shift towards the null. There is an identified need for future studies to investigate the association using different self-, informant-and clinician-based methods, ideally in the same sample, especially in high frequency and well-appreciated symptoms like depression.

There is also a need to utilize more specific approaches to measure MBI and employ more prospective measures. Short reference-range scales like the Geriatric Depression scale (1 week), often self-rated, are less likely to capture underlying neuropathology than the NPI, which has a longer reference range and is informant-rated. However, the NPI was primarily developed to assess NPS in patients with dementia. The MBI-C was developed to capture NPS in accordance with the MBI criteria, with a 6-month reference range, and questions framed expressly for functionally independent, dementia-free, community-dwelling older adults (Ismail et al., 2017a). Utilizing the MBI-C may provide more precise estimates of risk, leading to higher quality evidence about this association (Ismail et al., 2021).

The issue of publication bias established in the affective dysregulation domain needs to be addressed in future research. We urge the researchers and publishers to create portals or databases for publishing all conducted studies and research, particularly studies with non-significant findings, to help minimize the issue of publication bias.

3.6 Conclusion

The work presented in this dissertation has estimated the risk of incident cognitive decline, MCI, or dementia in cognitively normal older adults conferred by the presence at baseline of NPS in each of the 5 MBI domains. Several gaps in the literature have also been identified including: 1) a dearth of literature on this topic as evidenced by the small number of studies; 2) the need for more studies utilizing clearly defined exposure criteria of MBI (e.g., late-life onset and persistence over 6 months); 3) the need for better exploration of rater differences and misclassification bias; 4) the need to publish missing studies in the field due to publication bias. This dissertation is a starting point, and by building on the outcomes of this dissertation, progress can be accomplished in better understanding the nature of the association between NPS and dementia, generating more precise estimates, and further validating available instruments like the MBI-C, which was developed for this purpose. Ultimately this work can better inform research, clinical care, and public policy.

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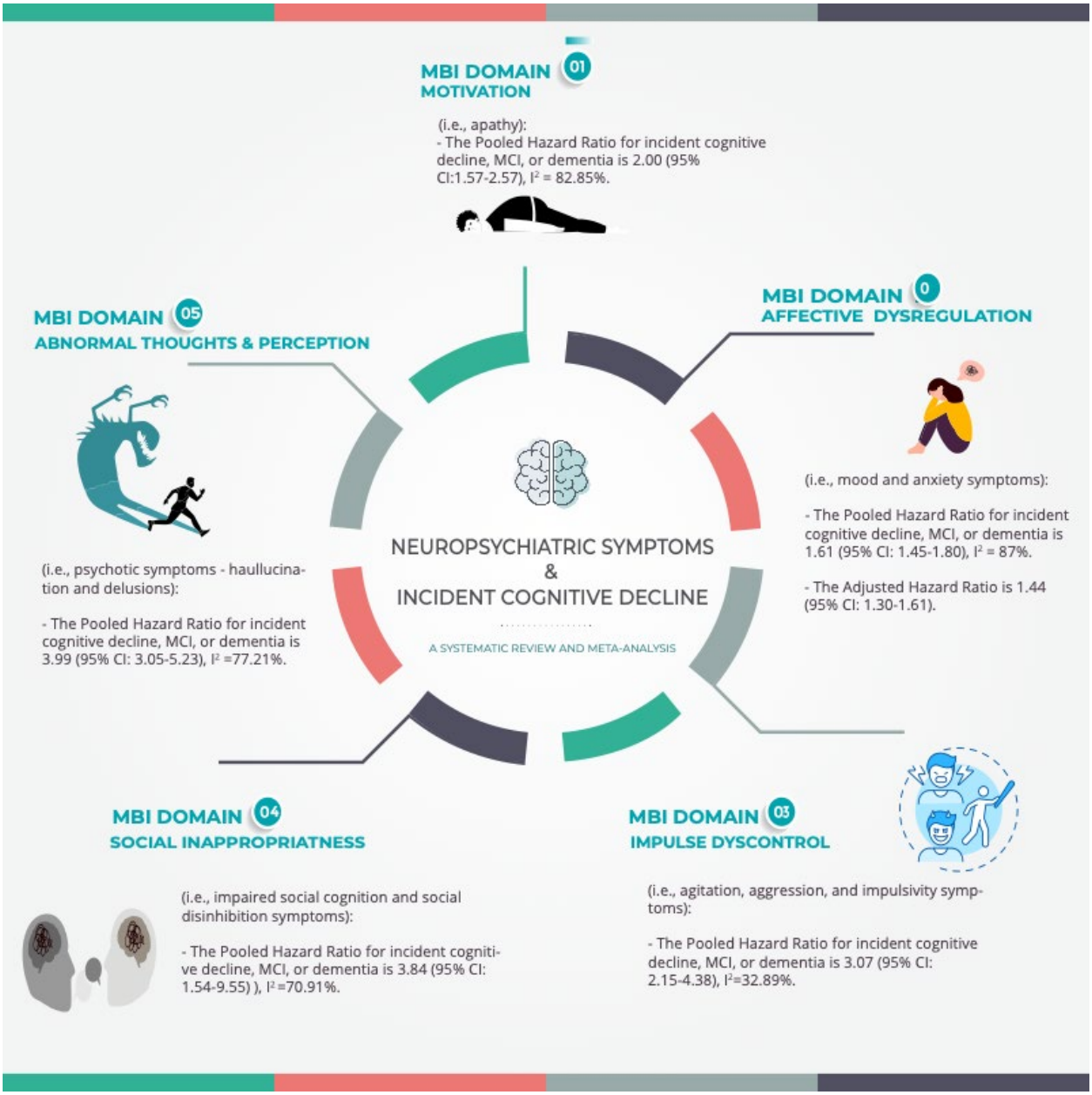
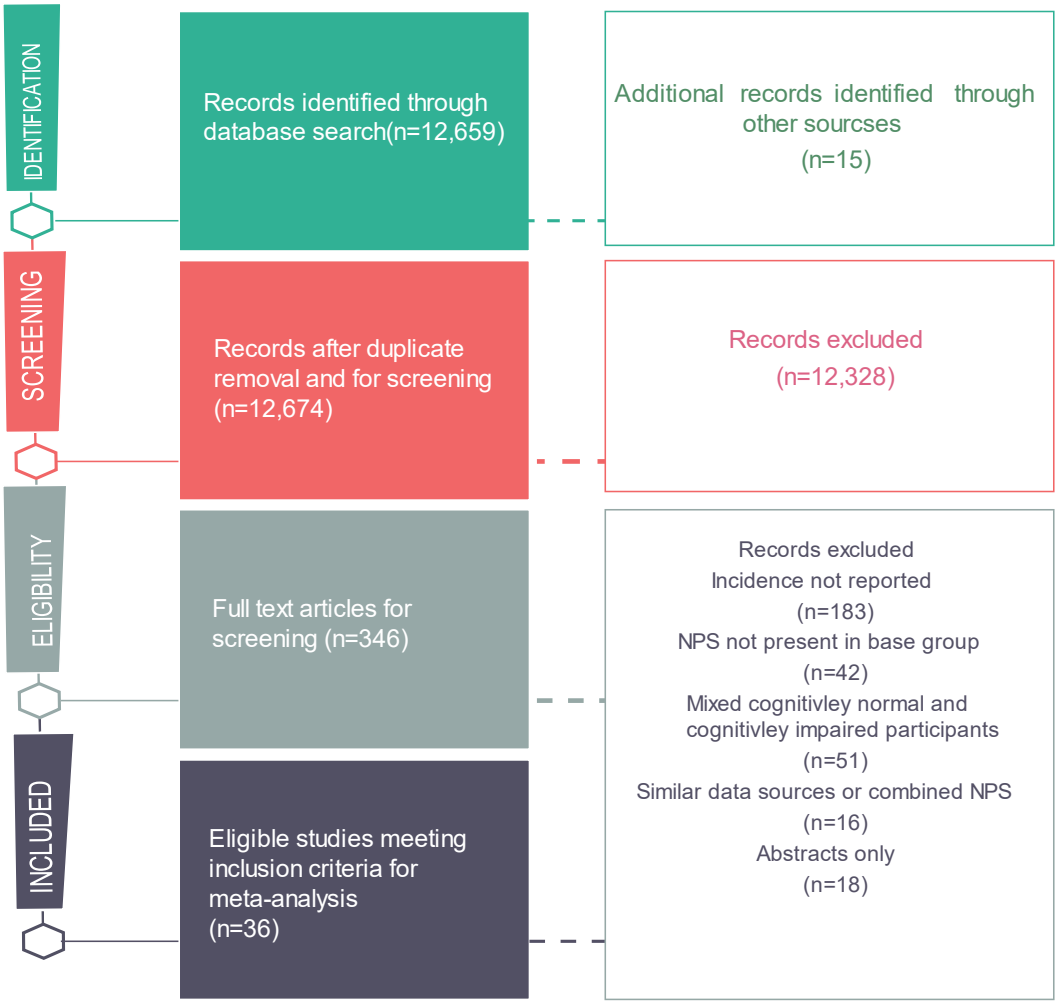
IV Figure 1. Infographic



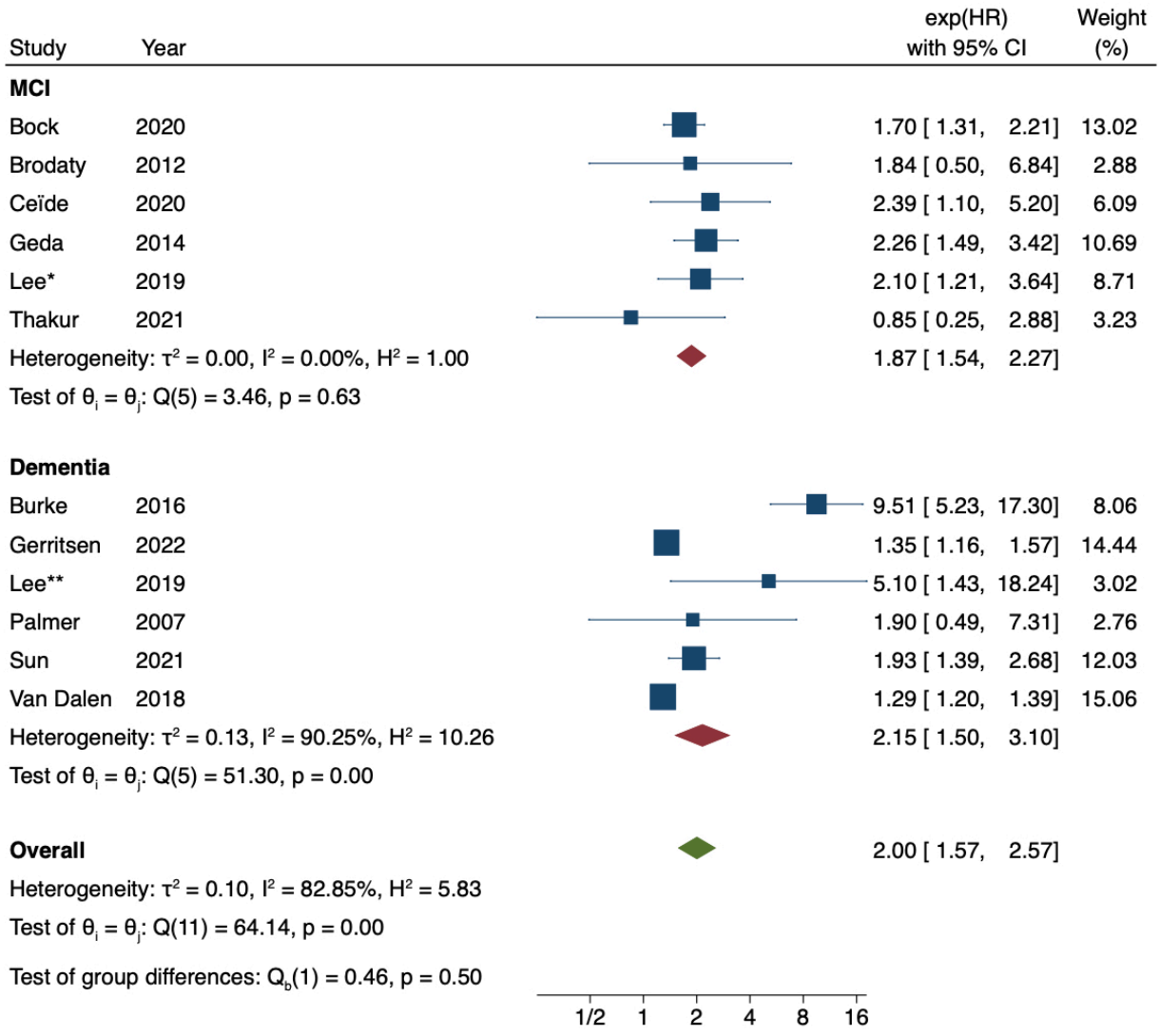
CI-Confidence Interval, HR-Hazard Ratio, MBI-Mild Behavioral Impairment, MCI -Mild Cognitive Impairment.

V Figure 2. The PRISMA Flowchart



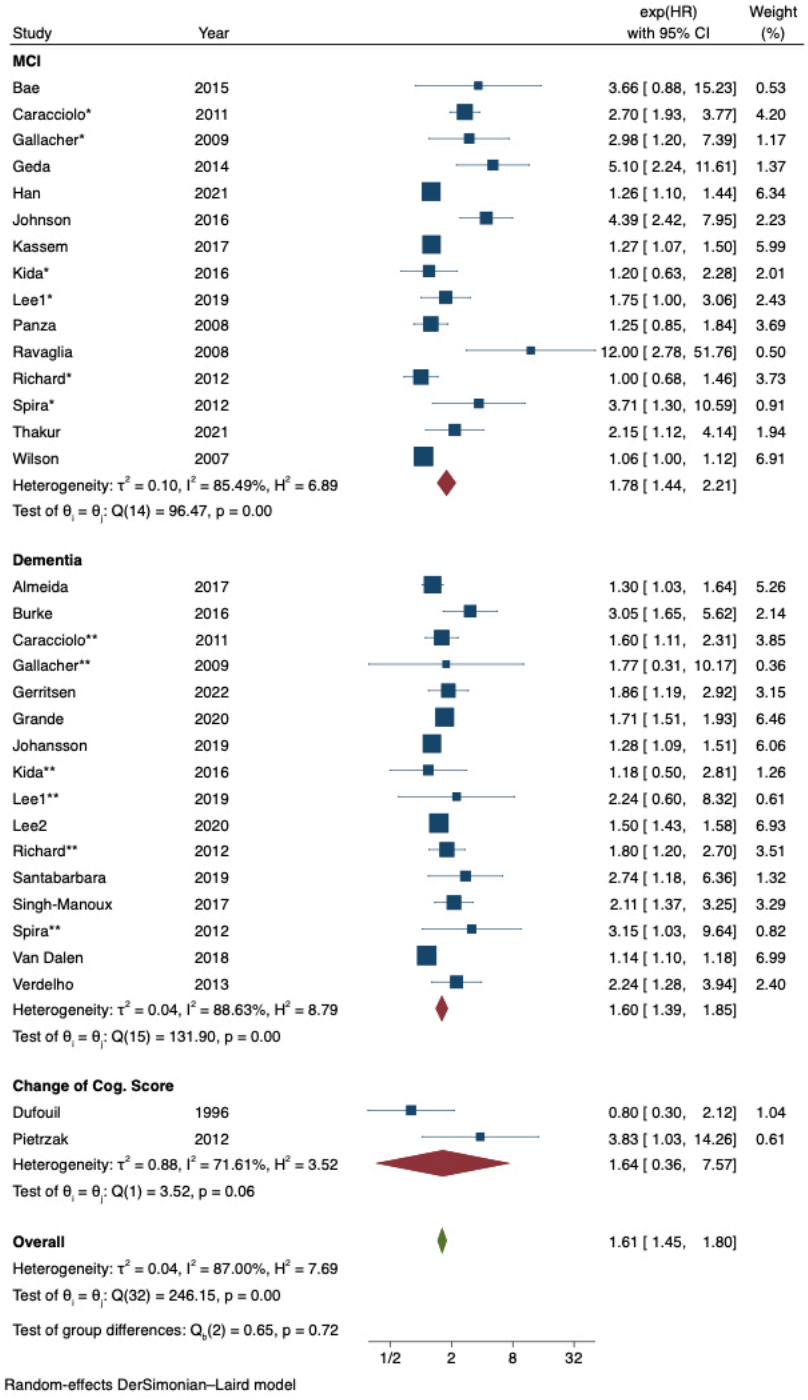
NPS-Neuropsychiatric symptoms.

VI Figure 3a. Apathy forest plots



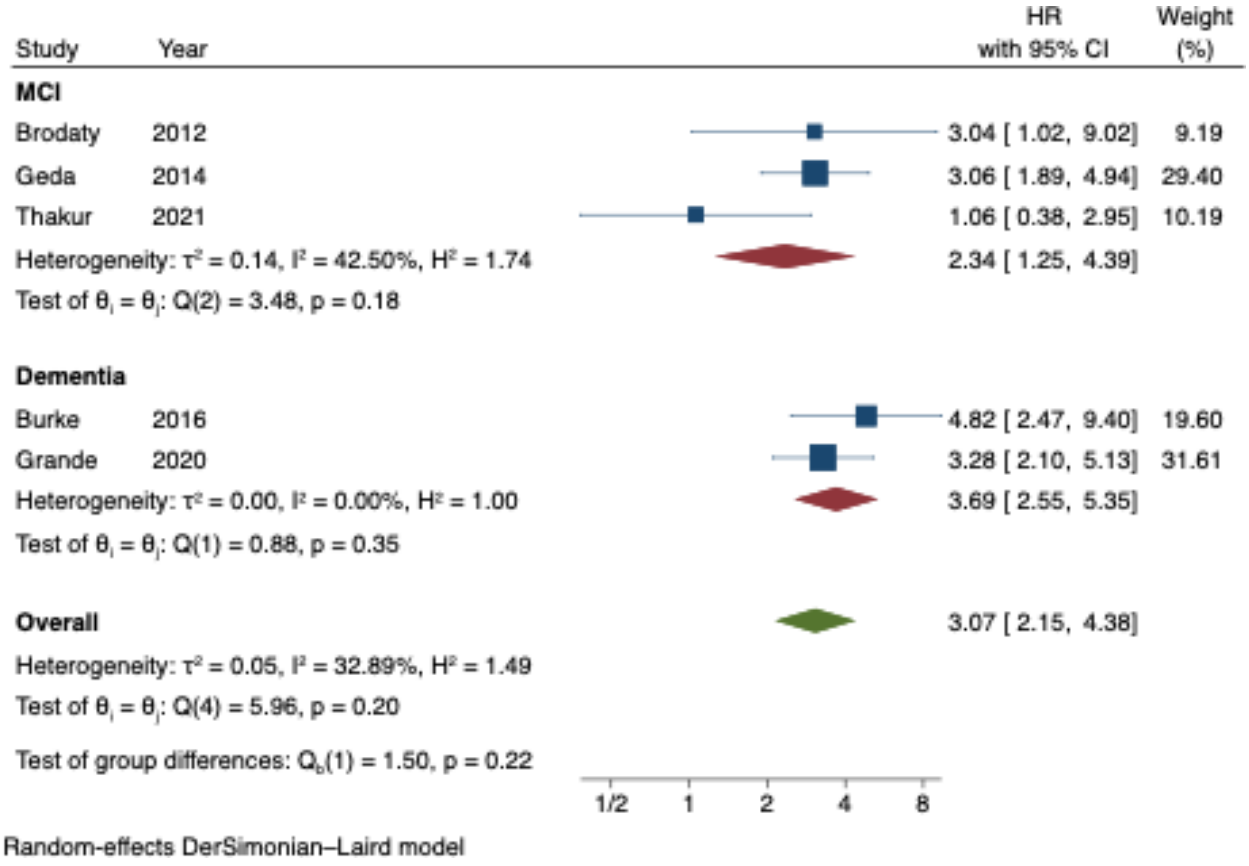
The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds.
CI-Confidence Interval, MCI -Mild Cognitive Impairment, HR-Hazard Ratio, *incident MCI, **Incident dementia.

VII 3b. Affective Dysregulation forest plots



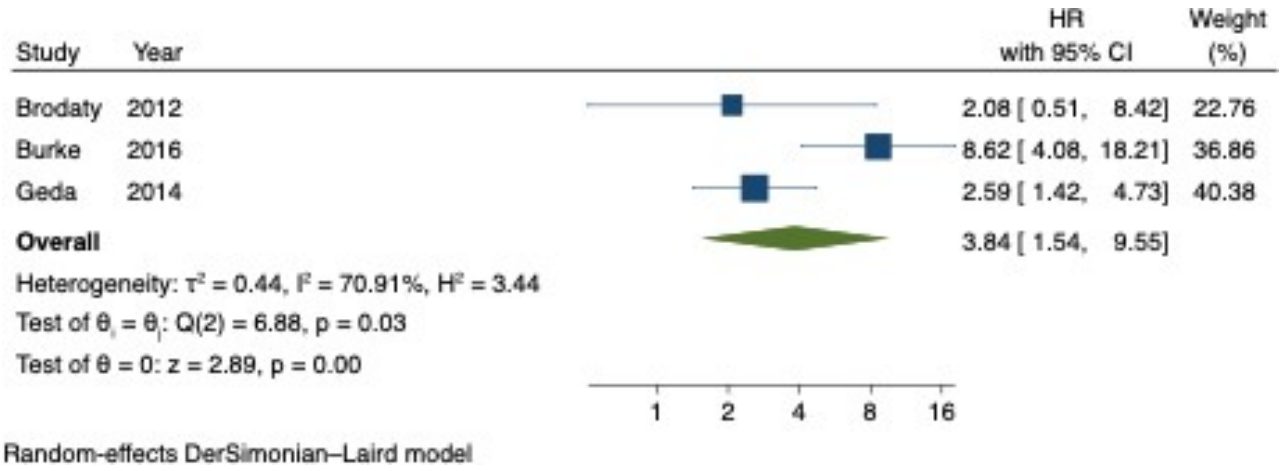
Forest plots showing the risk of depression and/or anxiety on cognitive decline outcome MCI or dementia. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds.
CI-Confidence Interval, HR-Hazard Ratio, MCI- Mild Cognitive Impairment, *Incident MCI, ** Incident dementia.

VIII Figure 3c. Impulse Dyscontrol forest plots



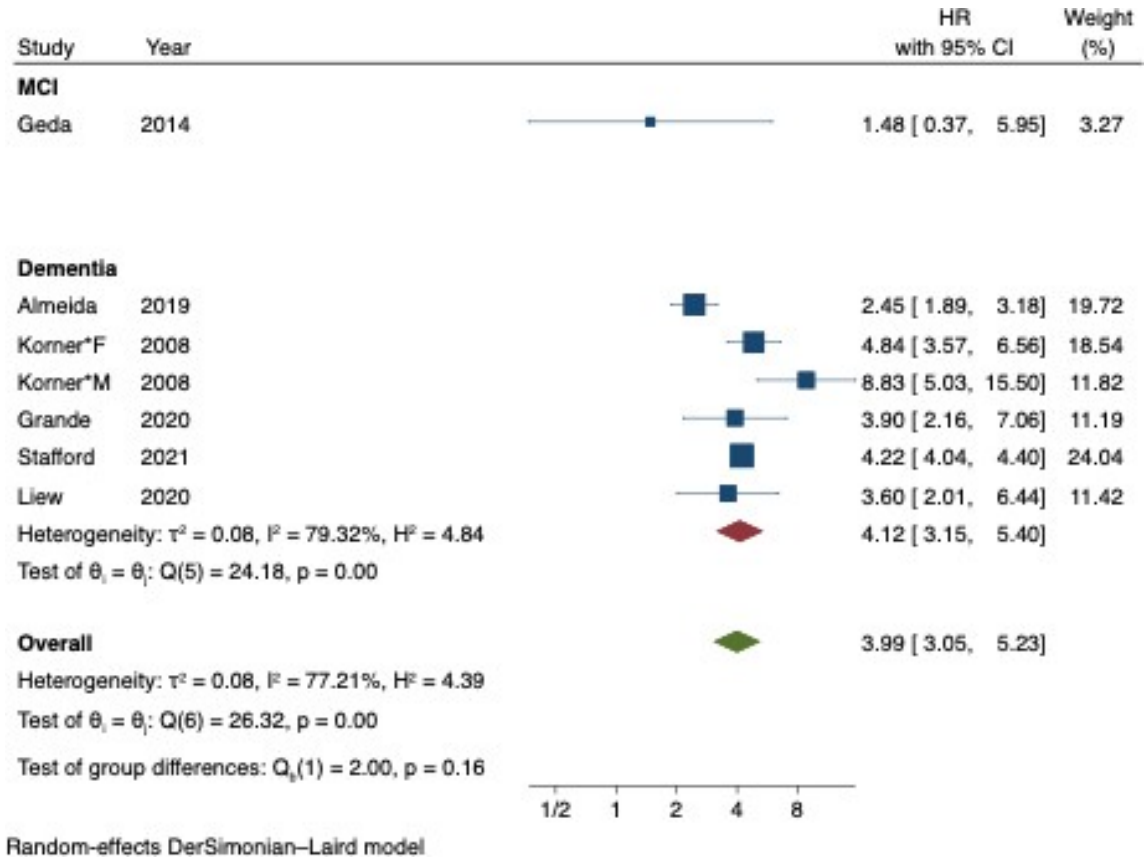
Forest plots showing the risk of agitation on cognitive decline and dementia. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds.
CI- Confidence Interval, HR-Hazard Ratio, MCI- Mild Cognitive Impairment.

IX Figure 3d. Social Inappropriateness forest plots



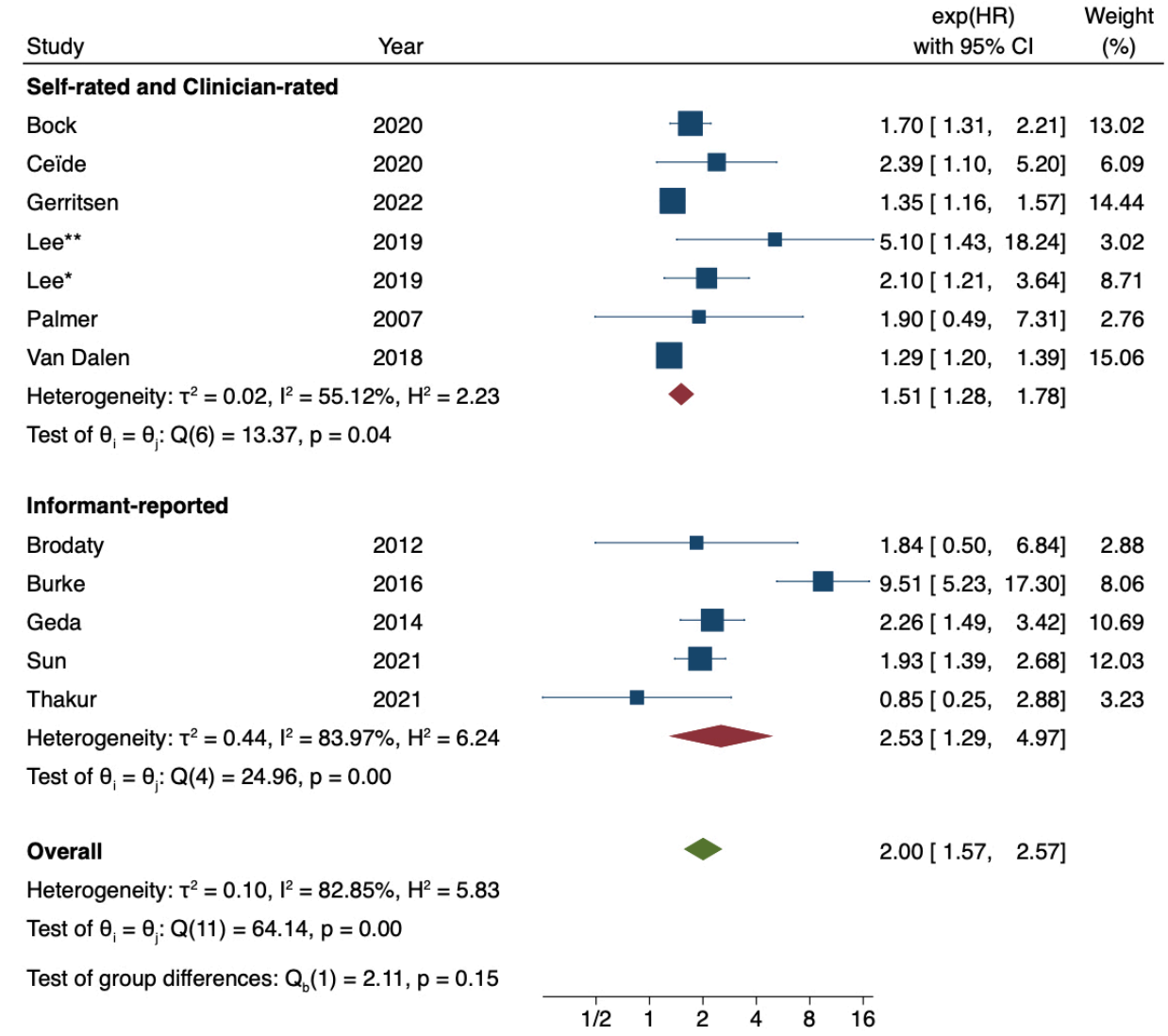
Forest plot showing the risk of social inappropriateness on cognitive decline outcome MCI or dementia. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds.
CI-Confidence Interval, HR-Hazard Ratio.

X Figure 3e. Psychosis forest plots



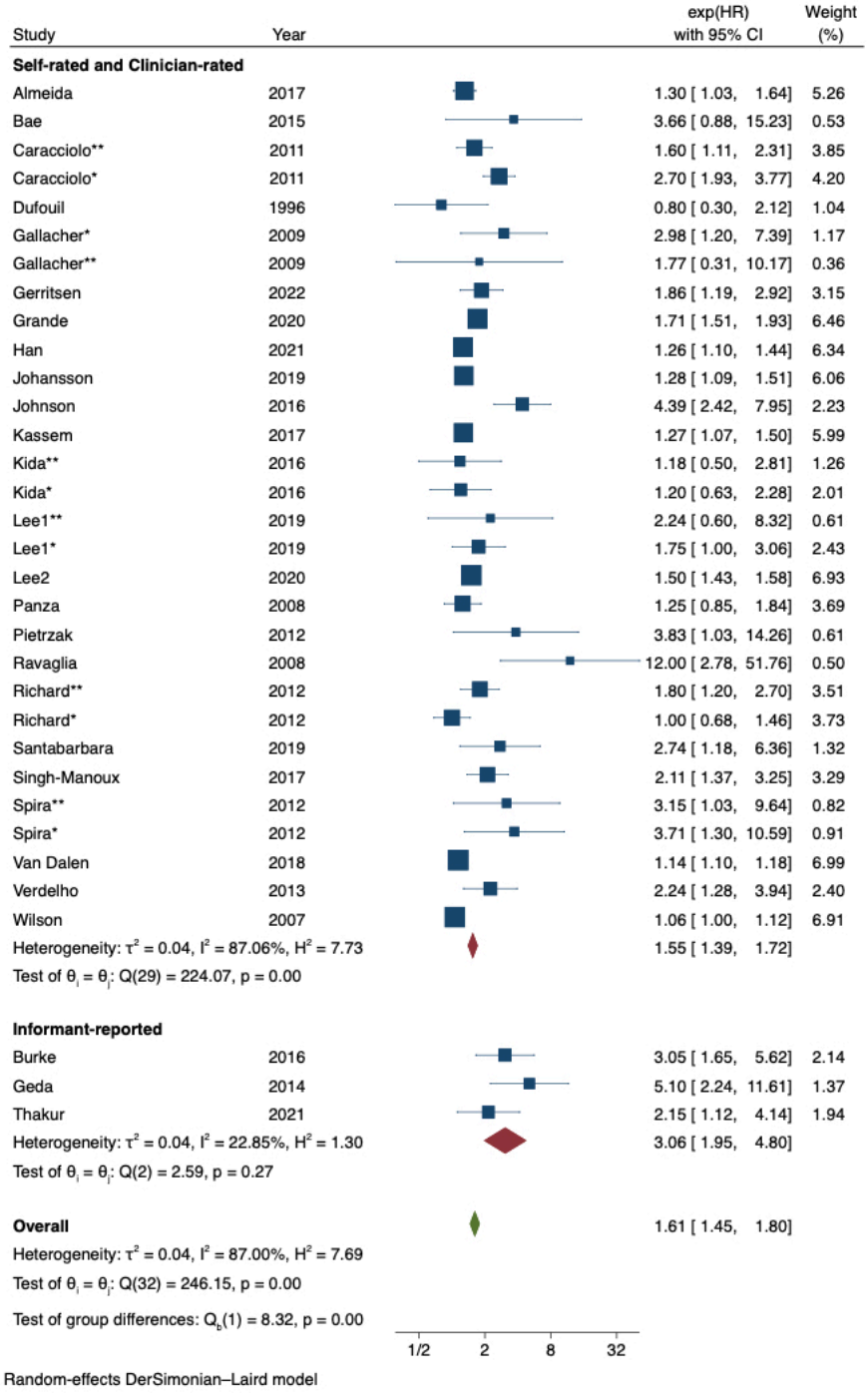
Forest plots showing the risk of psychotic symptoms on cognitive decline and dementia. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds.
CI-Confidence Interval, HR-Hazard Ratio, MCI -Mild Cognitive Impairment, *F-Female, *M-Male.

XI Figure 4a. Apathy forest plots stratified by NPS ascertainment approach



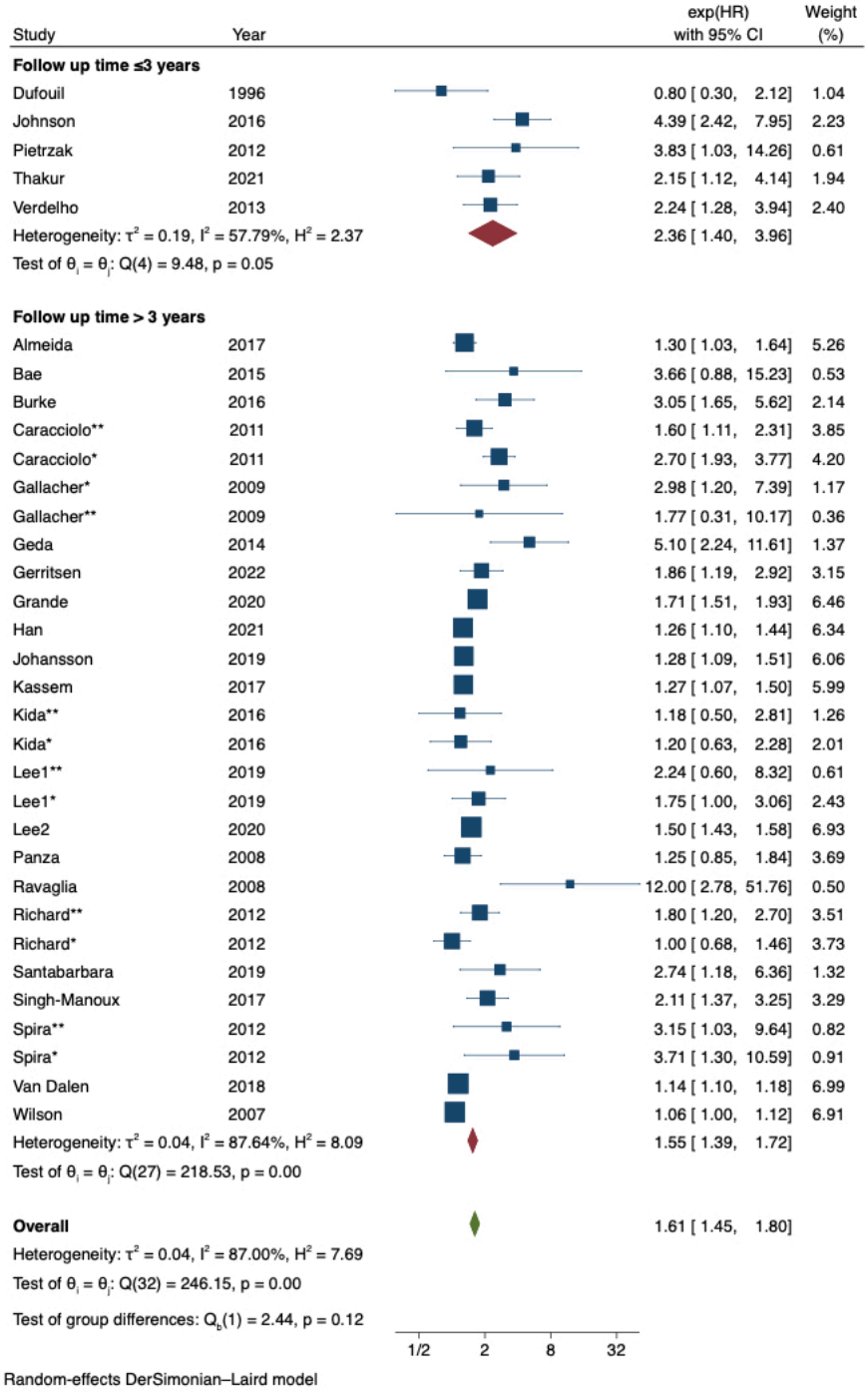
CI-Confidence Interval, HR-Hazard Ratio, MCI-Mild Cognitive Impairment, *Incident MCI, **Incident dementia.

XII Figure 4b. Affective Dysregulation Forest plots stratified by NPS ascertainment approach



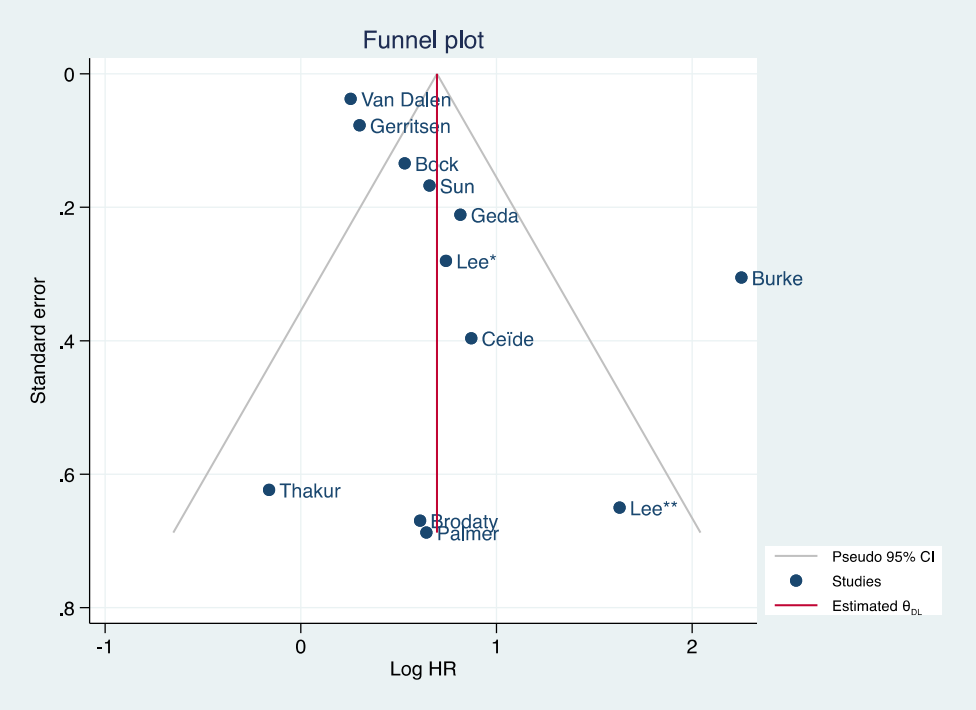
CI-Confidence Interval, HR-Hazard Ratio, MCI -Mild Cognitive Impairment, *Incident MCI, **Incident dementia.

XIII Figure 4c. Affective Dysregulation Forest plots stratified by follow up time



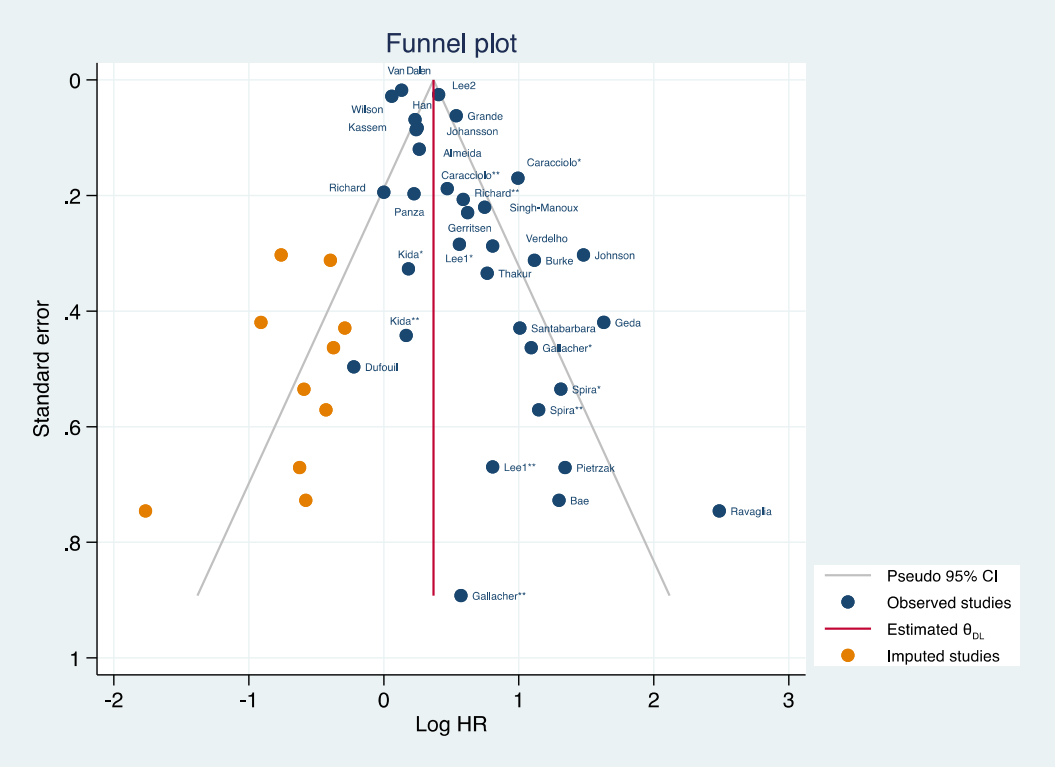
CI-Confidence Interval, HR-Hazard Ratio, MCI -Mild Cognitive Impairment, *Incident MCI, **Incident dementia.

XIV Figure 5a. Apathy funnel plot



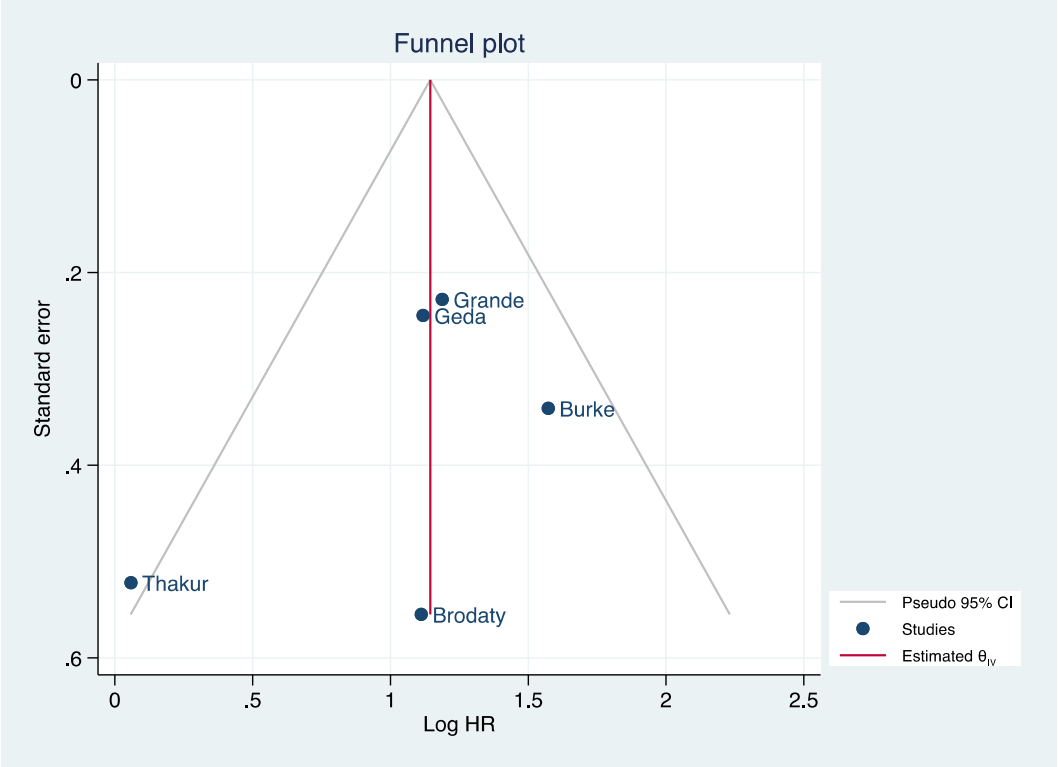
Study size is shown on the y-axis and log event rate is shown on the x-axis. Studies included in the meta-analysis are shown by circles. The mean incidence estimate is shown by the middle vertical line, and the pseudo 95% confidence limits are depicted by the contour lines.
HR-Hazard Ratio, *Incident MCI, **Incident dementia.

XV Figure 5b. Affective Dysregulation funnel plot including imputed studies



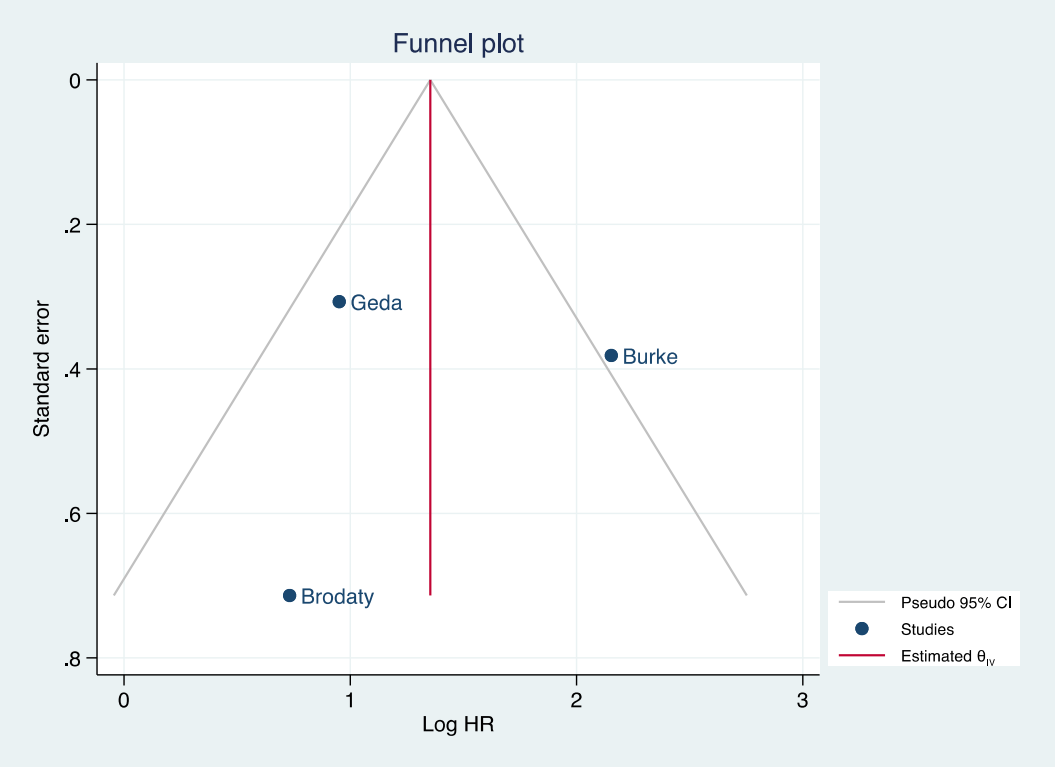
Study size is shown on the y-axis and log HR is shown on the x-axis. Studies included in the meta-analysis are shown by circles. The mean incidence estimate is shown by the middle vertical line, and the pseudo 95% confidence limits are depicted by the contour lines.
CI-Confidence interval, HR- Hazard Ratio, *Incident MCI, **Incident dementia.

XVI Figure 5c. Impulse Dyscontrol funnel plot



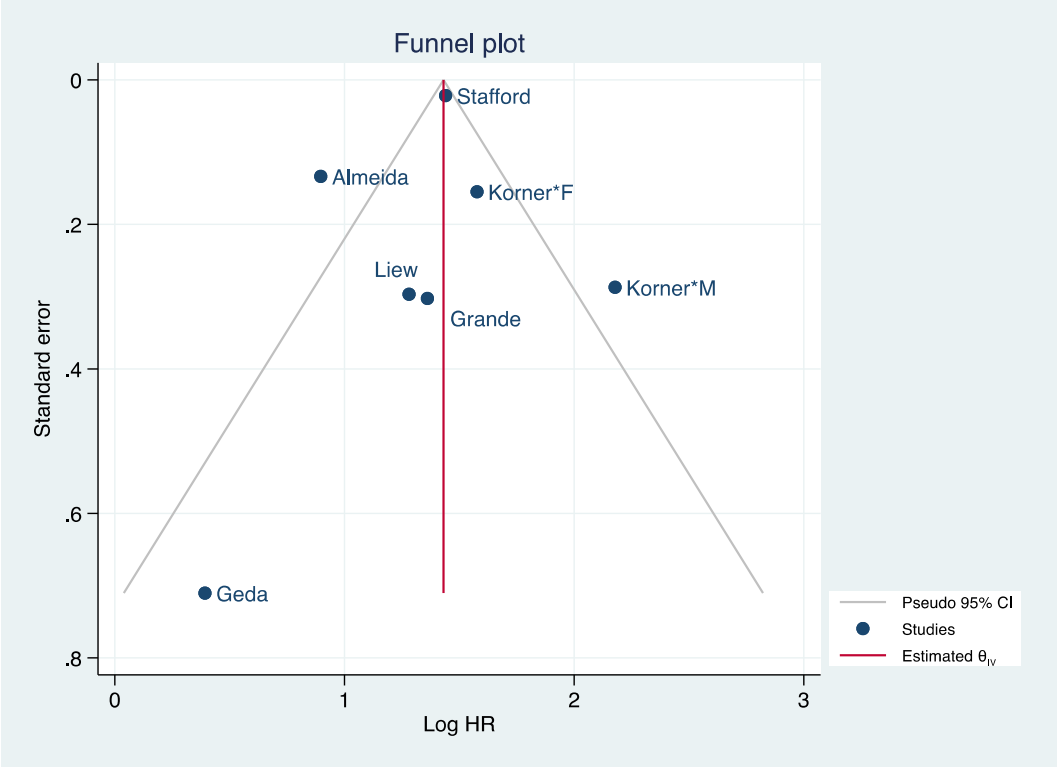
Study size is shown on the y-axis and log HR is shown on the x-axis. Studies included in the meta-analysis are shown by circles. The mean incidence estimate is shown by the middle vertical line, and the pseudo 95% confidence limits are depicted by the contour lines.
CI-Confidence interval, HR- Hazard Ratio.

XVII Figure 5d. Social Inappropriateness funnel plot



Study size is shown on the y-axis and log HR is shown on the x-axis. Studies included in the meta-analysis are shown by circles. The mean incidence estimate is shown by the middle vertical line, and the pseudo 95% confidence limits are depicted by the contour lines.
CI- Confidence interval, HR- Hazard Ratio.

XVIII Figure 5e. Psychosis funnel plot



Study size is shown on the y-axis and log HR is shown on the x-axis. Studies included in the meta-analysis are shown by circles. The mean incidence estimate is shown by the middle vertical line, and the pseudo 95% confidence limits are depicted by the contour lines.
CI-Confidence interval, HR-Hazard Ratio, *F-Female, *M-Male

I-Table 1. Characteristics of included studies

Last name, year, country	Total No	Female %	Reported measure of association	Mean age	NPI assessment tool/approach	Cognitive outcome	Diagnostic criteria for outcome	Years of follow up	Study population	Statistical adjustments
Almeida, 2018, Australia	435	0	HR	65	ICD-8, ICD-9, ICD-10	Dementia	ICD-8, ICD-9, ICD10	17.7	Participants from Perth metropolitan region	Adjusted for age, prevalent cardiovascular diseases, cancer, chronic respiratory diseases, gastrointestinal and renal diseases, hearing loss, alcohol use disorders, depressive and bipolar disorder.
Almeida, 2017, Australia	4922	0	HR	77.2	GDS-15	Dementia	ICD-9, ICD10	8.9	Participants from Perth metropolitan region	Adjusted for age, and history of diabetes and stroke.
Bae, 2015, Korea	181	55.2	HR	71.7	SGDS	MCI	Petersen criteria	3.5	NaSDEK	Adjusted for age.
Bock, 2020, USA	2018	53.3	HR	73.9	Modified AES	Dementia	3MS and DSST score	5.8	Health ABC study	Demographics, education, history of myocardial infarction, history of stroke, hypertension, APOE4 status, and cigarette smoking.
Brodaty, 2012, Australia	480	40.8	OR	78.41	NPI	MCI	Petersen criteria	2	MAS	Adjusted for age education and gender.
Burke, 2016, United States	1567	63	HR	71.2	NPI-Q	Dementia	NINCDS	3.6	NACC	Adjusted for sex, age, and race.
Caracciolo, 2011, Sweden	764	75	HR	75	CPRS, Clinician	Dementia	DSM-III-R	6	Kungsholmen Project	Adjusted for age and education.
Ceïde, 2020, USA	542	55.2	HR	76	GDS-15, GDS-30	MCI	RBANS	1.1	CCMA study	Adjusted for age and years of education, global cognition, and depression.
Dufouil, 1996, France	1600	60	RR	75.3	CES-D scale	Cognitive decline	MMSE	3	EVA study	Adjusted for age, gender, years of education, depressive symptoms, psychotropic drug use and cognitive score at 4 years follow up.
Gallacher, 2009, United Kingdom	916	0	OR	56.1	STAI-trait, GHQ	Dementia	DSM-IV	17.3	CaPS study	Adjusted for age, vascular risk, GHQ, and NART.

Geda, 2014, United States	1587	46.5	HR	79.3	NPI-Q	MCI	CDR, Short Test of Mental Status, Trail Making Test B	5	MCSA study	Adjusted for age.
Gerritsen, 2022, Iceland	4354	59	HR	76	GDS-15	Dementia	Clinician	8	AGES-Reykjavik study	Adjusted for age, sex, educational level, lifestyle, and vascular risk factors.
Grande, 2020, Italy	10096	N/A	OR	80	ICD-9	Dementia	MMSE	10	HSD	N/A
Han, 2021, Europe	14231	54.72	HR	68	EURO-D	MCI	The global cognitive score	9.8	SHARE	Adjusted for age, gender, country, marital status and living arrangement, educational attainment, smoking, alcohol consumption and other variables.
Johansson, 2019, Latin America	11472	64	HR	74	EURO-D	Dementia	Algorithm by 10/66 Dementia Research group	3.8	10/66 Dementia Research Group population-based survey	Adjusted for age, gender, education, stroke, and diabetes.
Johnson, 2016, United States	317	71.6	OR	60.7	DepE	MCI	Petersen criteria	1	HABLE	Adjusted for age and education.
Kassem, 2017, United States	2818	92	OR	76.1	GAS-SR	Cognitive decline	3MS, Global cognition, Trails B	3.4	SOF (anxiety)	Adjusted for clinic site, age, depression, poor sleep, and psychotropic medications.
Kida, 2016, Japan	526	54.6	HR	72.7	GDS-15	Dementia	DSM-III	5.2	Tone Project	Adjusted for age, gender, years of education, APOE, and vascular risk factors.
Korner, 2008, Denmark	1437	77.6	RR	79.4	ICD-10	Dementia	ICD-10	1.8	Danish Psychiatric Central Register	Adjusted for differences in age at first contact, a diagnosis of abuse and calendar time.
Lee1, 2019, Korea	2685	55	OR	68.2	DSM-IV	Dementia	DSM-IV	4	KLOSCAD	Adjusted for age, sex, and education.
Lee2, 2020, Korea	222056	58.3	HR	66	DSQ	Dementia	ICD-10	6.68	NHIS	Adjusted for sex, income, lifestyle, medical history, healthcare visit frequency, and medication history.

Liew, 2020, United States	12452	63.7	HR	72	NPI-Q	Dementia	DSM-IV	4.7	NACC	Adjusted for age, sex, and education.
Palmer, 2007, Sweden	185	84.9	RR	84	CPRS	Dementia	DSM-III-R	3.4	Kungsholmen Project	Adjusted for age and sex.
Panza, 2008, Italy	2963	48.8	RI	73.4	GDS-30	MCI	MMSE, Petersen criteria	3.5	ILSA	Adjusted for age and education.
Pietrzak, 2012, Australia	263	71.1	OR	61.6	PSWQ, PHQ-9	Cognitive decline	CPAL	2	older adults in Melbourne	Adjusted for age and PHQ-9 score.
Ravaglia, 2008, Italy	595	48.6	OR	72.3	GDS-30, Clinician	MCI	Winblad	4	CSBA	Adjusted for age and education.
Richard, 2012, United States	452	63.8	HR	77.7	CES-D scale	Dementia	DSM-III	5.4	WHICAP	Adjusted for age and sex, educational level, ethnicity, APOE genotype, and vascular risk factors.
Santabarbara, 2019, Spain	4057	66.6	HR	72.2	GMS-AGECAT	Dementia	DSM-IV	4.4	ZARADEMP study	Adjusted for gender, educational level, marital status and living alone.
Singh-Manoux, 2017, France	5552	30.4	HR	70	CES-D	Dementia	ICD-10	3.7	The Whitehall II study	Adjusted for age, year 0, sex, ethnicity, education, year of birth (5-year categories), time-dependent occupational position, and marital status.
Spira, 2012, United States	303	100	OR	86.9	GDS-15	Dementia	DSM-IV	5	SOF WISE (depression)	Adjusted for age, education, alcohol abuse, benzodiazepine use, and study site.
Stafford, 2021, Sweden	15409	60.56	HR	76	ICD-8, ICD-9, ICD-10	Dementia	ICD-8, ICD-9, ICD-10	2	Psychiatry Sweden register data	VOSLP group, sex, education level, family liability for non-affective psychotic disorder, disposable income at age 60, region of birth, matching variable, and any hospital diagnosis on the year either side of entry into the study.
Sun, 2021, China	1057	46.9	HR	72.72	NPI-Q	Dementia	MMSE, CDR	16.33	ADNI	Age, education years, sex, and APOE4 genotype.

Verdelho, 2013, Portugal	639	55	HR	74.1	GDS-15	Dementia	NINDS-AIREN	3	LADIS study	Adjusted for age, gender, educational level, WMC severity, MTA, and history of previous depression.
Thakur, 2021, USA	386	64.5	HR	69.2	NPI-Q	MCI	NINCDS-ADRDA	5.1	TARCC	Adjusted for age, gender, education, BMI, MMS exam and ethnicity.
Van Dalen, 2018, Netherlands	3,526	54.3	HR	74.3	GDS-15, GDS-30	Dementia	DSM-IV	6	PreDIVA	Age, sex, and disability.
Wilson, 2007, United States	1256	29.4	RR	77.05	NEO Five-Factor Inventory	MCI	Petersen criteria	12	Religious Orders Study	Adjusted for age, sex, and education.

ADNI-Alzheimer's Disease Neuroimaging Initiative, AES-Apathy Evaluation Scale, AGES-Reykjavik-Age, Gene/ Environment Susceptibility, BMI-Body Mass Index, CaPS-Caerphilly Prospective Study, CDR-Clinical dementia rating, CCMA-Central Control of Mobility in Aging, CES-D-Center for Epidemiologic Studies, CPAL-The Continuous Paired Associate Learning Test, CPRS-Comprehensive Psychopathological Rating Scale, CSBA-Conselice Study of Brain Ageing, DepE-Depression endophenotype score, DSM-Diagnostic and Statistical Manual of Mental Disorders, DSM-III-Diagnostic and Statistical Manual of Mental Disorders: 3rd, DSM-IV-Diagnostic and Statistical Manual of Mental Disorders: 4th edition, DSQ-Depression screening Questionnaire, DSRS score-Dementia severity rating scale, DSST-Digital symbol substitution test, EURO-D-European Depression scale, EVA-Epidemiology of Vascular Aging, HABLE-Health and Aging Brain among Latino Elders, Health ABC-Health, Aging, and Body Composition, HSD-Health Search Database, GAS-SR-Goldberg anxiety scale self-report, GDS-15-Geriatric Depression Scale 15-items, GDS-30-Geriatric Depression Scale 30-items, GHQ-General Health Questionnaire, GMS-AGECAT-Computerized psychiatric diagnosis in the elderly, HR-Hazard Ratio, ICD-International Classification of Diseases, ILSA-Italian Longitudinal Study on Aging, KLOSCAD-Korean Longitudinal Study on Cognitive Aging and Dementia, LADIS-Leukoaraiosis And DISability in the elderly, MCSA-Mayo clinic study, MAS-The Sydney Memory and Ageing Study, MMSE-Mini Mental state examination, N/A-Non applicable, MTA-Medical temporal lobe atrophy, NACC-National Alzheimer's Coordinating Center, NART-National Adult Reading Test, NHIS-National Health Insurance Service, NaSDEK-Nationwide Survey on Dementia Epidemiology, NINCDS-ADRDA-Alzheimer's Criteria by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, NINDS-AIREN-Clinical criteria for vascular dementia, NPI-Neuropsychiatric Inventory, NPI-Q-Neuropsychiatric Inventory Questionnaire, OR-Odds Ratio, PHQ-9-Patient Health Questionnaire, PreDIVA-Prevention of Dementia by Intensive Vascular Care trial, PSWQ-The Penn State Worry Questionnaire, RBANS-Repeatable Battery for the Assessment of Neuropsychological Status, RI-Rate of incidence, RR-Relative Risk, SHARE-The survey of Health, Ageing and Retirement in Europe, SGDS-Short Geriatric Depression scale, SOF-Study of

Osteoporotic Fractures, SOF WISE-Study of Osteoporotic Fractures /Women, Cognitive Impairment Study of Exceptional Aging, STAI-The State-Trait Anxiety Inventory, TARCC-Texas Alzheimer's Research and Care Consortium, VOSLP-Very-late onset schizophrenia-like psychosis, WHICAP-Washington Heights-Inwood Columbia Aging Project, WMC severity-White matter change, ZARADEMP-Zaragoza Dementia and Depression.

II-Table 2. Quality assessment using the Newcastle-Ottawa scale

Last name	Year	Total	Selection	Comparability	Outcome	Rating
Almeida	2019	7	2	2	3	Fair
Almeida	2017	8	3	2	3	Good
Bae	2015	6	1	2	3	Poor
Bock	2021	9	4	2	3	Good
Brodaty	2012	7	2	2	3	Fair
Burke	2016	8	3	2	3	Good
Caracciolo	2011	8	3	2	3	Good
Ceïde	2020	8	4	2	2	Good
Dufouil	1996	8	3	2	3	Good
Gallacher	2009	6	2	1	3	Fair
Geda	2014	7	3	1	3	Good
Gerritsen	2022	9	4	2	3	Good
Grande	2020	9	4	2	3	Good
Han	2021	9	4	2	3	Good
Johnson	2016	7	4	2	3	Good
Johansson	2019	7	2	2	3	Fair
Kassem	2018	7	2	2	3	Fair

Kida	2016	7	2	2	3	Fair
Korner	2008	9	4	2	3	Good
Lee	2019	7	3	2	2	Good
Lee	2020	8	3	2	3	Good
Liew	2020	8	3	2	3	Good
Palmer	2007	7	3	2	2	Good
Panza	2008	8	3	2	3	Good
Pietrzak	2012	8	3	2	3	Good
Ravaglia	2008	8	3	2	3	Good
Richard	2012	9	4	2	3	Good
Santabarbara	2019	7	2	2	3	Fair
Singh-Manoux	2017	8	3	2	3	Good
Spira	2012	8	3	2	3	Good
Stafford	2021	9	4	2	3	Good
Sun	2021	9	4	2	3	Good
Verdelho	2013	6	1	2	3	Poor
Van Dalen	2018	9	4	2	3	Good
Thakur	2020	7	3	2	2	Fair
Wilson	2007	7	2	2	3	Fair

Algorithm to generate study quality from the modified Newcastle-Ottawa Scale:
Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

III-Table 3. Hazard ratios for incident cognitive decline, MCI, or dementia for each MBI domain

MBI Domain	NPS	K studies	K measures	HR	95%CI: Lower-Upper	t^2	I^2	Q test	*P*-value
Domain 1	Apathy	11	12	2.00	1.57-2.57	0.10	82.85	64.14	0.00
Domain 2	Affective Dysregulation	27	33	1.61*	1.45-1.80	0.04	87.00	246.15	0.00
Domain 3	Impulse Dyscontrol	5	5	3.07	2.15-4.38	0.05	32.89	1.5	0.20
Domain 4	Social Inappropriateness	3	3	3.84	1.54-9.55	0.44	70.91	6.88	0.03
Domain 5	Psychosis	6	7	3.99	3.05-5.23	0.08	77.21	26.32	0.00

CI-Confidence Interval, HR-Hazard Ratio, NPS-Neuropsychiatric Symptoms.
* Pooled HR (The adjusted HR using the trim and fill method is 1.44 (95% CI: 1.30-1.61)).

IV-Table 4a. Apathy measures of effect

Author, Year, Country	Measure of association	Measure of effect 95% CI
Bock, 2020, USA	HR	1.70 95%CI 1.30-2.2
Brodaty, 2012, Australia	OR	1.84 95%CI 0.5-6.9
Burke, 2016, USA	HR	9.51 95%CI 5.23-17.31
Ceïde, 2020, USA	HR	2.39 95%CI 1.1-5.2
Geda, 2014, USA	HR	2.26 95%CI 1.49-3.41
Gerritsen, 2022, Iceland	HR	1.35 95%CI 1.16-1.57
Lee*, 2019, Republic of Korea	OR	2.1 95%CI 1.2-3.6
Lee**, 2019, Republic of Korea	OR	5.1 95%CI 1.4-17.9
Palmer, 2007, Sweden	RR	1.9 95%CI 0.5-7.4
Sun, 2021, China	HR	1.93 95%CI 1.4-2.7
Thakur, 2021, USA	HR	0.85 95%CI 0.25-2.88
Van Dalen, 2018, Netherlands	HR	1.29 95%CI 1.2-1.39

CI- Confidence Interval, HR- Hazard Ratio, OR- Odds Ratio, RR-Relative Risk, *Incident MCI, **Incident dementia.

V-Table 4b. Affective Dysregulation measures of effect

Author, Year, Country	Measure of association	Measure of effect 95% CI
Almeida, 2017, Australia	HR	1.3 95%CI 1-1.6
Bae, 2015, Korea	HR	3.66 95%CI 0.88-15.23
Burke, 2016, USA	HR	3.05 95%CI 1.65-5.61
Caracciolo*, 2011, Sweden	HR	2.7 95%CI 1.9-3.7
Caracciolo**, 2011, Sweden	HR	1.6 95%CI 1.1-2.3
Dufouil, 1996, France	RR	0.8 95%CI 0.3-2.1
Gallacher*, 2009, UK	OR	2.98 95%CI 1.2-7.38
Gallacher**, 2009, UK	OR	1.77 95%CI 0.31-10.24
Geda, 2014, USA	HR	5.1 95%CI 2.24-11.6
Gerritsen, 2022, Iceland	HR	1.86 95%CI 1.15-2.83
Grande, 2020, Italy	OR	1.71 95%CI 1.49-1.9
Han, 2021, Europe	HR	1.26 95%CI 1.1-1.44
Johansson, 2019, Latin America	HR	1.28 95%CI 1.09-1.51
Johnson, 2016, USA	OR	4.39 95%CI 2.41-7.9
Kassem, 2017, USA	OR	1.27 95%CI 1.07-1.5
Kida*, 2016, Tokyo	HR	1.2 95%CI 0.63-2.27
Kida**, 2016, Tokyo	HR	1.18 95%CI 0.5-2.83

Lee*, 2019, Republic of Korea	OR	1.75 95%CI 1-3.05
Lee**, 2019, Republic of Korea	OR	2.24 95%CI 0.6-8.28
Lee, 2020, Republic of Korea	HR	1.5 95%CI 1.42-1.57
Panza, 2008, Italy	RI	1.25 95%CI 0.85-1.84
Pietrzak, 2012, Australia	OR	3.83 95%CI 1.03-14.28
Ravaglia, 2008, Italy	OR	12 95%CI 2.8-52.1
Richard*, 2012, USA	HR	1 95%CI 0.7-1.5
Richard**, 2012, USA	HR	1.8 95%CI 1.2-2.7
Santabarbara, 2019, Spain	HR	2.74 95%CI 1.18-6.35
Singh-Manoux, 2017, France	HR	2.11 95%CI 1.37-3.25
Spira*, 2012, USA	OR	3.71 95%CI 1.3-10.59
Spira**, 2012, USA	OR	3.15 95%CI 1.03-9.65
Thakur, 2021, USA	HR	2.15 95%CI 1.18-4.38
Van Dalen, 2018, Netherlands	HR	1.14 95%CI 1.1-1.18
Verdelho, 2013, Portugal	HR	2.24 95%CI 1.27-3.92
Wilson, 2007, USA	RR	1.06 95%CI 1.002-1.12

CI- Confidence Interval, CIND- cognitive impairment no dementia, Hazard Ratio, MCI- mild cognitive impairment, OR- Odds Ratio, RR-Relative Risk, RI-Rate of incidence, *Incident MCI, **Incident dementia.

VI-Table 4c. Impulse Dyscontrol measures of effect

Author, Year, Country	Measure of association	Measure of effect 95% CI
Brodaty, 2012, Australia	OR	3.04 95%CI 1-8.8
Burke, 2016, USA	HR	4.82 95%CI 2.47-9.4
Geda, 2014, USA	HR	3.06 95%CI 1.89-4.93
Grande, 2020, Italy	OR	3.28 95%CI 2.1-5.13
Thakur, 2021, USA	HR	1.06 95%CI 0.38-2.94

CI- Confidence interval, HR- Hazard Ratio, OR- Odds Ratio.

VII-Table 4d. Social Inappropriateness included measures of effect

Author, Year, Country	Measure of association	Measure of effect 95% CI
Brodaty, 2012, Australia	OR	2.08 95% CI (0.5-8.2)
Burke, 2016, USA	HR	8.62 95% CI (4.08-18.2)
Geda, 2014, USA	HR	2.59 95% CI (1.42-4.73)

CI- Confidence interval, HR- Hazard Ratio, OR- Odds Ratio.

VIII-Table 4e. Psychosis measures of effect

Author, Year, Country	Measure of association	Measure of effect 95% CI
Almeida, 2019, Australia	HR	2.45 95% CI (1.89-3.19)
Geda, 2014, USA	HR	1.48 95% CI (0.37-5.99)
Grande, 2020, Italy	OR	3.9 95% CI (2.16-7.07)
Korner*F, 2008, Denmark	RR	4.84 95% CI (3.57-6.55)
Korner*M, 2008, Denmark	RR	8.83 95% CI (5.03-15.5)
Liew, 2020, USA	HR	3.6 95% CI (2-6.4)
Stafford, 2021, Sweden	HR	4.22 95% CI (4.05-4.41)

CI-Confidence Interval, HR-Hazard Ratio, OR- Odds Ratio, RR-Rate Ratio, *F-Female, *M-Male.

IX-Table 5. Meta-regression models

MBI Domain	NPS	K studies	K measures	Variable	β-coefficient	SE	Z	*p*-value	CI lower	CI upper	I^2 (%)
Domain 1	Apathy	11	12	NPS ascertainment	.4794792	.2236001	2.14	0.032	.041231	.9177274	73.91
Domain 2	Affective Dysregulation	27	33	Follow up time	-.4538475	.1971288	-2.30	0.021	-.8402128	-.0674823	86.40
Domain 2	Affective Dysregulation	27	33	NPS ascertainment	.3413878	.119151	2.87	0.004	.1078562	.5749194	86.32
Domain 5	Psychosis	6	7	Study quality	-.6096294	.2511424	-2.43	0.015	-1.101859	-.1173994	49.41

CI-Confidence Interval, SE-Standard Error.

X-Table 6. Affective Dysregulation trim and fill outcome

below	HR	95% CI lower	95% CI Upper
Observed	1.61	1.45	1.80
Observed + Imputed	1.44	1.30	1.61

CI-Confidence Interval, HR- Hazard Ratio.

XI-Supplementary Table A. The literature search included terms related to NPS

Source	Search Strategy
Medline (Pubmed)	*Alzheimer Disease/or *Dementia/ or exp Mild Cognitive Impairment/ or *Aged/ or MCI.mp. or *Cognition Disorders/
	(Preclinical dementia or prodromal dementia).mp
	(CIND or Pre-MCI or cognitive decline or cog normal at risk or subjective cognitive decline).mp.
	1 or 2 or 3
	(NPS or NPI or MBI).mp.
	*Mental Disorders/ or Mild Behavioral Impairment.mp.
	(Neuropsychiatric and neuropsychological factors).mp.
	*Neuropsychological Tests/
	5 or 6 or 7 or 8

	prospective studies/ or risk/ or cohort studies/ or longitudinal studies/
	exp Proportional Hazards Models/
	exp Incidence/
	exp Disease Progression/
	10 or 11 or 12 or 13
	4 and 9 and 14
Embase	(NPS or NPI or MBI).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device tr floating subheading]
	*mental disease/co, di, dm, ep [Complication, Diagnosis, Disease
	Management, Epidemiology] exp mini international neuropsychiatric interview/ or exp neuropsychiatry/
	exp neuropsychological test/ or Neuropsychological Assessment.mp.
	1 or 2 or 3 or 4
	*risk factor/ or *risk/ or *risk assessment/
	*high risk population/

	*epidemiology/
	*disease course/
	*risk/
	6 or 7 or 8 or 9 or 10
	exp cognitive defect/
	*memory/
	exp mild cognitive impairment/
	(MCI or CIND or Pre-MCI).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, de keyword, floating subheading]
	Prodromal dementia.mp.
	Subjective Cognitive Concerns.mp.
	cognitive aging/ or Preclinical dementia.mp.
	*cognition/ or subjective cognitive decline.mp.
	*memory disorder/co, di, dm, ep, et, pc [Complication, Diagnosis, Disease Management, Epidemiology, Etiology, Prevention]
	*dementia assessment/
	*dementia/di, ep, pc [Diagnosis, Epidemiology, Prevention]
	*Alzheimer disease/
	*Alzheimer disease/ep [Epidemiology]
	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 24
	prospective studies/ or risk/ or cohort studies/ or longitudinal studies/
	11 or 27

	5 and 25 and 28
PsycINFO	*Alzheimer's Disease/ or exp Cognitive Impairment/ or Mild cognitive impariment.mp.
	(MCI or CIND or Pre-MCI).mp.
	exp Cognitive Ability/ or *Dementia/ or *Memory/ or exp Cognitive Impairment/ or *Aging/ or *Cognitive Processes/ or *Alzheimer's Diseas
	Preclinical dementia.mp. or exp Cognition/
	Prodromal dementia.mp.
	Subjective Cognitive Concerns.mp.

	subjective cognitive decline.mp.
	cognitive normal at risk.mp.
	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
	(NPS or NPI or MBI).mp.
	*Mental Disorders/ or exp Psychiatric Symptoms/ or exp Neuropsychiatry/ or exp Neuropsychological Assessment/
	(Neuropsychiatric and neuropsychological factors).mp.
	10 or 11 or 12
	prospective studies/ or risk/ or cohort studies/ or longitudinal studies/
	exp PROGNOSIS/
	exp Risk Factors/ or exp Epidemiology/ or exp At Risk Populations/ or exp Disease Course/
	exp HAZARDS/

	14 or 15 or 16 or 17
	9 and 13 and 18

APPENDIX A: MOOSE & PRISMA Checklists

MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition	Yes	5-6
Hypothesis statement	Yes	7
Description of Study Outcome(s)	Yes	8
Type of exposure or intervention used	Yes	8
Type of study design used	Yes	7
Study population	Yes	7
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)	Yes	7
Search strategy, including time period included in the synthesis and keywords	Yes	8
Effort to include all available studies, including contact with authors	Yes	8
Databases and registries searched	Yes	8
Search software used, name and version, including special features used (eg, explosion)	Yes	9
Use of hand searching (eg, reference lists of obtained articles)	Yes	8
List of citations located and those excluded, including justification	Yes	12
Method for addressing articles published in languages other than English	Yes	8
Method of handling abstracts and unpublished studies	Yes	Figure 2
Description of any contact with authors	Yes	N/A
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	12
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	12
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	12
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate	Yes	10

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	9
Assessment of heterogeneity	Yes	10
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	10
Provision of appropriate tables and graphics	Yes	1-26
Reporting of Results		
Table giving descriptive information for each study included	Yes	Table 1
Results of sensitivity testing (eg, subgroup analysis)	Yes	Figure 3
Indication of statistical uncertainty of findings	Yes	14
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)	Yes	20
Justification for exclusion (eg, exclusion of non–English-language citations)	Yes	8 & 24
Assessment of quality of included studies	Yes	25
Reporting of Conclusions		
Consideration of alternative explanations for observed results	Yes	16-23
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	24
Guidelines for future research	Yes	25-26
Disclosure of funding source	Yes	26

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	6 &7
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	8 & 9
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix A
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	10
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	10
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	10
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	12
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	12
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	12
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	11

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	25
Study characteristics	17	Cite each included study and present its characteristics.	Table 1& P13
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	14, 15 &16
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	14 , 15 &16
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	14,15 &16
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	14 , 15 &16
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	14 , 15 &16
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	14 , 15 &16
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	14,15 &16
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	17 to 20
	23b	Discuss any limitations of the evidence included in the review.	24
	23c	Discuss any limitations of the review processes used.	24&25
	23d	Discuss implications of the results for practice, policy, and future research.	26
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	8
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	8
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	1
Competing interests	26	Declare any competing interests of review authors.	1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	1

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

APPENDIX B: Quality Assessment Using the NEWCASTLE - OTTAWA SCALE

(Adapted version for observational studies)

Selection
(Maximum 5 stars)

41. Representativeness of the sample

Truly representative of the normal MCI/dementia in the target population. * (all subjects or random sampling)
Somewhat representative of the normal MCI/dementia in target population. * (non-random sampling)
Selected group of users, eg nurses, volunteers
No description of the sampling strategy.

42. Sample size:

Justified and satisfactory. *
Not justified.

43. non-respondents:

Comparability between respondents and non-respondent's characteristics is established, and the response rate is satisfactory. *
The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
No description of the response rate or the characteristics of the responders and the non-responders

44. Ascertainment of the exposure (risk factor):

Validated measurement tool. **
Non-validated measurement tool, but the tool is available or described.*
No description of the measurement tool.

Comparability
(Maximum 2 stars)

45. The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

The study controls for the most important factor (select one). *
The study control for any additional factor. *
Other (please specify)

Outcome
(Maximum 3 stars)

46. Assessment of outcome

Independent blind assessment. **
Validated assessment scale rating scale. **
Record linkage. **
Validated self-report scales. *
No description.

47. Statistical test:

The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *
The statistical test is not appropriate, not described, or incomplete.