Università della Svizzera italiana

Faculty of Biomedical sciences

Thesis Manuscript

28 December 2021

Detecting Alzheimer's disease (AD):

From the asymptomatic stages of healthy adults with AD genetic disposition to late stages of severe neurocognitive impairment

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A dissertation presented by
Aliaa Ibnidris

Supervised by
Prof. Emiliano Albanese

Submitted to the
Faculty of Biomedical Sciences
Università della Svizzera italiana

For the degree of
Ph.D. In Neurosciences/Human Neurosciences

Board of examiners

Thesis director
Prof. Emiliano Albanese - Università della Svizzera italiana

Internal expert
Dr. Paolo Paganetti - Università della Svizzera italiana

External expert
Prof. Alessio Toraldo – University of Pavia

External expert
Prof. Crick Lund - King's College London

Acknowledgment

I would like to sincerely thank my husband for his unconditional love and support and for his understanding when I had to keep writing during our honeymoon. A big thank you to my parents who always encouraged me to keep reaching further. I especially thank my sister and her son whose laughter lightened up the final days of writing the PhD thesis. I thank Dr. Silke Matura for the wonderful time I spent working with her at Goethe University Frankfurt. Finally, I thank my supervisor, Prof. Emiliano Albanese, for his guidance and kindness throughout my time as a PhD student in Lugano.

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Abbreviations

AD	Alzheimer's Disease
ApoE	Apolipoprotein E
AUC	Area Under the Receiver Operating Characteristics Curve
CAMDEX	Cambridge Mental Disorders of the Elderly Examination
CCI	Cognitive Change Index
CDQ	Cognitive Dysfunction Questionnaire
CDS	Cognitive Difficulties Scale
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CFA	Confirmatory factor analysis
CFI	Cognitive Functions Instrument
CFQ	Cognitive Failures Questionnaire
CI	Confidence interval
COREQ	Consolidated criteria for reporting qualitative research
COSMIN	Consensus-based standards for the selection of health measurement instruments
CPI	Complainer Profile Identification
CSI-D	Community Screening Instrument for Dementia
CVLT	California Verbal Learning Test
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
EFA	Exploratory factor analysis
EMQ	Everyday Memory Questionnaire
EURO-D	Euro-Depression scale
FDG-PET	Fluorodeoxyglucose positron emission tomography
FDR	False discovery rate
FNV	False negative value
FPV	False positive value
GWAS	Genome-wide association study
HIC	High-Income country
IRT	Item response theory
LIC	Low-income country
LMIC	Low-and-Middle-Income country
LOAD	Late-onset Alzheimer's disease

MAC-Q	Assessment of Memory Complaint Questionnaire
MCI	Mild Cognitive Decline
MeSH	Medical Subject Headings
MFQ	Memory Functioning Questionnaire
MIC	Middle-income country
MMSE	Mini-mental state examination
MTL	Medial temporal lobe
NCD	Neurocognitive disorder
NIA-AA	National Institute on Aging – Alzheimer's Association
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association
NPV	Negative predictive value
PCC	Posterior cingulate cortex
PIC	Personality in intellectual aging contexts inventory
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRMQ	Prospective and retrospective memory questionnaire
PROM	Patient-reported outcome measure
PRS	Polygenic risk score
REDCap	Research Electronic Data Capture
RMSEA	Root mean square error of approximation
ROI	Region of interest
Rs-fMRI	Resting-state functional Magnetic Resonance Imaging
Rs-fMRI	Resting-state functional magnetic resonance imaging
SCD	Subjective Cognitive Decline
SCD-I	Subjective cognitive decline initiative
SCD-Q	Subjective cognitive decline questionnaire
SMCQ	Subjective Memory Complaints Questionnaire
SNP	Single nucleotide polymorphism
SOP	Standard operating procedure
SRMR	Standardized Root Mean Square Residual
SRQR	the Standards for Reporting Qualitative Research
TM	Therapeutic misconception
TMT-A	Trail Making Test – Part A

WHO	World Health Organization
WHO-DAS II	WHO Disability Assessment Schedule

Chapter 1: Outline and abstract

Thesis outline

This PhD thesis aspires to provide an in-depth examination of the assessment of cognitive functions in Alzheimer's disease (AD) at different stages of the disease's course. Complex problems require complex solutions. We attempted to apply the approach of population neuroscience which entails using tools from the fields of epidemiology, genetics, and cognitive neuroscience to answer the research questions. Identification of people at risk of AD and dementia is critical from both a clinical and public health perspective. Reliable biomarkers, and cognitive assessment methods can assist in characterizing the population and participants for clinical trials of disease-modifying treatments that target specific brain pathologies and damage. Secondly, while such treatments are still not available, timely detection of AD is important to plan and organize interventions and care arrangements in order to manage symptoms and improve the quality of life of people with dementia. In this PhD thesis, we first zoom in on the individual level to investigate genetic risk factors and their influence on the expression of AD symptoms. We also provide a critically appraised overview of assessment tools of clinical symptoms in preclinical AD. We then zoom out to the population level and present methods and techniques to detect and adjudicate dementia diagnosis in the community. Next, we report updated prevalence figures of dementia in both high and low-income settings based on a structured evidence synthesis work. To achieve our objectives, we used mixed research methodologies including systematic reviews, validation and test accuracy studies, and qualitative research methods.

Chapter 2 provides a general background and an introduction to the definition of AD, epidemiology, genetics, and current practices in the assessment of cognitive decline in various settings and contexts. Chapter 3 is a manuscript, still in preparation, of a study on the association of AD-associated genetic variants with alteration in intrinsic brain functional connectivity and cognitive performance. Chapter 4 is the second manuscript in preparation in which we report the results of a systematic review that aimed to evaluate the psychometric properties of available self-reported questionnaires used to assess subjective cognitive decline (SCD) in older adults. Chapter 5 is a recently published, peer-reviewed paper that fills a crucial gap in dementia epidemiology research, which is the validation of the 10/66 dementia diagnostic schedule and algorithm in a high-income country setting. This validation study is at the core of this PhD project and thesis, and it is an indispensable step to pave the way to a new era of epidemiological studies in Europe and western countries in general. We explored and demonstrated the validity,

reliability, usability, acceptability, and applicability of the short 10/66 dementia schedule for older adults living either in the community or in nursing homes with innovative electronic, secured solutions for data collection, management, and storage. Chapter 6 is a published systematic review and meta-analysis of dementia prevalence in Low- and Middle-Income Countries (LMIC) that defined the state of the art before the commencement of the STRiDE study in these settings. Chapter 7 and 8 are two peer-reviewed, published qualitative studies that examine relevant and often neglected aspects of dementia epidemiology: the role of informed consent and return of research results as mechanisms to enhance or hinder participation in dementia epidemiological research. In Chapter 9 we summarize the key findings of each chapter and provide recommendations as well as possible directions for future research. Finally, Chapter 10 outlines the PhD candidate's methodological contribution to each of the presented chapters.

Abstract

Background: Dementia is a syndrome characterized by progressive cognitive impairment, psychological and behavioural symptoms, and functional deficits. It is one of the leading causes of disability worldwide; its impact and the associated costs are enormous. Consequently, dementia is a global public health priority, and so is Alzheimer's disease (AD), the most common cause of dementia in late life. Because dementia is an age-associated disease, the number of people living with dementia is expected to rise worldwide from in 2015 to 2030 because of the current demographic transition. Research in dementia diagnosis is of great importance both from a clinical and a public health perspective.

Objectives: The main objectives of this PhD thesis are to examine the assessment of cognitive functions in different stages of dementia and AD, from the preclinical to late stages. In the preclinical stage, we aimed to investigate the relationship between a polygenic risk score (PRS) of genetic variants that are associated with AD and intrinsic brain functional connectivity and with cognitive performance in cognitively healthy adults. Next, we evaluated the self-reported questionnaires currently in use to assess Subjective Cognitive Decline (SCD) in older adults. SCD may be an initial symptom of AD, but evidence is still limited. We moved to the symptomatic stage of dementia and took a population perspective to provide an up-to-date estimate of dementia prevalence in selected Low- and Middle-Income Countries (LMIC) in preparation for a large-scale dementia prevalence study in these settings (STRiDE). Linked to the latter, we conducted a long overdue validation study of a brief dementia diagnostic schedule (the brief version of the 10/66 Dementia Diagnostic Schedule and Algorithm) to demonstrate its criterion and concurrent validity, before its use at scale in large epidemiological studies. We also tested the acceptability and usability of an innovative, cost-efficient and secure electronic data collection system for dementia epidemiology. Finally, we aimed to explore the role of informed consent and participatory research mechanisms in improving participation in dementia research in High-Income Counties (HIC) (i.e., Switzerland), where participation rates are traditionally low.

Methods: To achieve the objectives of this PhD thesis, we used mixed methodologies. To investigate the **first objective** (PRS of AD and brain functional connectivity), we conducted a cross-sectional study with 139 healthy adults (age range 20 – 77 years old) between November 2020 and October 2021. Participants were recruited from a previous longitudinal study titled 'Funktionelle und strukturelle neuronale Diskonnektion als Grundlage früher episodischer Gedächtnisstörungen der Alzheimer-Krankheit' ('Functional and structural neuronal

disconnection as a basis/prerequisite for early neuronal memory dysfunction in Alzheimer's Disease') which was conducted at Goethe University Frankfurt, Germany. All participants had undergone rs-fMRI, DNA genotyping and PRS calculation, and neuropsychological testing for global cognition, working memory, verbal fluency, and executive functions.

For the **second objective** (SCD assessment), we conducted a systematic review between April 2020 and June 2021 using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) methodology. 16 studies met the inclusion criteria and reported development and/or validation of a total of 17 SCD questionnaires. We critically evaluated each questionnaire's development process, its structural validity, internal consistency, test-retest reliability, convergent validity, and cross-cultural validity.

For the **third objective** (dementia prevalence in LIMCs), we conducted a systematic review and meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta (PRISMA) guideline, between March 2018 and November 2019. 28 studies met the inclusion criteria and were included in the final analysis.

For the **fourth objective** (validation of dementia diagnostic schedule)**,** we carried out a cross-sectional validation study between March and August 2019. We included 229 participants (69% females) from the community and from nursing homes in Switzerland and Italy. To be eligible, participants needed to be at least 60 years old and to have an informant. 74 participants (32%) had a previous clinical diagnosis of dementia and 155 (68%) were cognitively healthy older adults. For each participant we also recruited and interviewed an informant. We administered the Italian version of the brief 10/66 dementia diagnostic schedule to all participants and their informants. The 10/66 schedule comprises the Community Screening Instrument for Dementia (CSI-D), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 10-word list learning task with delayed recall, and Euro-Depression (EURO-D) scale. We measured disability using the WHO Disability Assessment Schedule (WHO-DAS II) for convergent validity testing.

For the **final objective** (role of informed consent), we conducted a qualitative study with 22 participants following the validation phase of the brief version of the 10/66 dementia diagnostic schedule. None of the 22 participants reported to have a dementia diagnosis at the time of the interview. From this work we published two papers which are presented below.

Results: We found that high PRS was not significantly associated with alteration of the intrinsic functional connectivity of the PCC with other ROIs in the brain (q-FDR > 0.05). Moreover, higher

PRS showed a significant association with lower scores (i.e., worse performance) in verbal fluency tests in participants older than 60 years (semantic fluency test: p-value = 0.019; phonemic fluency test: p-value = 0.033).

Our systematic review of measurement properties of SCD questionnaires revealed that for none of the 17 identified questionnaires a content validity evaluation had been performed. 81.25% of the included studies performed and reported aspects of patient-reported outcome measures (PROM) development procedure (n = 13). None of the included studies tested for content validity of the developed PROMs. On the other hand, the majority of studies tested and reported structural validity (75%, n = 12) for thirteen PROMs. Internal consistency using Cronbach's alpha was reported in 68.75% of studies (n = 11) for 13 PROMs. Test-retest reliability was reported in four studies. Only four studies (25%) indicated cross-cultural validation of SCD PROMs in other languages. Two studies evaluated and reported convergent validity with other SCD PROMs.

Results from our systematic review and meta-analysis showed that pooled estimates of dementia prevalence in the selected middle-income countries ranged from 2% to 9% based on DSM-IV criteria. Prevalence was higher in studies using other diagnostic criteria (e.g., the 10/66 algorithm). Only Brazil, Mexico and India had data based on studies and methods with low risk of bias. The majority of the included studies did not explicitly state the representativeness of their sample, or whether there was non-response or selection bias.

Findings from the validation study of the Italian version of the brief 10/66 dementia diagnostic schedule and algorithm demonstrated the acceptable criterion validity of the schedule against the clinical dementia diagnosis (i.e., DSM-V dementia diagnosis), with sensitivity of 87%, specificity of 61%, and agreement with the clinical diagnosis of dementia (kappa=0.40, area under the receiver operating characteristics curve=0.74). Lower false negatives than false positives were deemed acceptable for the subsequent epidemiological study, but we also highlighted a number of alternative explanations of the findings.

Findings from the qualitative analysis of the validation study showed that participants held inaccurate and potentially trust-threatening beliefs regarding the role and use of informed consent. We also found that individuals welcomed the return of their individual-specific results, provided these meet a number of validity, clinical, and personal utility criteria. They justify researchers' duty to return study findings with the principles of beneficence (e.g., providing information that can help participants' medical decision-making) and justice (e.g., acknowledging participants' efforts to help research by sharing their personal information). Furthermore,

individuals anticipate societal benefits of the return of individual specific study findings, including improved interpersonal relationships among individuals and decreased dementia-related stigma.

Conclusion: Each of the conducted studies is an effort to provide an examination and an answer to the posed research question. In our exploratory analysis of the PRS and intrinsic functional connectivity, our results contribute to the growing body of research exploring the complex polygenicity of AD and its association with alteration in functional connectivity at rest. Further investigation of the interaction between genetic risk factors and other sociodemographic variables is warranted to understand the epigenetic nature of AD in older adults and why some individuals express the phenotype (i.e., clinical symptoms of AD) while others do not. Regarding the assessment of SCD, we conclude that the available evidence suggests that currently available measurements do not address important aspects of psychometric properties. Further work is needed to develop and validate SCD self-reported measurement with good quality measurement properties. Valid and feasible measurements would enhance the screening of older adults at risk of AD and provide a tool to follow up the progress of clinical symptoms. On the other hand, our systematic review showed that there are methodologies in use to diagnose and estimate dementia prevalence, but the various approaches and methods do vary considerably between studies. Comparison of dementia rates between countries and settings is therefore difficult. Our validation study provides evidence that the brief version of the 10/66 schedule can be used to detect dementia, and that its feasibility, acceptability, and strong cross-cultural validity can contribute to conduct studies and allow comparisons of dementia rates across different sites. We found that the fair sensitivity and specificity of the brief version of the 10/66 dementia diagnostic schedule makes it a practical instrument to identify dementia in older adults, both in the community and in residential care facilities, where up to fifty percent of people with dementia reside, at least in high income countries. Lastly, our qualitative study highlights the importance of a transparent and thorough informed consent process, especially in dementia research. This includes providing information on the scope and process, and the content of the informed consent document in a focused, age-appropriate manner. Furthermore, researchers should address the return of individual-specific study results early on during study design. Importantly, prospective participants should be involved in identifying the conditions under which results should be returned to them. Results should be shared with careful considerations regarding the perceived individual and societal benefits as well as the clinical implications that disclosing such results can have.

Chapter 2: Introduction

Aliaa Ibnidris

Historical background of AD and dementia

The origin of the word dementia comes from the Latin word "*Demens*", meaning "madness" or being "without a mind" (1). The term has been widely used, by physicians and researchers alike to describe a wider syndrome that is characterized by a decline in cognitive functions including memory, executive function, attention, language, and social cognition (2). The condition poses great burden on the individual and affects one's independence in daily activities. Moreover, dementia causes functional impairments and a progressive reduction of autonomy and increasing need of care. Dementia is also associated with further neuropsychiatric symptoms in the late stages, such as depression, apathy, agitation, and delusion (2,3).

AD is the most commen cause or subtype of dementia, making up 50-60% of all dementia cases (4,5). Progressive forgetfulness and deterioration of spatial navigation skills are two of the most characteristic symptoms of typical, late-onset AD (6,7). However, atypical presentation of AD can affect other cognitive functions such as executive functions or language before memory (6). Other subtypes of dementia include vascular dementia, Parkinson's disease dementia, Lewy body dementia, and Frontotemporal dementia (4). While AD is one of the main underlying pathologies of dementia as a syndrome, the two terms, AD and dementia, are often used interchangeably, arguably erroneously.

In recent years, calls to change the term "dementia" have been made (1,8,9). Proposals for less stigmatizing terms include replacing the word dementia with "*cognitive impairment*" or "*cognitive disorder*" (9). In response to this, in the latest version of the diagnostic and statistical manual of mental disorders (the DSM-5), the term dementia is no longer used. Dementia is now referred to as major "Neurocognitive Disorder" (NCD) (2). This is further described according to the cause of neurocognitive dysfunction, e.g., Major NCD due to AD. The renaming is extended to Mild Cognitive Impairment, which is now referred to as Mild NCD due to AD (2). To enhance readability, we will refer to major NCD due to AD using the term "dementia" in the following chapters of this PhD thesis, without dismissing the negative implications of the term dementia and its uses, including stigma and potential discrimination, and violations of human rights. These topics are of paramount importance but exceed the scope of the present PhD thesis.

The first documented cases of Alzheimer's disease were both reported in the early 1900s by Alois

Alzheimer, a young assistant physician at the psychiatric ward in Frankfurt Psychiatric Hospital at the time (10). Auguste D. and Josef F. were two older patients who were admitted to the Frankfurt Psychiatric Hospital in Frankfurt am Main, Germany, in 1901 and 1910, respectively (11). Both patients complained of progressive forgetfulness accompanied by feeling of sadness, aggression, or disorientation. Dr. Alzheimer did not only describe the symptomatology of the disease but he thoroughly examined and described the underlying histopathology after death (12). Postmortem histopathological investigations of the brains of both cases, performed by Alzheimer, revealed what are now considered to be the two hallmarks of AD – depositions of extracellular plaques of amyloid, and intracellular neurofibrillary tangles of phosphorylated tau proteins originated from the disassembling of the microtubules (13). The presence of amyloid plaques and neurofibrillary tangles, as found in the first case of Auguste D., were believed to be the only histopathological marker of AD. Nonetheless, samples of Josef F. brain only had plaques, which somewhat did not conform to Alzheimer's previous findings and description of the disease.

Recent studies that investigated the archived brain samples of both patients showed that Alzheimer's finding at the time confirm the current understanding of the different stages of AD based on the presence of plaques and neurofibrillary tangles (14,15). He presented both cases, the clinical description of the disease accompanied by the histological results at the Southwest German Psychiatrists meeting in Tübingen as a "peculiar disease of the cerebral cortex" (*Über eine eigenartige Erkrankung der Hirnrinde*). The importance of his findings were recognized soon after and the description of the disease was introduced in psychiatry textbooks under the diagnostic term "Alzheimer's disease" (16), in an epoch of eponym illnesses allure.

Biomarkers for the early detection of AD: The role of genetics and neuroimaging

In chapter 3, we explore the relationship between genetic disposition to AD and alteration in intrinsic functional connectivity in cognitively healthy adults. The following paragraphs provide a brief overview of the genetic nature of the disease as well as the use of neuroimaging in detecting AD.

AD pathology is present many years before clinical symptoms (13,17). Previously, AD pathological changes could only be detectable either by autopsy or on post-mortem evaluation of the brain (18). However, great advances in non-invasive techniques enabled the establishment of several AD biomarkers. This includes genotyping of DNA samples for ApoE/ε4 allele detection, structural and functional magnetic resonance imaging, FDG-PET scan, and the investigation of amyloid and tau levels in the cerebrospinal fluid (CSF).

Genetic mutations associated with the development of AD differ between familial, early-onset cases and late-onset AD (LOAD). Mutation in the amyloid precursor protein (APP) gene was established in trisomy 21 patients as the main causal event in familial, early onset AD (19,20). Individuals with such a mutation typically exhibit AD symptoms starting in their forties (21). Mutation in the APP gene leads to the misprocessing of amyloid-β protein and the ensuing accelerated deposition of amyloid- β plaques in the brain, neurodegeneration, neuronal deaths and synaptic disruption, and the associated decline in neurocognitive functions. However, APP gene mutation explains less than 1% of all AD cases (22). On the other hand, 99% of the remaining cases are sporadic, i.e., LOAD, typically prevalent in older adults aged 65 years and above (21,22). LOAD is associated with several genetic variants, the most important of which is the ε4 polymorphism of the Apolipoprotein E (ApoE) gene on chromosome 19 (23).

Evidence suggests that allelic variants of the ApoE gene are present in both familial and sporadic late-onset AD (23). ApoE gene has three main isoforms, ε2, ε3 and ε4. Homozygous carriers of ε4 allele (i.e., ε4/ε4) have a greater risk of developing AD in late life than heterozygous carriers (e.g., ε3/ε4) (22,24). Thus far, being a carrier of ApoE/ε4 continues to be the strongest and most studied genetic risk factor for LOAD. Contrarily, the expression of ε2 appears to have a protective effect against AD (25). From an evolutionary point of view, an interesting finding suggests that ε2 and ε3 variants of the ApoE gene are derived from the more ancestral ε4 (26). In addition, ε2 and ε3 have become increasingly more prevalent in human populations over the past 200,000 years. While ε3 has 60% frequency, ε4 is found in only 10% of humans (26). This suggests that ε2 and ε3 variants have been passed on successfully due to their potential protective effects from brain damage. Translating this to clinical research, recent studies demonstrate that carriers of ε2 and ε3 indeed show greater synaptic plasticity – an important mechanism in learning and consolidation of processed information that is affected by AD pathology (27).

Although LOAD does not seem to share the same APP gene mutation that is prevalent in cases of familial AD, the amyloid cascade hypothesis, first established with familial AD, has dominated and directed research and the development of disease-modifying therapeutics for AD in the past decades (28). While the presence and toxic effects of amyloid-β in the brain is well-established, targeting the amyloid cascade pathway did not yield significant and consistent results so far (29,30). Clinical trials that targeted the amyloid cascade pathway aimed at eliminating amyloid plaques in the brain in the hope of reversing cognitive decline. However, this proved to be unsuccessful because clinical symptoms (i.e., cognitive decline) start many years after amyloid deposition, which likely caused irreversible neuronal death and network loss, hence, irreversible

cognitive dysfunction. Nonetheless, a randomized, double blinded, clinical trial on Aducanumab, a monoclonal anti-amyloid antibody, showed a dose-dependent effect of the proposed immunotherapy in reducing amyloid plaques in the brain in patients in the prodromal AD and mild AD dementia stages, and a statistically significant, though clinically almost negligible effect (31). In 2021, the United States Food and Drug Administration (FDA) approved the use of Aducanumab under the Accelerated Approval Pathway (32). Nonetheless, this approval is dependent on further evidence of the expected clinical benefit from a post-approval clinical trial (32). The FDA's decision is considered controversial since the clinical trial followed patients for 12 months and further analysis in two subsequent studies on the long-term improvement of cognitive functions showed inconsistent results on clinical efficacy (33).

Due to the previous unsuccessful attempts in targeting the amyloid pathway, a new direction has emerged to investigate and identify new genetic risk factors in AD patients. Genome-Wide Association studies (GWAS) have made major advances in identifying several genetic variants found in AD patients. The main objective of a GWAS is to identify statistically significant associations between alleles or genotype frequency and trait status (i.e., phenotype) (34). GWAS in AD have so far identified several variants in relation to AD, including CLU, CR1, PICALM, BIN1, ABCA7, MS4A, CD33, EPHA1, and CD2AP (35,36). Expression of these variants is linked to disruption to a number of cellular mechanisms including the regulation of inflammation and immunity, intermediate metabolism, or cell trafficking which have been observed in people with AD dementia (35,36). GWAS can thus elucidate mechanisms that may be targeted for prevention or treatment, and that can advance understanding of the causes of AD.

On the other hand, brain imaging has advanced greatly in recent years as it offers a non-invasive tool to detect AD-related pathological changes in vivo. In this PhD thesis, we are particularly interested in the use of functional magnetic resonance imaging (fMRI) to observe the intrinsic functional connectivity in a specific region that is commonly affected in AD patients – the posterior cingulate cortex (PCC) which is part of the Default Mode Network (DMN) (37). The DMN consists of neural substrates that show increased connectivity during rest when the individual is not engaged in any cognitive activity. Anatomically it includes the medio-temporal lobe, the medial prefrontal cortex, the PCC, ventral precuneus, and the medial, lateral, and inferior parietal cortex (38). Previous evidence shows that the PCC, which is the computational hub of the DMN, is particularly susceptible to amyloid-β deposition in AD (39). Other studies also show that decreased connectivity between the PCC and the hippocampus is observed in people with MCI and AD dementia (40). This suggests a subsequent synaptic and functional disconnection in

the brain as a result of the neuropathological alteration in AD. The hippocampus is a critical region for memory, learning, information processing, and spatial navigation (41–43) – all of which are affected in AD. A previous study aimed to investigate whether healthy carriers of genetic risk factors show a similar disruption in intrinsic functional connectivity of the PCC and the hippocampus. However, this was only assessed in carriers of ApoE/ε4 (38). No recent studies investigate this relationship with other genetic variants with smaller effect sizes than ApoE/ε4. Chapter 3 of the PhD thesis aims to examine whether the expression of other, less dominant genetic variants than ApoE/ε4, detected as single nucleotide polymorphisms (SNP), modulates the intrinsic connectivity between the PCC and brain regions affected in AD (i.e., medial temporal lobe structures). Here, we consider alteration of functional connectivity as the resulting phenotype of the expression of genetic variants of small size effects.

Although there is currently no available cure to reverse the neuronal damage or improve cognitive functions, it is of particular importance to be able to identify people at risk of AD as early as possible. This is critical for two main reasons. Firstly, late stages of AD cause a great burden on the individual, their loved ones, and society at large, early and timely detection may still offer the opportunity for meaningful interventions aimed at buffering the effects of brain damage and delaying symptoms. This includes lifestyle changes that target brain and vascular health, cognitive exercises, earlier start of treatment to manage associated neuropsychiatric symptoms, as well as the chance for better planning for late stages when independence in daily activities is affected. Secondly, because there is no cure, clinical trials of proposed disease-modifying medications as well other non-pharmaceutical interventions, require accurate identification of people at risk of AD; that is of dementia due to AD. This would enable directed efforts of clinical research to target the right population at the right time to effectively test proposed interventions.

Detection of cognitive impairment in AD: From preclinical stages to dementia in late life

In this section, we move from the genetic and neuroimaging biomarkers to explore the detection of cognitive impairment in clinical practice in two stages of AD, the preclinical and dementia stages.

Preclinical AD is a theoretical proposition at this stage of AD research. The NIA-AA diagnostic criteria for AD proposes three distinct stages of AD: preclinical, Mild Cognitive Impairment, AD dementia (44). In this section, we explore the importance of early detection of AD pathological and clinical changes that are associated with the preclinical stage of AD and the emerging

construct of SCD. Finally, we aim to provide an overview of the current state of detection of severe cognitive dysfunction and diagnosis of AD dementia both in older adults living in the community and in long-term residential care facilities (e.g., nursing homes).

Subjective cognitive decline

Chapter 4 of this thesis examines the quality of the available questionnaires and scales that are used to assess SCD in older adults. This was done by conducting a systematic review to evaluate the psychometric properties of available SCD self-reported outcome measures. The aim of the systematic review is to provide ratings of each psychometric property of each questionnaire in order to enable an overall evaluation of the quality of the measurement properties and ultimately provide a recommendation for the best SCD questionnaire to use. We also aimed to evaluate the feasibility of the available SCD questionnaires by collecting information on feasibility aspects such as time required to administer the questionnaire as well as the mode of administration.

The construct of SCD in relation to preclinical AD has gained attention in recent years. It is defined as a self-perceived worsening of cognitive abilities compared to a previous state, despite the person having normal performance for their age, gender and education on objective cognitive tests (45). SCD is suggested to be one of the very first clinical symptoms of people who are otherwise cognitively normal (46). Evidence shows that the rate of progression to AD dementia in people expressing SCD is twofold after 5-year follow-up period (47). Previous studies have shown that the presence of SCD is correlated with ApoE/ε4 allele frequency (48), as well as with AD-associated biomarkers such as increased deposition of amyloid-β on Positron Emission Tomography (PET) imaging, atrophy of the hippocampus and entorhinal cortex, and disruption of glucose metabolism in AD-vulnerable brain regions (49).

Early intervention in AD is critical to prevent or delay the progression from the preclinical stage to further cognitive and functional decline in late life. That is why it is important to identify feasible and practical methods to recognise subtle changes in cognition as early as possible. In this sense, SCD is suggested to be the first clinical manifestation that could be used to screen older adults at risk of MCI or dementia in late life (47). However, this subjective feeling of a sudden worsening of cognitive function should be accompanied by worry expressed by the older adult and confirmed by an informant, when possible (46). Detection and close follow-up of SCD in older adult may decrease the rate of missing or late diagnosis of AD in older adults. The ability to detect, assess, and follow up on SCD requires using psychometrically validated questionnaire

that are sensitive to reliably detect SCD (50). Thus far, no standardized SCD questionnaire is available (50). In order to fully operationalize the construct of SCD, both in research and in clinical settings, standardized methodology of assessment and diagnosis is needed. Furthermore, there is considerable variability in the available SCD questionnaires (51). Current questionnaires vary in terms of the characteristics of questionnaire items and the response options, which affects the interpretation of responses and the overall rate of SCD in the older population (52). Moreover, available questionnaires mostly focus on subjective decline in memory functions. Nonetheless, atypical cases of AD may be missed if the early subjective feeling of worsening concerns other cognitive abilities such as executive function or language (52). Lastly, SCD questionnaires must be sensitive enough to differentiate between expressed complaint as an early manifestation of cognitive dysfunction or due to other causes (e.g., depression) (46).

AD dementia

The World Health Organisation (WHO) recognizes dementia in old age as a worldwide public health priority (53). Because the risk of developing dementia rises with age, the number of people suffering from old age-related disease such as AD and dementia is expected to increase (54). This is due to the observed population ageing as a result of the increasing life expectancy around the world (54). In fact, demographic changes are more rapid and significant in LMICs compared to HICs. In LMICs health systems are unprepared for age-associated diseases, lack any long-term care component, and are more often than not underprepared for the potential burden posed by this predicted increase of dementia cases in the coming years (54). In efforts to bridge the gaps in dementia diagnosis and treatment and to reduce the impact of dementia, the WHO recommends seven target areas to also improve the overall quality of care offered to people with dementia (55). One target is about addressing and bridging the diagnostic gap of dementia in older adults both in research and in clinical settings (55,56). Exact calculations and improvements of the dementia diagnostic gap require epidemiological studies to enumerate the regional prevalence of dementia, combined with registry-based data of the number of diagnoses made over a given time period. Neither of which are available in the vast majority of countries, low and high-income countries alike.

According to the diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's disease and Related Disorders Association (ADRDA), the diagnosis of probable AD dementia is made if cognitive impairment/decline is established clinically, which is further confirmed by neuropsychological testing, and if there is

evidence of progressive impairment in memory and other cognitive domains (57). Moreover, the cognitive impairment must interfere with the individual's independence and social life, and it cannot be explained by other medical or neurological disorders. Definite AD dementia, however, could only be reached if the same criteria for probable AD is present but there is a histopathological evidence on biopsy or at autopsy (7,18).

On the other hand, the DSM-5 differentiates between MCI and dementia stages and refers to them as mild or major NCD due to AD (2). Major NCD is defined as a decline from "a previous level of performance in one or more of the cognitive domains (learning and memory, complex attention, executive function, language, perceptual motor, or social cognition)" (2). The decline must also disrupt independence in daily activities and cannot be better explained by another recognized mental disorder (2). Mild NCD differs in that the cognitive deficit does not interfere with the individual's capability to perform everyday tasks, although greater effort may be required. If the criteria for diagnosing mild or major NCD is met, it is further divided into probable or possible AD (2). Mild or major NCD due to probable AD is diagnosed if there is clear evidence of AD such as genetic mutation from family history or from genetic testing. If no such evidence exists, then possible AD is diagnosed if there is a clear evidence of a steady and progressive decline in memory and cognition in the absence of other aetiologies (2).

Most AD dementia cases are currently diagnosed by clinicians worldwide following either the NINCDS-ADRDA or DSM 5. However, both criteria do not integrate the operationalization of AD biomarkers in supporting the diagnosis. Although neuroimaging biomarkers and genetic screening have great potential to facilitate dementia diagnosis in the future, they are not in use, as some have not been validated yet, and therefore not approved in routine clinical practice. Specific expertise is required that only specialized memory clinics may have. And they still need validation and standardization across research sites to enable their assimilation into diagnostic criteria. As such, improving detection of clinical symptoms remains the main approach to assess cognitive impairment and diagnose dementia.

While severe cognitive impairment may be apparent and easy to detect, diagnosing dementia due to AD is a challenge. This is specifically important not only for older adults still living in the community who are still independent, but also for those living in nursing homes and in long-term, residential care facilities. Previous evidence from HICs shows that more than 50% of dementia cases in the community in HICs are undiagnosed (58). The rate of undetected dementia in the community is even higher in Middle-Income Countries (MIC), with up to 90% of cases never

receiving a diagnosis (58). No evidence from Low-Income Countries (LIC) is currently available (58). Regarding people living with dementia who are residing in long-term care facilities, evidence from HICs indicates that between 40 and 80% of residents in nursing homes have dementia (59–62). More importantly, measures used to identify dementia in residential care facilities vary significantly (63). This may explain the different reported dementia rates between studies. Varying prevalence rates could also be a result of different study designs. For example, some studies only consider newly admitted cases of dementia and overlook those who develop dementia during their stay in nursing homes (63).

Population-based studies that provide updated figures on the current prevalence of dementia in HICs have stagnated in the past 30 years (64,65). In addition, evidence from the majority of LMICs is extremely scarce and there is an urgent need to establish up-to-date estimates in order to inform national policies and strategies to address dementia diagnosis, treatment and management in a cost-effective manner (66). As said, epidemiological evidence of dementia occurrence is indispensable to estimate the current dementia diagnostic gap. Dementia diagnosis, or adjudication of dementia caseness in population-based samples is not easy. Reliable yet feasible diagnostic tools to identify dementia cases in the community and in long-term residential care facilities in both high and low-income settings are lacking. This PhD thesis aimed to examine this issue from two angles. In chapter 5, we aimed to present a valid and reliable brief tool to diagnose dementia in two HICs in older adults either living in the community or in nursing homes. More details regarding the validation of this tool are presented in chapter 5. We maintained that reliable, valid yet brief tools would facilitate dementia diagnosis both in research and in clinical settings and we hypothesized that the 10/66 brief diagnostic schedule is a valid and reliable tool to detect dementia in both high and low-income settings. Secondly, in chapter 6, we attempted to provide a current estimate of dementia prevalence in LMICs in a systematic review and meta-analysis of the available prevalence studies of dementia in such settings. This systematic review was conducted in the preliminary phase to a large-scale prevalence study in two LMICs, South Africa and Indonesia. The aim was to use the validated, brief dementia diagnostic schedule in the planned prevalence study in two LMICs to demonstrate its utility and practicality in population-based studies. In the following chapters we addressed a largely neglected area of research that pertains to the perception, expectations, and understanding of participants of dementia epidemiological studies.

Ethical considerations in dementia research

Chapters 7 and 8 of the PhD thesis present important findings regarding the understanding of informed consent, and the preference of return of research results in older adults participating in dementia research. Both factors may contribute to enhancing or hindering participation rates in studies on dementia and may contribute to selection bias. As discussed earlier, population-based research into dementia has stagnated in HICs and has been scarce in LMICs. Besides feasibility aspects regarding the diagnostic tools commonly deployed in such studies, a decrease in participation rates have also affected progress in dementia research. This can be attributed to several factors, two of which are mentioned above and are addressed in chapters 7 and 8.

Informed consent is one of the main pillars of conducting ethical research with human participants (67). Enhancing participation requires sharing sufficient information with participants about the purpose of the study, the associated risks and potential benefits. However, previous evidence suggests that commonly used written informed consent forms often are difficult to understand for study participants. This may be due to complicated language, little information or lengthy forms. (68,69). On the other hand, for informed consent to be valid, participants should be fully competent to provide consent, be able to decide to take part in any study on a voluntary basis and be able to withdraw at any point during the study (70). These conditions are particularly challenging to meet when interacting with vulnerable study populations, such as older adults living with dementia (71). Moreover, voluntary and active participation of individuals donating their time and health information is instrumental in the success of population-based studies. Therefore, the expectation of participants from taking part in any study should be thoroughly addressed and discussed before the start of the study. This includes discussing the return of research results to participants, especially when such information may have consequences on their health. Previous evidence suggests that current ethical practices in dementia studies do not focus on the alignment of participants' preferences in terms of research results (72,73). This in turn may affect equitable opportunities to participate in dementia epidemiological research, which is often overlooked and rarely considered as non-fulfillment of ethical requirements. Besides innovative approaches of community sensitization and extensive preparatory phases before the start of data collection, it is crucial to be able to communicate effectively with participants throughout the study. Moreover, this communication is even more critical after the end of the study as research findings may greatly impact people’s lives. This is particularly important in dementia research where participants may discover through the study that they are at risk or have been diagnosed with dementia.

Objectives of the PhD thesis

Chapters 3 to 8 consist of six different studies, each exploring one of the above-mentioned topics by conducting five unique studies (chapter 7 and 8 are two publications written on data from the same qualitative study). The chapters also correspond to publications which have been either published in high-quality, peer-reviewed journals (chapter 5 to 8) or are currently in preparation (chapter 3 and 4). Some of the reported studies also resulted from collaborations with several research teams worldwide. The reported study in chapter 3 was conducted with the Department of Psychiatry, Psychosomatic Medicine and Psychotherapy at Goethe University Frankfurt (GUF), Germany. Chapter 4 presents a systematic review that was carried out with researchers from the University of the West Indies, Jamaica. Chapter 5 presents the validation study conducted as a collaboration between our research team at the Università della Svizzera italiana, Switzerland and the University of Turin, Italy. Lastly, the reported systematic review in chapter 6 was carried out in collaboration with researchers from Brighton and Sussex Medical School, London School of Economics and the STRiDE project.

While each publication touches upon a different topic, the **overarching objective** is to provide an overview of the current status and practice in dementia research. The aim of this PhD thesis is to investigate how cognitive decline is assessed in different stages in Alzheimer's disease, from preclinical, asymptomatic stages to the late stages of severe cognitive impairment, taking a public health perspective on dementia, which is in line with the WHO action plan on a public health response to dementia. Importantly, the PhD thesis emphasizes the use of different research methodologies and study designs in each of the reported studies and in the corresponding chapters. Because AD and dementia are complex conditions, this PhD thesis is an ambitious attempt to provide a comprehensive investigation into the topic from a wider lens, using the approach of population neuroscience. More precisely, the **main objectives** of this PhD thesis are discussed and presented in each chapter as follows:

- Chapter 3: To examine the association between PRS for AD and the resting-state functional connectivity in the DMN in the PCC with other brain regions of interests that are affected by AD pathology.
- Chapter 4: To conduct a systematic review to evaluate the psychometric properties of self-reported outcome measures of SCD in older adults. The systematic review was conducted using the COSMIN Methodology.
- Chapter 5: To determine the criterion and the concurrent validity of the short version of the 10/66 Dementia Diagnostic Schedule and Algorithm in identifying dementia in older adults living in the community and in nursing home in two HICs.

- Chapter 6: To carry out a systematic review to provide up-to-date estimate of the prevalence of dementia in seven LMICs (India, Indonesia, Kenya, South Africa, Mexico, Brazil, and Jamaica). A secondary objective the systematic review is conduct an extensive analysis of the commonly used methodologies in dementia prevalence research in LMICs.
- Chapters 7 and 8: To explore methodological challenges in dementia research with regard to providing informed consent for older adults with dementia and the ethical considerations of return of study results.

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Chapter 3: Investigating the association between polygenic risk scores for Alzheimer's Disease with cognitive performance and intrinsic functional connectivity in healthy adults

Aliaa Ibnidris, Fabian Fußer, Thorsten Kranz, David Prvulovic, Andreas Reif, Johannes Pantel, Emiliano Albanese, Silke Matura.

Submitted to Frontiers in Aging Neuroscience:

Ibnidris A, Fußer F, Kranz T, Prvulovic D, Reif D, Pantel J, Albanese E, Matura S. Investigating the association between polygenic risk scores for Alzheimer's Disease with cognitive performance and intrinsic functional connectivity in healthy adults.

Abstract

Background: Alzheimer's disease (AD) pathology is present many years before the onset of clinical symptoms. AD dementia cannot be treated. Timely and early, detection of people at risk of developing AD is key for primary and secondary prevention. Moreover, understating the underlying pathology that is present in the earliest stages of AD, and the genetic predisposition to that might contribute to the development of targeted disease-modifying treatments.

Objectives: In this study, we aimed to explore whether genetic disposition to AD in asymptomatic individuals is associated with altered intrinsic functional connectivity as well as cognitive performance on neuropsychological tests.

Methods: We examined 139 cognitively healthy adults (old group: mean age = 69.32, SD = 4.23; young group: mean age = 31.07, SD = 12.95). All participants had undergone resting-state functional magnetic resonance imagining (fMRI), DNA genotyping to ascertain polygenic risk scores (PRS), and neuropsychological testing for global cognition, working memory, verbal fluency, and executive functions.

Results: PRS did not show significant modulations of the intrinsic functional connectivity of the posterior cingulate cortex (PCC) with other regions of interest in the brain that are affected in AD. Higher PRS showed a significant association with lower scores (i.e., worse performance) in verbal fluency tests in participants older than 60 years old.

Conclusion: Allele polymorphisms may modify the effect of other AD risk factors. This potential modulation warrants further investigations in particularly in cognitively healthy adults.

Keywords:

Resting state fMRI, polygenic risk score, Alzheimer's disease, cognition, genetic risk, intrinsic functional connectivity, biomarker, correlation

Background

Alzheimer's disease (AD) is a neurodegenerative disorder that is characterised by a progressive decline in cognitive function (McKhann et al., 2011). The neuropathological hallmark of AD in the brain is the presence of extracellular Aβ amyloid plaques and intracellular neurofibrillary tangles (NFT) (Braak and Braak, 1991). Previous evidence shows that specific biomarker abnormalities consistent with these neuropathological changes are detectable years before the commencement of clinical symptoms (Jack et al., 2010; Sperling et al., 2011). The U.S. National Institute on Aging – Alzheimer's Association (NIA-AA) proposed a biological definition of AD, allowing for the diagnosis of AD in the presence of β-amyloid and neurofibrillary tau in cognitively healthy elders (Jack et al., 2010, 2018; Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). Because irreversible cognitive dysfunction is caused by neuronal cell death, network dysfunction and eventual neurodegeneration, it is critical to identify people at risk before this occurs. In order to design disease-modifying drugs for AD, it is widely accepted that treatments should be administered as early as possible before clinical symptoms have appeared, and ideally, earlier than the start of neuronal damage (Jessen et al., 2014, 2018). The NIA-AA criteria are not meant for clinical uses, but only for research purposes and in clinical research settings.

Resting state functional magnetic resonance imaging (rs-fMRI) may be a viable biomarker to detect altered intrinsic functional connectivity in people at risk of AD (Sorg et al., 2007). Rs-fMRI shows the intrinsic functional connectivity between brain regions at rest when no task is being performed. Previous evidence suggests that AD may be conceived as a disconnection syndrome, both structural and functional (Delbeuck et al., 2003; Sorg et al., 2007). The Default Mode Network (DMN), a set of brain regions that shows functional activity during rest, is one of the most widely studied functional networks in AD (Raichle et al., 2001; Krajcovicova et al., 2014). The Posterior Cingulate Cortex (PCC) is the posterior anatomical/computational hub in the DMN and brain in general (Hagmann et al., 2008; Greicius et al., 2009). It is suggested that the neuropathological changes and the resulting structural lesions in the brain may be associated with alteration in intrinsic brain activity in AD in the DMN (Buckner and Vincent, 2007). Previous studies show that the PCC is especially susceptible to the deposition of amyloid plaques in AD (Sperling et al., 2009; Mormino et al., 2011). Evidence from fluorodeoxyglucose positron emission tomography (FDG-PET) studies demonstrate diminished resting state glucose metabolism in the PCC of patients with early AD or MCI as well as in cognitively healthy older adults at risk of AD (Ishii et al., 2003; Buckner et al., 2005). This might reflect a possible hypometabolism or synaptic dysfunction in this region (Fessel, 2021). Previous studies

investigating the functional connectivity using functional MRI observed decreased connectivity between the PCC and the hippocampus, both in MCI and AD (Greicius et al., 2004; Krajcovicova et al., 2014). On the other hand, increased connectivity is observed in the anterior DMN and in the hippocampal-medial prefrontal and the frontoparietal connectivity in similar groups (Zhang et al., 2009; Zarei et al., 2013). However, alterations in the DMN alone could only differentiate between healthy controls and people with AD but not between the different prodromal stages of AD where cognitive performance may be still preserved (Teipel et al., 2018). Because of its important role in the DMN and its vulnerability towards AD pathology, the PCC is an ideal candidate region for investigating associations between intrinsic functional connectivity and its relation to other biomarkers and risk factors of AD.

Besides alterations in intrinsic functional connectivity, there are several candidate genes that constitute another frontier for early detection of people at risk of AD. The Apolipoprotein E gene on chromosome 19 is the most commonly associated genetic risk factor for late-onset AD (LOAD), as the ε4 allele is most commonly associated with LOAD (Belloy et al., 2019; Chaudhury et al., 2019). Previous research suggests that people with MCI due to AD who were carriers of APOE e4 allele indeed showed altered functional connectivity as well as lower cognitive performance compared to healthy controls (Wang et al., 2015; Harrison et al., 2016). In an earlier study that investigated the relationship between resting state connectivity and genetic risk, carriers of the APOE ε4 allele were found to have a higher activation across several cortical regions (Bookheimer et al., 2000). However, the study only looked at carriers of AD-related, APOE variants, and investigated connectivity alterations on task-based fMRI where participants were asked to perform a memory-activation task that is sensitive to the identification of neuropathological changes in the medial temporal lobe (MTL) structures (Bookheimer et al., 2000). Nonetheless, despite the strong genetic association with AD, clinical trials for disease-modifying treatments targeting the amyloid cascade pathway and focusing on carriers of ApoE/ε4 did not yield successful results yet (Yiannopoulou et al., 2019; Serrano-Pozo et al., 2021). Moreover, the relationship between specific alterations of functional connectivity on rs-fMRI should not be attributed to a single gene and further investigation of the impact of other genetic variants should be considered (Harrison and Bookheimer, 2016).

This has directed the focus on investigating other pathways and other possible genetic variants associated with AD. Genome Wide Association Studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) that are associated with an increased risk of developing AD in late life (Baker and Escott-Price, 2020). These include CLU, PICALM, and CR1 as well as BIN1,

ABCA7 and EPHA1 (Harrison and Bookheimer, 2016). Homozygous carriers of CLU, for example, show a stronger magnitude of intrinsic functional connectivity compared to non-carriers (Zhang et al., 2015). A suggested approach would be to investigate the effect of these SNPs combined in a polygenic risk score (PRS), as a biomarker to reliably detect an elevated risk to develop AD already in its earliest stages. A PRS is a method to predict the genetic susceptibility of an individual to a specific disease by its summarized genetic risk for the disease based on previous evidence, and that can be used for clinical prediction rules in conjunction with the clinical history and physical examination. However, consistent evidence on the effect of other genetic variants, calculated in a PRS, on intrinsic functional connectivity in cognitively healthy older adults at risk of AD is still lacking. Therefore, the association between alterations in functional connectivity and a PRS that combines the summed and weighted risk of several genetic variants in one metric would increase the prediction power for people at higher risk of developing AD dementia.

The aim of this study was to explore whether a higher PRS in cognitively healthy adults has an effect on the intrinsic functional connectivity between the PCC and other regions of interest (ROIs) in the brain. We examined this association using PRS and rs-fMRI data in a cohort of healthy adults. We also aimed to examine the association of PRS with cognitive performance in validated neuropsychological tests. We hypothesised that individuals with a higher PRS show altered intrinsic functional connectivity between the PCC and other brain regions that are implicated in AD (i.e., medio-temporal lobe, MTL) as well as lower cognitive performance.

Materials and Methods

Participants

We examined a subset of 139 cognitively healthy participants. The sample was divided into two groups with a young group including participants aged 60 years and younger (n = 83). 55% of the young group were females (n =46). The mean age of the young group was 31.07 (SD = 12.95). The old group included those who were above 60 years of age (n = 56). The mean age for the old group was 69.32 (SD = 4.23). 60.71% of the old group were females (n = 34). Participants were drawn from a cohort of participants from the project B4 of the Neuronal Coordination – Research Network Frankfurt (NeFF) titled ‘Funktionelle und strukturelle neuronale Diskonnektion als Grundlage früher episodischer Gedächtnisstörungen der Alzheimer-Krankheit’ (‘Functional and structural neuronal disconnection as a basis/prerequisite for early neuronal memory dysfunction in Alzheimer’s Disease’) (Matura et al., 2014a, 2014b, 2016, 2020, 2021). The project was performed at the Laboratory of Neuroimaging of the Department of Psychiatry, Psychosomatic

Medicine and Psychotherapy at the Goethe University, Frankfurt am Main, Germany. The methodology of this project has been extensively described in previous publications (Matura et al., 2014a, 2014b, 2016, 2020, 2021). All participants had no history of neurological or psychiatric disorders. Eligible participants were selected based on the presence of a PRS and fMRI data. Sociodemographic variables of the included participants were age, gender, education, family history of Alzheimer's disease dementia, handedness, weight, height, Body Mass Index (BMI), and smoking status. For the purpose of the current study, we only analysed the association of PRS, in younger and older participants, with cognitive performance, and intrinsic functional connectivity with the PCC as a seed region. The ethics committee of the Medical Faculty of the Goethe-University Frankfurt approved the study, and all subjects signed a written informed consent. The study was undertaken in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) (Rickham, 1964).

Neuropsychological measures

We used the Mini-Mental State examination (MMSE) to assess general cognition (Folstein et al., 1975), and the German version of the California Verbal Learning Test (CVLT) for verbal learning and short-term memory (Delis et al., 1987; Niemann et al., 2008). Working memory and attention were also assessed using the Trail Making Test - Part A (Spreen and Strauss, 1998). We tested verbal fluency tested using two subsets of the CERAD-NP (Consortium to Establish a Registry for Alzheimer's Disease) - the semantic fluency and phonemic fluency tests (Morris et al., 1988). Finally, we used the Memory Complaint Questionnaire (MAC-Q) to assess subjective memory decline, (Crook et al., 1992).

MRI hardware and procedure

All details about the study design and methods have been previously reported (Matura et al., 2014a, 2014b, 2016, 2020, 2021). All MR images were acquired using a Trio 3-T scanner (Siemens, Erlangen, Germany) with a standard head coil for radiofrequency transmission and signal reception. Participants were outfitted with protective earplugs to reduce scanner noise. For T1-weighted structural brain imaging, an optimised 3D modified driven equilibrium Fourier transform sequence (Deichmann et al., 2004) with the following parameters was conducted: acquisition matrix = 256 x 256, repetition time (TR) = 7.92 ms, echo time (TE) = 2.48 ms, field of view (FOV) = 256mm, 176 slices and 1.0-mm slice thickness. Functional resting state images were acquired using a blood oxygen level-dependent-sensitive echo-planar imaging sequence comprising the following parameters: 300 volumes, voxel size: 3 × 3 ×3 mm3, TR = 2000 ms, TE =

30ms, 30 slices, slice thickness =3mm, distance factor = 20%, flip angle = 90°, and FOV= 192mm. Resting state measurements were part of a larger fMRI study on episodic memory. For the resting state measurements, all participants were instructed to keep their eyes open, to lie still, not to engage in any speech, to think of nothing special and to look at a white fixation cross-presented in the centre of the visual field during the whole scan procedure.

Resting-state functional MRI (rs-fMRI) data analysis

To analyse the resting state functional data, we used the Connectivity (CONN) Toolbox (CONN toolbox). CONN is an open-source Matlab/SPM-based cross-platform software for the computation, display, and analysis of functional connectivity Magnetic Resonance Imaging (fcMRI). CONN is used to analyse resting state data (rsfMRI) as well as task-related designs. We first imported the raw/partially processed Digital Imaging and Communications in Medicine (DICOM) functional and anatomical files into the CONN graphical user interface (GUI). We then ran the default pre-processing pipeline (direct normalization to MNI-space) in CONN's GUI. The pipeline performs the following steps:

Functional realignment using SPM12 realign & unwarp procedure (Andersson et al., 2001);

Correction of temporal misalignment of slices of functional data using SPM12 slice-timing correction (STC) procedure (Henson et al., 1999);

Outlier identification from the observed global BOLD signal and the amount of subject-motion in the scanner;

Direct segmentation and normalization into standard MNI space and segmented into grey matter, white matter, and CSF tissue classes using SPM12 unified segmentation and normalization procedure (Ashburner and Friston, 2005);

Functional smoothing using spatial convolution with a Gaussian kernel of 8mm full width half maximum (FWHM).

After pre-processing was completed, we ran the default denoising pipeline in CONN. The pipeline performs two general steps: linear regression of potential confounding effects in the BOLD signal, and temporal band-pass filtering. Once completed, we evaluated the effect of denoising by assessing the CONN Quality Control Plots. These plots provide a visualisation of the distribution of functional connectivity values (FC) between randomly selected pairs of points within the brain before and after denoising. After denoising, FC distributions showed approximately centred

distributions, with small but noticeable larger tails in the positive side, and considerably reduced inter-session and inter-subject variability.

Selection of seed region

To analyse DMN connectivity, we used a seed region-based approach. Because we were specifically interested in DMN resting state activity and whether any alteration is associated with the PRS we investigated the intrinsic functional connectivity of a region anatomically co-localised with the major posterior hub of the DMN, the posterior cingulate cortex (PCC). We also explored the connectivity of the PCC as the region-of-Interest (ROI) with other ROIs in the brain that are commonly affected by AD pathology such as the hippocampus, parahippocampus, and the amygdala.

DNA extraction, genome-wide genotyping and Polygenic Risk Scores (PRS) calculation

DNA was extracted from whole-blood samples. The DNA extraction and genotyping process were conducted at bio.logis laboratories (Frankfurt am Main., Germany). DNA was genotyped on the Infinium Global Screen Array (GSA) with multi-disease drop in (MD) covering in total ca. 700K SNPs per person at Broad Institute, Cambridge, Massachussetts. For PRS calculation, 177 persons were originally considered, after quality control measures using PLINK v1.9 (Chang et al., 2015) regarding relatedness and missingness per individual (< 0.1), 142 participants remained for further analysis. Regarding SNP quality, SNPs were filtered excluding minor allele frequencies (MAF < 0.01) and genotyping missing rate per marker (< 0.05). Furthermore, SNPs were LD-pruned (--indep-pairwise window-size 100 kb, step size 50 kb, r2 threshold 0.5).

PRS were calculated using the PRSice software version 2.3.1.e with default options (clumb-kb 250, clump-p 1.0, clump r2 0.1, interval 5e-05, lower 5e-08, stat BETA) (Choi and O'Reilly, 2019). The used summary statistics from the International Genomics of Alzheimer´s Project (IGAP) were used (Lambert et al., 2013) and subjected to INFO score filtering (INFO > 0.8). Neither the present study sample nor the IGAP sample show any overlap. PRS values with p-threshold 1 were used for further statistical analysis. We excluded 3 participants from the analysis in this study because they did not have rs-fMRI data. The final sample in this study included 139 participants who had both rs-fMRI data and PRS.

Statistical analysis

All statistical analysis for the correlation between neuropsychological test scores and the PRS was conducted using RStudio (RStudio Team, 2020). A Shapiro-Wilk test was used on the PRS and

all cognitive variables to test for the assumption of normality. Shapiro-Wilk test is considered the most powerful test for normality (Razali and Wah, 2011). Association between PRS and cognitive scores was investigated with Pearson's correlation for normally distributed cognitive scores and Spearman's partial correlation for variables that were not normally distributed. For normally distributed cognitive scores, we also investigated the association of cognitive performance with the interactions of PRS, gender and education, using simple linear regression analysis. For linear regression analysis, a correlation value closer to +1 reflected a positive relationship while a correlation value closer to -1 reflected an inverse relationship between the variables of interest.

To examine the association of PRS and connectivity values of the included participants, we performed a group-level analysis using multiple linear regression analysis in the CONN Toolbox. Functional connectivity values at rest between the PCC as the seed region and other ROIs were encoded as the dependent variable. PRS and age were entered as the independent, explanatory variables.

Results

Participants' demographic characteristics

Table 1 describes the demographic characteristics and neuropsychological tests scores of the included participants. The final sample size was 139 participants. 58% of all participants were female (n = 80). The mean age of the young group was 31 years (SD = 12.95) while for the old group the mean age was 69 years (SD = 4.23).

Table 1: Demographic characteristics and neuropsychological tests scores on the study sample

Variable	*Young group (n = 83)*	*Old group (n = 56)*
Age	31.07 (12.95)	69.32 (4.23)
Gender (% female)	46 (55%)	34 (60.71%)
Years of education	16.7 (3.1)	15.33 (3.14)
MMSE	29.33 (1.54)	29.05 (1.10)
CVLT immediate recall trial 1 list A	65.66 (7.09)	55.72 (10.24)
CVLT immediate recall trial 1 list B	8.25 (2.23)	5.66 (2.04)
CVLT total immediate recall list A	9.42 (2.37)	7.21 (2.23)
CVLT short delayed free recall	14.07 (2.10)	11.30 (3.10)
CVLT short delayed cued recall	14.34 (1.88)	12.42 (2.48)
CVLT long delayed free recall	14.47 (1.99)	12.19 (3.25)
CVLT long delayed cued recall	14.64 (1.72)	12.47 (2.84)
CVLT recognition discriminability	15.70 (0.64)	14.96 (1.39)

TMT-A	23.74 (7.64)	39.21 (10.02)
CERAD semantic fluency (Animals)	26.53 (3.48)	22.52 (4.97)
CERAD phonemic fluency (s-words)	15.60 (3.64)	15.50 (4.62)
MAC-Q	26.07 (2.97)	26.47 (4.19)

Values are presented by mean of raw values ± standard deviation (SD) unless stated otherwise. MMSE: Mini-Mental State Examination; CVLT: California Verbal learning Test; TMT-A: Trail Making Test – Part A; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; MAC-Q: Assessment of Memory Complaint Questionnaire.

Relationship between PRS and intrinsic connectivity

After controlling for age, seed-based correlation and ROI-to-ROI analysis of a pooled group of both young and old adults (n =139) revealed no significant association between the PRS and intrinsic functional connectivity of the PCC with other ROIs (q-FDR > 0.05). More specifically, we looked at the connectivity of the PCC with largely implicated regions in AD pathology that are critical for episodic and spatial memory (i.e., the medial temporal lobe (MTL) and whose functional connectivity is also altered in early AD (Cutsuridis and Yoshida, 2017; Berron et al., 2020). Our results did not show a significant association between the connectivity of the PCC and bilateral hippocampus in participants with PRS (right: beta = - 0.33, q-FDR = 0.986712; left: beta = -3.41, q-FDR = 0.986712). Moreover, there was no significant association between the connectivity of both the right posterior parahippocampus (beta = 14.58, q-FDR = 0.918222) and the left posterior parahippocampus (beta = 2.51, q-FDR = 0.986712) with the PCC with regard to individual PRS. We furthermore explored alterations of connectivity of the PCC with the amygdala with regard to PRS and could not find significant results for the right amygdala (beta = -18.05, q-FDR = 0.918222), nor for the left amygdala (beta = 7.65, q-FDR = 0.986712).

To verify the results, we extracted the beta connectivity values of the PCC and the above-mentioned regions and examined their association with the respective PRS of each individual in RStudio. For normally distributed connectivity values, we examined the linear relationship with Pearson's correlation between the connectivity and PRS. For non-normally distributed connectivity values, we used Spearman's Partial correlation. This additional analysis did not yield any significant association between the PRS and PCC connectivity with other ROIs, neither in the young nor in the old group (p-values > 0.05).

Relationship between PRS and cognitive performance of young and old groups

For both normally and non-normally distributed cognitive scores, we performed a simple correlation analysis between PRS and cognitive scores. We obtained Pearson's or Spearman's

correlation coefficients and their p-value of correlation test in R. Table 2 provides a summary of the correlation coefficients (and their level of significance) between the PRS and cognitive scores for the young and old group. In the young group, there was no significant association between the PRS and scores of all neuropsychological tests. Similarly, no significant association was observed between the PRS and all cognitive scores in the old group.

We also performed multiple linear regression analysis to examine the relationship between the scores of each neuropsychological test, PRS and gender. Linear regression results indicate that there is a significant negative correlation between the performance in the semantic fluency test and PRS (p-value = 0.02) as well as the phonemic fluency test and PRS (p-value = 0.03). However, the association between verbal fluency test scores and PRS only becomes significant when we take gender into account. The interaction between PRS and gender on verbal fluency is demonstrated in Figure 1. This means that higher PRS is significantly correlated with worse cognitive performance in verbal fluency tests, however, this is true only in older male participants. No other significant association was observed between the PRS and other cognitive scores in the old group.

Table 2: Summary of the correlation results between the PRS and cognitive scores of young and old groups

	Young (n = 83) *Pearson's/Spearman Correlation coefficient (p-value)*	*Old (n = 53)* *Pearson's/Spearman Correlation coefficient (p-value)*
MMSE	r_s = 0.39 (0.1559)	r_s = 0.02 (0.896)
CVLT immediate recall trial 1 list A	r_s = 0.028 (0.7956)	r = -0.115 (0.4083)
CVLT immediate recall trial 1 list B	r_s = 0.080 (0.4721)	r = -0.068 (0.6298)
CVLT total immediate recall list A	r = 0.126 (0.254)	r = -0.199 (0.1524)
CVLT short delayed free recall	r_s = -0.034 (0.7534)	r_s = 0.0185 (0.8954)
CVLT short delayed cued recall	r_s = -0.095 (0.3927)	r_s = -0.010 (0.9398)
CVLT long delayed free recall	r_s = 0.029 (0.7921)	r_s = 0.0468 (0.7415)
CVLT long delayed cued recall	r_s = -0.057 (0.6132)	r_s = -0.057 (0.6808)
CVLT recognition discriminability	r_s = 0.0145 (0.8973)	r_s = -0.033 (0.8141)
CERAD semantic fluency (Animals)	r = 0.19 (0.489)	r = 0.017 (0.9005)
CERAD phonemic fluency (s-words)	r = 0.02 (0.950)	r = 0.0431 (0.7544)
TMT-A	r_s = - 0.13 (0.259)	r = -0.05 (0.705)
MAC-Q	r = 0.24 (0.434)	r = -0.01 (0.954)

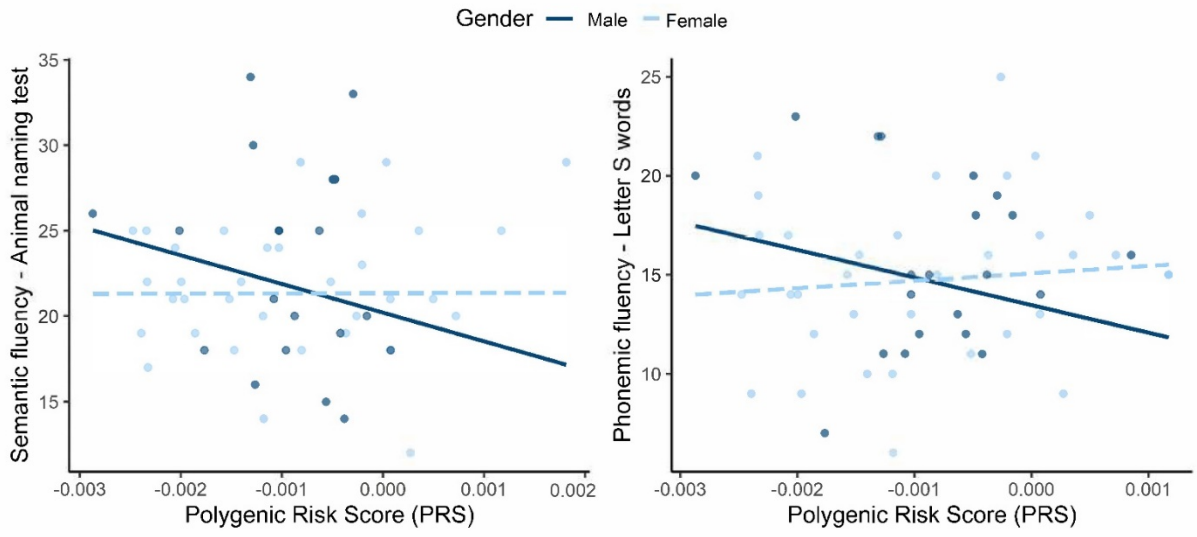

Figure 1: Association between PRS and gender and performance on verbal fluency tests in older participants

We also performed multiple linear regression analysis to examine the relationship between the scores of each neuropsychological test, PRS and gender. Linear regression results indicate that there is a significant negative correlation between the performance in the semantic fluency test and PRS (p-value = 0.02) as well as the phonemic fluency test and PRS (p-value = 0.03). However, the association between verbal fluency test scores and PRS only becomes significant when we take gender into account. The interaction between PRS and gender on verbal fluency is demonstrated in Figure 1. This means that higher PRS is significantly associated with worse cognitive performance in verbal fluency tests, however, this is true only in older male participants. No other significant association was observed between the PRS and other cognitive scores in the old group.

Discussion

In a cohort of cognitively healthy adults, we conducted an exploratory analysis to investigate the association between the genetic risk for AD reflected in a polygenic risk score (PRS) and intrinsic functional connectivity. Our findings demonstrate that PRS did not have a significant predictive effect on the intrinsic functional connectivity of the PCC with other regions in the brain. In addition, we investigated the effect of PRS on cognitive performance. Our results show that a PRS seems to only have a significant association with performance in verbal fluency tests in male participants older than 60 years. In this group, a higher PRS was significantly associated with worse performance in tests of semantic and phonemic fluency. In the next paragraphs, we aim to contextualise our findings, and to interpret their implication in practical terms as well as

account for the limitations of the present study.

Previous evidence suggests that the DMN and the PCC connectivity are greatly disrupted in AD by amyloid deposition in DMN regions (Greicius et al., 2004; Sperling et al., 2009; Beason-Held, 2011; Binnewijzend et al., 2012; Damoiseaux et al., 2012; Palmqvist et al., 2017). Altered functional connectivity of the DMN has also been observed in cognitively healthy ApoE4 carriers as well as i n patients with MCI or AD (Lambert et al., 2013). Nonetheless, clinical trials targeting the amyloid cascade hypothesis have shown inconsistent results so far (Yiannopoulou et al., 2019; Walsh et al., 2021) Anti-amyloid monoclonal antibody treatments such as the recently approved Aducanumab showed reduction in amyloid load in people with MCI or early AD (Sevigny et al., 2016; Commissioner, 2021; Walsh et al., 2021). However, the clinical benefits (i.e., reversal or slowing of cognitive decline of this drug are yet to be confirmed in further post-approval clinical trials (Commissioner, 2021). The previous inconsistent results of clinical trials have directed research into looking for other potential genetic risk factors that are linked to AD. We investigated whether an elevated genetic risk for AD in healthy persons, reflected in a polygenic risk score may also have similar alterations in intrinsic functional connectivity to that observed in patients with MCI and AD. This was done by calculating a polygenic risk score based on Single Nucleotide Polymorphisms (SNPs) that are significantly associated with AD. Results from our sample could not demonstrate a significant correlation between individual PRS and intrinsic functional connectivity of the PCC and other regions in the brain. We found that a higher PRS was negatively associated with worse performance in verbal fluency tests. However, this was true only in male participant older than 60 years. Verbal fluency facilitates the cognitive ability to retrieve information from memory (Patterson, 2011). It is most commonly tested by examining two parameters, semantic and phonemic fluency, and by asking the person to generate and report either objects belonging to a specific category or words starting with a specific letter (Patterson, 2011). Previous evidence shows that verbal fluency is also impaired in patients with MCI and AD (Paek et al., 2020). Studies have shown Verbal fluency tests to be sensitive towards AD pathology and to differentiate healthy controls from patients with MCI or early Alzheimer's Dementia (García-Herranz et al., 2020; McDonnell et al., 2020). Moreover, both semantic and phonemic fluency tests have also been shown to predict conversion from MCI to AD (Vaughan et al., 2018).

Our findings suggest that a higher genetic risk of AD may drive similar mechanisms that lead to cognitive impairment and the affection of verbal fluency performance. Previous studies suggest a possible effect of age on verbal fluency tasks with older adults producing a smaller number of

words in verbal fluency tests than younger groups (Bolla et al., 1990). In line with our findings, a previous study showed a significant association between a high PRS for AD and disruption in verbal fluency in older adults (≥ 65 years old) (Vivot et al., 2015). Overall, literature on verbal fluency in the context of AD dementia is scarce (Paek et al., 2020). Nonetheless, in a cognitively healthy group, women seem to generally retrieve more words and have an overall better performance than men in verbal fluency tasks (Bolla et al., 1990; Aronson et al., 1991). A previous study showed that there is a significant difference between cognitively healthy men and women in verbal fluency tests, with women generating more words in the semantic and phonemic fluency tests (Monsch et al., 1993). The same study showed that in participants with AD dementia, there was no significant difference between the performance of men and women on the same task (Monsch et al., 1993). In our study, older male participants seem to show an expected difference in performance in verbal fluency tests (i.e., smaller number of generated words), both in terms of their age as well as gender.

A major limitation of this present study is that we only investigate the association of the PRS and intrinsic functional connectivity in cognitively healthy adults. We did not compare this cohort of participants to a group of patients with MCI or AD. Therefore, we could not compare the results and identify potential similarities or differences between the two groups. However, our results still provide a significant insight into the potential role of genetic variants of AD beyond ApoE4 on the modulation of brain connectivity. As this was conducted as an exploratory analysis, further investigation, and comparison between cognitively healthy and people with MCI/AD is imperative to compliment the presented findings. Another potential limitation is the unavailability of longitudinal data of the analysed sub-sample of this cohort. We analysed the functional connectivity data that was taken at a cross-sectional point in time. Insightful information could be gathered if we follow-up this sample and investigate first, whether there is further significant modulation in the intrinsic functional connectivity in relation to their PRS. Secondly, carriers of genetic variants associated with AD may not necessarily express the phenotype (i.e., typical clinical symptoms of AD) in their lifetime. Therefore, it is important to track those who may have showed a decreased connectivity in the PCC/hippocampus as well as lower performance in neuropsychological tests and examine whether some of them started to express clinical symptoms and develop further cognitive decline.

In conclusion, our results contribute the growing body of research exploring the complex polygenicity of AD and its association with alterations in functional connectivity at rest. Further investigation of the interaction between genetic risk factors and other sociodemographic

variables is warranted to understand the epigenetic nature of AD in older adults.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Authors' contributions

Aliaa Ibnidris conducted the data analysis, interpretation of results and the write up of the manuscript. Fabian Füßer was in charge of participant recruitment, data collection and the write up of the manuscript. Thorsten Kranz contributed to the DNA genotyping of participants and the calculation of the final individual PRS. David Prvulovic, Andreas Reif and Johannes Pantel contributed to designing the study, data collection phase and the revision of the manuscript. Emiliano Albanese contributed to the revision of the manuscript. Silke Matura contributed to the conception of the study, study design, supervision of the data analysis and interpretation, and the write up and revision of the manuscript.

Funding

The original study was supported by the Neurodegeneration & Alzheimer's Disease Research grant of the LOEWE program 'Neuronal Coordination Research Focus Frankfurt' (NeFF).

Acknowledgment

We would like to thank all participants for contributing their time to take part of the study. We thank all co-authors for their contribution to the data collection, data analysis, writing and revision of the final manuscript.

Data availability

Data is available upon reasonable request.

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Chapter 4: Evaluating measurement properties of Subjective Cognitive Decline self-reported outcome measures: A systematic review

Aliaa Ibnidris, Janelle Robinson, Marissa Stubbs, Giovanni Piumatti, Ishtar Govia, Emiliano Albanese

Submitted to BMC Systematic Reviews:

Ibnidris A, Robinson J, Stubbs M, Piumatti G, Govia I, Albanese E. Evaluating measurement properties of Subjective Cognitive Decline self-reported outcome measures in observational studies: A systematic review.

Abstract

Background: Subjective Cognitive Decline (SCD) is present in the early stage of preclinical Alzheimer's disease (AD) and is associated with an increased risk of further cognitive decline and AD dementia later in life. Early detection of at-risk groups with subjective complaints is critical for targeted dementia prevention at the earliest. Accurate assessment of SCD is crucial. However, current measures lack important psychometric evaluations and or reporting.

Objectives: To systematically evaluate measurement properties of self-reported outcome measures (PROMs) used to assess SCD in older adults' population with or at risk of AD.

Methods and analysis: We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols 2015 checklist for reporting. We conducted a literature search, screened and included validation studies of SCD based on self-reported questionnaires from both population-based and clinical studies, conducted in older adults (≥55). We critically appraised the included primary studies using the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) guidelines.

Results: 16 studies met the inclusion criteria. The included studies reported psychometric properties of 17 SCD self-reported questionnaires. We extracted data on the structural validity, internal consistency, test-retest reliability, and cross—cultural validity, and found a widespread proneness to bias across studies, and a marked heterogeneity in assessed and reported measurement properties that prevented the consolidation of results.

Conclusion: Our findings suggest that available SCD questionnaires lack content validity evaluation. Currently available measurements of SCD lack development and validation standards. Further work is needed to develop and validate SCD self-reported measurement with good quality measurement properties.

Keywords: Subjective, Cognitive dysfunction, Preclinical AD, Measurement properties, Assessment, PROM

Introduction

Targeted dementia prevention requires the early detection and diagnosis of at-risk individuals of Alzheimer's disease (AD) dementia. Several biomarkers (e.g., amyloid plaques and neurofibrillary tangles) are present in the brain many years before dementia develops [1]. Furthermore, neuronal damage and loss may already occur in earlier stages such as Mild Cognitive Impairment (MCI), leading to irreversible cognitive dysfunction [2]. The U.S. National Institute on Aging – Alzheimer's Association (NIA-AA) proposed a preclinical stage of AD characterised by normal cognitive performance in standardised neuropsychological tests and the presence of AD biomarkers [3–6]. This stage may be accompanied by subtle cognitive decline that is only perceived subjectively but not captured by standardised tests [7]. Therefore, detection at this stage is of particular interest for AD prevention, including disease-modifying trials [7,8].

Subjective cognitive decline (SCD) is defined as self-perceived, sudden change in cognitive abilities such as memory, executive functions, or language [7]. Previous evidence that suggests the older adults who express SCD have an increased risk of further cognitive decline and conversion to MCI or AD dementia in late life [9–12]. SCD as a separate construct has been gaining more attention and is being suggested to be one of the earliest symptoms in the preclinical stage of AD [7,13]. The Subjective Cognitive Decline Initiative (SCD-I) working group has stablished key concepts of SCD and propose it as a symptomatic stage of preclinical AD [7]. However, assessment of SCD varies greatly between studies and is not yet standardized [7]. Recommendation from the SCD-I working group include a thorough evaluation of psychometric properties of available self-reported measures used in the current literature [14].

Building on the recommendation of the SCD-I, the main aim of this work is to conduct a systematic review to evaluate the psychometric properties of self-reported output measures used to assess SCD in older adults with or at risk of AD. The main aim of this systematic review is to evaluate reported measurement properties of self-reported questionnaires used to assess Subjective Cognitive Decline in older adults (55 years old and above). The research question follows the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) format [15–17]:

- The construct or the name(s) of the outcome measurement instrument(s) of interest: Subjective Cognitive Decline in AD.
- The target population: Older adults 55 years old and above.
- The type of measurement instrument of interest: self-reported questionnaires used to assess SCD in older adults in the context of AD.

- The measurement properties on which the review focuses: structural validity, internal consistency, test-retest reliability, and cross-cultural validity

Methods

The protocol of this systematic review was registered on PROSPERO (CRD 42020166905). The protocol and the systematic review were reported following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [18,19].

Study selection

We attempted to identify original studies that reported PROM development to assess SCD in older adults in the context of Alzheimer's disease. We included studies that performed and reported validation of psychometric properties, specifically on validity and reliability of SCD PROMs. We included community-based studies as well as studies conducted in memory clinics or research settings. We excluded studies that used SCD PROMs to recruit participants for specific studies or studies that did not aim to validate PROMs. We also excluded studies that developed and validated SCD PROMs for the purpose of screening or diagnosing SCD in other diseases (e.g., depression).

Inclusion criteria:

- *Participants*

We included studies with older adults (55 years and older) in studies of Alzheimer's disease (including studies about Mild Cognitive Impairment and AD dementia studies). We attempted to include studies that tested SCD PROMs in cognitively healthy adults as well as adults diagnosed with SCD, MCI, or AD dementia. We excluded studies with older adults with SCD due to any other specific, previously identified conditions such as stroke, neuropsychiatric conditions (i.e., mood disorders, psychotic disorders, etc.), trauma or delirium.

- *Time frame*

We included relevant studies published between 1982 and 2020 that were published in English. We chose the year 1982 because the concept of SCD was first described in 1982 [20,21].

Data sources

We searched for published studies using the main and most relevant biomedical databases to our study focus:

- MEDLINE/PubMed
- Embase
- PsycINFO

For grey literature, we used OpenGrey database. To look for thesis and dissertations we used Open Access Theses and Dissertations and WorldCat databases. For conference proceedings and abstracts used Web of Science and Scopus. Studies included in the review were not be limited to a certain geographical location. However, only studies published in English were included.

Search strategy

Our search strategy included iterations of the concepts Subjective Cognitive Decline AND Preclinical Alzheimer's disease AND self-reported questionnaire AND measurement properties. The full search strategy is available in Appendix 1.

Study records

- *Data management:* We stored all records, articles and related material using OneDrive. We used Zotero for bibliographic management for all retrieved studies and to remove duplicates.

- *Selection process:* Three independent reviewers (AI, JR, and MS) screened study titles and abstracts against the eligibility criteria. The first reviewer (AI) then imported the selected studies to Rayyan – a web-based software for the title and abstract screening in systematic reviews [22] - for the title and abstract screening phase. Any conflict between the three reviewers was resolved through discussion. Full-texts of the included records were independently reviewed by the three reviewers to determine the eligibility for data extraction and analysis. This was followed by another session to resolve discrepancies between the three reviewers. In case of unresolved conflict, a senior researcher (EA) was consulted to make the final decision.

- *Data collection process:* The first reviewer (AI) abstracted the data from full records independently using the COSMIN data abstraction tables. When full articles were not available, we contacted the corresponding authors and requested the full text. The three reviewers (AI, JR, and MS) completed the risk of bias checklist and rating of the quality of measurements using the COSMIN material.

Main outcomes

We used the COSMIN methodology in a modular manner to evaluate any reported psychometric property in the included study. However, for the purpose of this systematic review, we focused on the internal structure of PROMs and qualitatively analyse the structural validity, reliability (internal consistency and test-retest reliability), and cross-cultural validity. The main outcomes are the following measurement properties:

- *Content validity*
    1. Self-reported outcome measurement development
    2. Content validity evaluation

- *Internal structure*
    3. Structural validity
    4. Internal consistency and test-retest reliability
    5. Cross-cultural validity

Because there is no gold standard measurement to assess SCD, we ignored results on criterion validity in the included studies and did not include them in the analysis. Furthermore, a number of the included studies also reported construct validity (convergent and concurrent validity) of the SCD PROM, however with clinically administered assessment measures of cognitive decline (e.g., MMSE). We ignored these results as well because construct validity should be tested with other validated measures that assess SCD.

Data extraction

Data extraction was conducted independently by three reviewers. We used the developed extraction sheet by COSMIN and piloted it the start of data extraction. We extracted the following information variables:

- The characteristics of the self-reported outcome measurement, including the name of the measure, a reference to the article in which the development of the measure is described, constructs being measured, language and study population for which the measure was developed, intended context of use, the available language version of the measure, number of items in each scale, and response options.

- Characteristics of the included samples including geographical location, language, target population, sample size, percentage of female participants, and mean age of

the study sample.

- Methodological quality ratings per measurement property per PROM.

Measures of effect

Each measurement property is evaluated by rating the relevant sub-items listed below. For example, in internal consistency, if the validation study of the PROM reports that Cronbach's alpha was calculated for continuous scores, then this sub-item is rated "Very good". If not, it is rated "Doubtful" or "Inadequate" depending on which other statistical tests was performed. The measures of effects per psychometric property are presented in table 1.

Table 1: Outcome measures per measurement properties

Measurement property	Measure(s) of effect
Self-reported outcome measurement development	Concept elicitation: Sample size (evaluated based on COSMIN guidelines)[15,17,17]
	Cognitive interview study: Number of patients per item
	Comprehensiveness: Number of patients per item
Content validity	Relevance (patients): Number of patients per item
	Comprehensiveness (patient): Number of patients per item
	Comprehensibility (patient): Number of patients per item
	Relevance (professionals): Number of professionals per item
Structural validity	Exploratory factor analysis (EFA)
	Confirmatory factor analysis (CFA)
Internal consistency	Continuous scores: Cronbach's alpha or Omega
	Dichotomous scores: Cronbach's alpha or KR-20
	Item response theory (IRT)-based scores: SE (θ) or reliability coefficient
Reliability	Continuous scores: Intraclass correlation coefficient (ICC)
	Dichotomous/nominal/ordinal scores: Kappa, weighted Kappa (ordinal scores)
Cross-cultural validity	whether the PROM shows similar structural validity and reliability when validated in another cultural context or translated to another language

Risk of bias

We evaluated the risk of bias using the COSMIN Risk of Bias Checklist [15–17]. The checklist

assesses the quality of the relevant main outcomes described above. Each psychometric property is evaluated by scoring a set of items about the conduction and reporting of the specific property. Each item is scored either "V" (very good), "A" (adequate), "D" (doubtful) or "I" (inadequate) according to the instruction of the COSMIN rating guideline. The total score for each psychometric property is given based on the "worst score count" method. The COSMIN guidelines instruct the raters to rate the overall quality of a property by taking the lowest rating given to any of the sub-items. The risk of bias per psychometric property per PROM was evaluated by the three reviewers (AI, JR, and MS). Any discrepancy between the three reviewers was discussed to reach consensus.

Strategy for data synthesis

We did not conduct a meta-analysis and we only described the quality of psychometric properties testing in the selected studies. We used the COSMIN criteria to evaluate each psychometric property that was tested and reported for each SCD PROM. We evaluated validity (structural validity) and reliability (internal consistency and test-retest reliability) properties. We further evaluated cross-cultural validity and convergent validity when possible. We evaluated each reported psychometric property per PROM before judging its risk of bias. Based on the statistical analysis and reported results of each psychometric property, we also provided a qualitative assessment on whether the results are "sufficient", "indeterminate", or "insufficient".

Analysis of subgroups or subsets

We did not conduct an analysis of subgroups or subsets in this review.

Confidence in cumulative evidence

The COSMIN guidelines recommend using the modified version of the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) to grade the strength and quality of the collected evidence. Because the identified studies did not have content validity studies, we were not able to grade the selected SCD PROM studies using the modified GRADE approach.

Results

Results of the search

We completed the search on 10 June 2021. We identified 364 records in the initial database search. We further identified 13 records through hand-searching the references of some of the

relevant studies. After duplicates removal, there were 290 records remaining. The three reviewers (AI, JR, and MS) screened the title and abstract of the 290 records using Rayyan software. After the completion of the screening phase, the inter-rater reliability and agreement between the three reviewers was measured using Fleiss kappa [23] and agreement percentage in RStudio [24]. The results indicate substantial agreement between the reviewers (Fleiss kappa = 0.662, p-value < 0.0001). Moreover, the percentage agreement with zero tolerance was 78.4%. After the resolution of conflict between the three reviewers, we excluded 208 records that did not meet the inclusion criteria and 3 records that did not have the full-text available (three conference proceedings). We screened the full texts of the remaining 79 records.

Included studies

The final number of included studies was sixteen studies. The search and selection of studies is demonstrated in a PRISMA flow chart (figure 1). All studies developed and validated SCD PROMS in high income settings, mainly in the USA (37.5%) and Europe (56.25%). Only one study was conducted in Asia (South Korea). Table 2 summarises the characteristics of the included studies that reported measurement properties of SCD self-reported questionnaires in older adults.

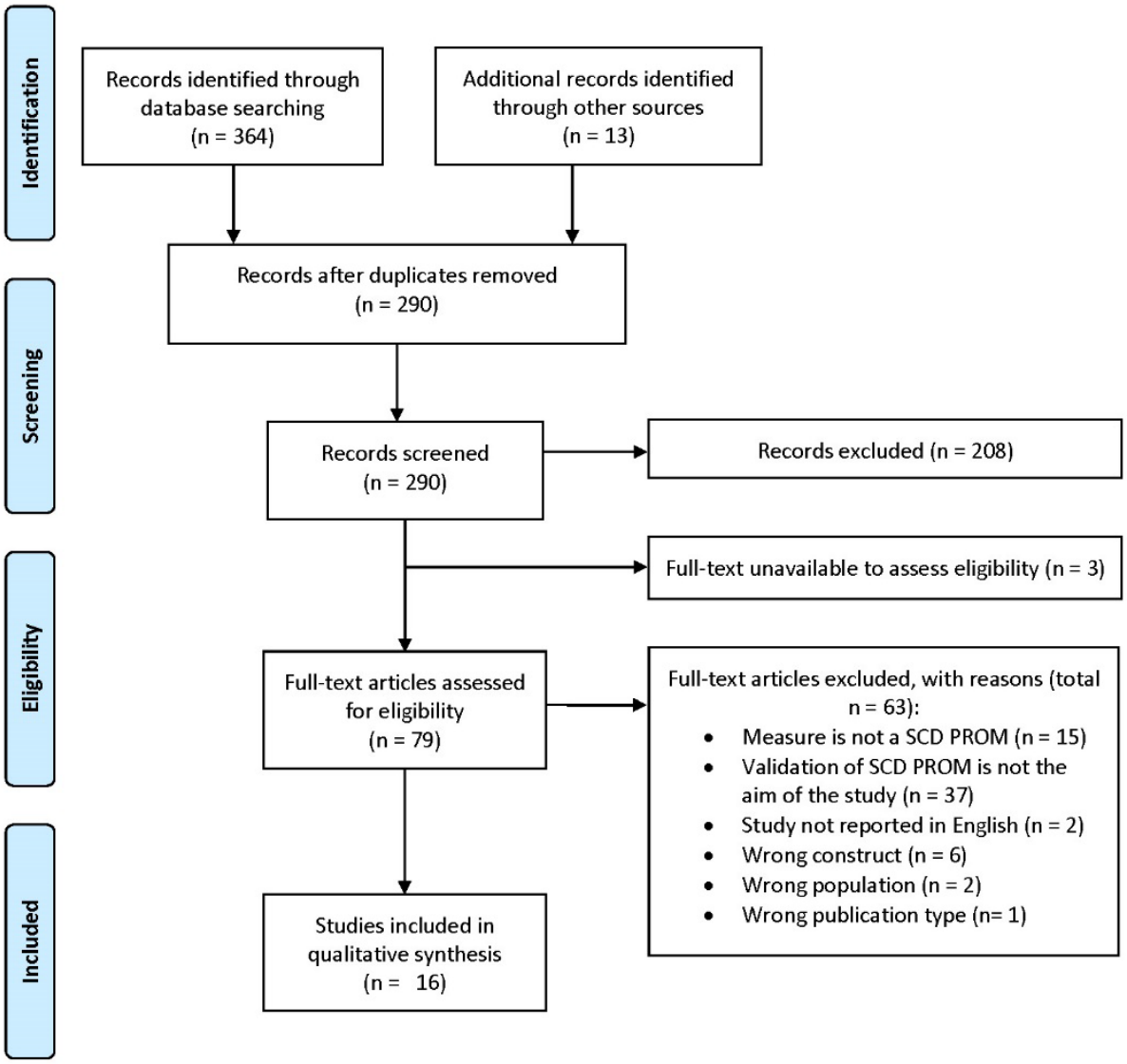

Figure 1: Flow chart of the screening and selection process of the identified records

Table 2: Details and characteristics of the studies included in the systematic review

First author (year)	***Location***	***Sample size***	***Study population***	***Mean age (SD)***	***Female (%)***	***Study design***	***Setting***	***Language of development***	***Language of validation***
Allison et al. (2019)	USA	91	Cognitively healthy adults	69 (6)	54 (59.34)	Cross-sectional	Laboratory	English	English
Avila-Villanueva et al. (2016)	Spain	844	Cognitively healthy adults (n = 766); MCI (n = 78)	Cognitively healthy =74.07 (3.80); MCI =76.08(4.06)	Cognitively healthy = 63% Female; MCI = 50%Female	Longitudinal	Research setting (unspecified)	English	Spanish
Chipi et al. (2018)	Italy	257	Cognitively healthy adults	70.9 (5.1)	158 (61.2%)	Cross-sectional	Memory clinic	English	Italian
Crook et al. (1992)	USA	232	Cognitively healthy adults	59.2 (6.9)	117 (50.43%)	Clinical trial	Unspecified	English	English
Crowe et al. (2016)	USA	55	MCI	76 (NA)	39 (71%)	Longitudinal	Unspecified	English	English

Crowe et al. (2016)	USA	55	MCI	76 (NA)	39 (71%)	Longitudinal	Unspecified	English	English
Gifford et al. (2015)	USA	191	Cognitively healthy adults (n = 115); MCI (n = 43); Other (n =33)	Cognitively healthy = 75.9 (7.5); MCI = 77.0 (6.5); Other = 78.5 (8.5)	Cognitively healthy = 72.24 (63%); MCI = 21.9 (51%); Other = 19.14 (58%)	Longitudinal	Unspecified	English	English
Gilewski et al. (1990)	USA	778	Cognitively healthy adults	56.9 (20.8)	435 (55.91%)	Cross-sectional/Longitudinal	Unspecified	English	NA
La Joie et al. (2016)	France	185	Cognitively healthy (n = 74); MCI (n = 78); SCD (n = 33)	Cognitively healthy = 69 (7.2); MCI = 73 (7.2) ; SCD = 68 (7.3)	Cognitively healthy = 40 (54%); MCI = 38 (49%); SCD = 14 (42%)	Cross-sectional	Memory clinic	English	French

Lubitz et al. (2018)	Germany	734 above 65 = 83.67 (11.4%)	Cognitively healthy adults	43.15 (17.17);	401 (62.26%) of subsample of 644 participants	Longitudinal	Community-based	German	German
Papaliagkas et al. (2017)	Greece	295 - older adults (n = 53) - older-old adults (n = 28)	Cognitively healthy adults	- Older adults = 69.9 (3.6) '- Older-old adults = 83.5 (3.3)	- Older adults = 31 (56.6%) - Older-old adults = 18 (64.3%)	Cross-sectional	Unspecified "quiet and comfortable environment."	English	Greek
Papaliagkas et al. (2017)	Greece	295 - older adults (n = 53) - older-old adults (n = 28)	Cognitively healthy adults	- Older adults = 69.9 (3.6) '- Older-old adults = 83.5 (3.3)	- Older adults = 31 (56.6%) - Older-old adults = 18 (64.3%)	Cross-sectional	Unspecified "quiet and comfortable environment."	English	Greek

Rami et al. (2014)	Spain	397	Cognitively healthy (n = 124); MCI (n = 83), AD (n = 46); SCD (n = 144)	Cognitively healthy = 60.2 (9.2); P-SCD = 56.8 (10.4); C-SCD = 67.0 (8.9); MCI = 70.5 (9.2); AD = 74.5 (8.8)	Cognitively healthy = 66 (59%); P-SCD = 33 (58%); C-SCD = 58 (71%); MCI = 39 (49%); AD = 29 (64%)	Cross-sectional	Unspecified	Spanish	Spanish
Rattanabannakit et al. (2016)	USA	267	Cognitively healthy (n = 149); MCI (96); AD (n = 22)	67.8 (11.2)	138 (51.7)	Cross-sectional	Memory clinic	English	English
Valech et al. (2018)	Spain	68	Cognitively healthy (n = 37); SCD (n = 31)	Cognitively healthy = 64.49 (6.89); P-SCD = 59.33 (5.82);	Cognitively healthy = 23 (62.2%); P-SCD = 6 (100%);	Cross-sectional	Memory clinic/home	Spanish	Spanish

				C-SCD = 65.72 (7.02)	C-SCD = 17 (68.0%)				
Vestergren et al. (2011)	Sweden	370	Cognitively healthy adults	65 (15)	194 (52.7)	Longitudinal	Home	Swedish	Swedish
Vestergren et al. (2012)	Sweden	1115	Cognitively healthy adults	63.0 (14.5)	598 (53.7)	Longitudinal	Unspecified	Swedish	Swedish
Youn et al. (2009)	South Korea	1651	Cognitively healthy (n = 1464); AD (n = 187)	74.3 (8.2)	945 (57.3)	Longitudinal	Unspecified	Korean	Korean

Abbreviations: AD, Alzheimer's disease; MCI, Mild Cognitive Impairment; SCD, Subjective Cognitive Decline; P-SCD, SCD sample from the population; C-SCD, SCD sample from clinical settings.

Participants

Fifteen studies validated questionnaires in a sample including both cognitively healthy older adults as well as adults diagnosed with SCD, MCI or AD. Seven included studies developed and validated SCD questionnaires only in cognitively healthy older adults [25–31]. One study included participants with MCI only [32]. Older adult with MCI were further included in 6 of the included studies [33–38]. Only two studies included participants who received a prior diagnosis of SCD [36,39]. Participants with clinically diagnosed AD dementia were included in two studies [37,40].

Assessed cognitive domains

Sixteen of the seventeen SCD PROMs included items to assess subjective decline in memory function. Nine PROMs looked only at memory and included different aspects of memory function such as facial recognition, spatial topographic memory, word and fact recall/semantic memory, general forgetfulness, everyday task-oriented memory, numeric recall, and remote personal memory [34]. Other PROMs focusing on memory aimed to assess retrospective and prospective memory [29,36], episodic memory [26], or to capture self-perceived change in memory functioning overall [32]. One PROM was developed to assess subjective decline in spatial navigation skills only [25]. Six PROMs assess subjective complaints in executive functions and praxis [26,28,33,36–38,41]. Self-perceived decline in language abilities was assessed only in three PROMs, [36–38,41]. Lastly, social cognition was assessed in one PROM [26].

Reported psychometric properties

As shown in table 2, of the included studies, 81.25% performed and reported aspects of PROM development procedure (n = 13) [25–30,32–37,40] 75% (n = 12) of which reported conducting a cognitive interview or piloting the generated pool of questionnaire items to assess comprehensibility and comprehensiveness of the selected items [25–28,30,32–37,40]. However, all studies but one [28] did not report details regarding the piloting phase. None of the included studies tested for content validity of the developed PROM. On the other hand, the majority of studies tested and reported structural validity (75%, n = 12) for thirteen PROMs. [25,27–31,33,35–37,40,41]. Four of which (25%) used Exploratory Factor Analysis (EFA) only [25,33,36,41], while two studies used EFA followed by Confirmatory Factor Analysis (CFA) [27,35]. Four studies only reported and/or conducted CFA only [28,29,31,40]. Internal consistency using Cronbach's alpha was reported in 68.75% of studies (n = 11) for 13 PROMs [25–32,34,37,38,40]. One study used Item Response Theory (IRT) to test for internal consistency and reported the standard error (SE θ) [35]. One study reported that internal consistency was tested,

however, no statistic was provided [33]. Test-retest reliability was reported in four studies [25,27,34,40]. Only four studies (25%) indicate cross-cultural validation of SCD PROMs in other languages [26,29,33,36]. Two studies evaluated and reported convergent validity with other SCD PROMs [30,34].

Risk of bias

All twelve studies that reported PROM development steps received "I" rating (i.e., high risk of bias) due to the lack of conducting or reporting a cognitive interview or asking about comprehensibility or comprehensiveness of the PROM items. Seven of the thirteen PROMs performed CFA and received a "V" rating in structural validity testing, therefore had a low risk of bias [27–29,31,37,40]. One study was rated "A" for structural validity and was judged to have a moderate risk of bias [33]. The remaining five PROMs were judged to have a high risk of bias due to having an inadequate sample size and receiving "I" rating on the reported structural validity [25,28,30,35,42].

Regarding internal consistency, of the 15 PROMs that were tested for internal consistency studies, 12 were judged to have a low risk of bias ("V" rating) [27–30,32,35,37,38,40,43]. One PROM, the spatial navigation questionnaire was judged to have a moderate risk of bias ("A" rating) [25]. The EMQ and the CFI both had a D rating, i.e., show a high risk of bias [26,33]. The remaining PROMs were judged to have a high risk of bias as well ("I" rating) [36,42].

Moreover, two PROMs, the spatial navigation questionnaire and the MFQ [25,27], had a V rating for the test-rest reliability and were therefore of low risk of bias. On the other hand, the MAC-Q and the SMCQ were of high risk of bias ("D" rating) [34,40]. All four PROMs that evaluated cross-cultural validity of the translated version of the questionnaire were of low risk of bias ("V" rating) [29,33,36]. The risk of bias evaluation is available in the appendix in table S1.

Included SCD PROMS and the quality of the reported psychometric properties

The included studies evaluated 17 PROMs in total that are used to assess SCD in adults. Table 3 provides details of the validated SCD PROMS, which cognitive domains are covered, and the response options and their scoring system. The results of reported psychometric property per PROM as well as a summary of the quality of each measurement property of the above-mentioned SCD PROMs, as rated against the COSMIN criteria of good measurement property is available in the appendix (in tables S2-S3). The focus of each PROM is elaborated below.

The spatial navigation questionnaire is a self-report questionnaire that assesses self-perceived decline in spatial navigations skills over the past several years [25]. It includes self- and informant-reports and each part consists of 20 items of statements regarding change in navigation abilities. The response options range from 1 (strongly disagree) to 7 (strongly agree). The questionnaire was validated in a laboratory setting with a sample of 91 cognitively healthy older adults (mean age = 69, SD = 6). The questionnaire was administered to participants and their informants in two visits, three months apart. The authors report using Exploratory Factor Analysis (EFA) to identify 20 out of 30 initial items that measure self-perceived change in navigation skills. However, due to deploying EFA only, the quality of the structural validity was deemed "indeterminate". Internal consistency for the participant's form was sufficient (Cronbach's α = 0.965, CI = 0.953–0.974), and for the informant's form (Cronbach's α = 0.957, CI = 0.942–0.970) as well as test-rest reliability for the participants (ICC = 0.838, CI = 0.743–0.900) and the informant part (ICC = 0.723, CI = 0.552–0.835) [25].

Everyday Memory Questionnaire (EMQ) is a 25-items questionnaire that comprises of a five-factor structure [33]: 1) Forgetfulness of Immediate Information (FII) was associated with fails in immediate retrieval as well as naming impairment; 2) Executive functions; 2) Prospective memory (PM); 4) Forgetfulness of Common Objects (FCO); and 5) Spatial Orientation (SO). The PROM was validated in a sample of 844 participants, 766 of which were cognitively healthy controls (90.8%) and 78 had MCIs (9.2%). The mean age for cognitively healthy participants was 74.07 (SD = 3.80) and 76.08 (SD = 4.06) for participants with MCI. Items were scored on a 3-point scale, with 0 representing ''never, rarely'', 1 ''occasionally, sometimes'' and 2 ''frequently, almost always''. The total score ranged from 0 to 56. The authors report testing for structural validity (EFA) and internal consistency. However, no statistical test for internal consistency was reported. Cross-cultural validity in implicitly indicated because the EMQ was translated from English to Spanish and was validated in a Spanish-speaking population.

The Cognitive Functions Instrument (CFI) contains 14 questions and has two parts, a participant and an informant's form [26]. It assesses the presence of subjective cognitive concerns in older adults. The response options are Yes = 1, Maybe = 0.5, No = 0, and total score of the questionnaire ranges from 0 to 14. The CFI was validated in the Italian language in a sample of (mean age = 70.9, SD = 5.1). The authors report a more detailed and through translation and cultural adaptation process which indicated sufficient cross-cultural validity. The CCFI was only evaluated for the internal consistency for the participant's (Cronbach's α = 0.77, 95% CI = 0.72–0.83) as well as the informant's part (Group 1: Cronbach's α = 0.77, 95% CI 0.70–0.85, group 2:

Cronbach's α = 0.72, 95% CI = 0.66 to 0.78) [26].

The Memory Complaint Questionnaire (MAC-Q) is 6 items self-report questionnaire that assess age-associated memory decline in older adults in a clinical trial for experimental treatment of age-associated cognitive decline [34]. The response options are either yes or no and the total score ranges from 7 to 35. Authors reported that MAC-Q was administered again after 12 weeks to assess test-retest reliability; however, the reported statistic was not specified. Reported internal consistency of the MAC-Q was not sufficient (Cronbach's α = 0.57). The study also evaluated convergent validity another validated SCD questionnaire, the MAC-S. Note that the authors referred to this as "concurrent validity". The Memory Assessment Clinics-Self-rating (MAC-S) is a 49-item memory questionnaire [43]. 21 items assess the person's ability to remember specific types of information and 24 items evaluates how often specific memory problems are experienced. The last 4 items ask about the person's overall assessment of his or her memory. The MAC-S assess different memory skills (e.g., facial recognition, spatial topographic memory, word and fact recall). The response options are rated on a 5-point Likert scale and the total score of the 49 items. The reported concurrent validity was sufficient (r = .41, p-value < 0.001).

One study reported measurement properties of two different PROMs. The first was a set of six items extracted from the Attitude Toward Intellectual Aging scale of the Personality in Intellectual Aging Contexts (PIC) Inventory [44]. The response options ranged from 1 (strongly agree) to 6 (strongly disagree) and were summed for the overall score. The second PROM is General Frequency of Forgetting scale of the Memory Functioning Questionnaire (MFQ) [27]. The subscale of the MFQ has 14 items that assesses change in memory. Response options ranged from 1 (always) to 7 (never) and were summed to obtain the overall score. For both scales, higher scores reflected greater perception of cognitive decline. The authors report sufficient internal consistency for both scales (Cronbach α = 0.81 and 0.92, respectively).

Gifford et al [35] developed a scale of 9 items to assess SCD using EFA followed by Confirmatory factor Analysis (CFA) to evaluate the unidimentionality of the scale, as well as item-response theory (IRT) to test for internal consistency. Participants were mailed a questionnaire containing 57 items that ask about everyday memory failures. In the final version, the response options were dichotomous (yes/no) for the first 6 questions. For the remaining questions the responses were rated on a 3-point Likert scale, ranging from "always", "sometimes", or "never a problem". The final version of the 9 item-questionnaire shows sufficient structural validity (CFA was

performed) and internal consistency (The mean SE (θ) score was 20.12 - 0.90 for cognitively healthy participants and 0.34 - 0.83 for participants with MCI).

The Memory Functioning Questionnaire (MFQ) was developed and validated in 778 cognitively healthy older adults [27]. It contains 64 items that assess subjective memory worsening. The items are rated on a 7-point Likert scale that ranges from. Structural validity was tested by EFA followed by CFA. The final version of 64 items consists of four factors: 1) General Frequency of Forgetting, 2) Seriousness of Forgetting, 3) Retrospective Functioning, and 4) Mnemonics Usage. Reported Cronbach α for internal consistency of each factor was 0.94, 0.94, 0.89, and 0.83, respectively. The authors refer to test-retest reliability being measured; however, no ICC or weighted Kappa was calculated and therefore, test-retest reliability was rated “insufficient”.

The Cognitive Difficulties Scale (CDS) is a 39-item questionnaire that asseses how often someone is currently experiencing cognitive difficulties in everyday life [36,45]. The items are rated on a 5-point scale, ranging from “never” = 0 to “very often” = 4. The authors of the included study validated the SCD in the French language in a sample of 185 older adults (mean age: Cognitively healthy = 69, SD = 7.2; MCI = 73, SD = 7.2; SCD = 68, SD = 7.3). The reported structural validity assessment was rated “inadequate” due to the sample size.

The Complainer Profile Identification (CPI) is a 17-item scale that assesses subjective change in Memory, attention, and executive function [28]. It was validated in a sample of 734 German adults, 83.67 (11.4%) of which were above 65 years old (mean age =4 3.15, SD = 17.17). The items are rated on a 5-points Likert scale, ranging from with “never” = 0 to “very often” = 4. Both structural validity (CFA) and internal consistency (Cronbach’s α = 0.87) were sufficient as rated by the criteria COSMIN of good measurement property.

Papaliagkas et al. [29] reported structural validity, reliability and cross-cultural validity of the Greek versions of the Cognitive Failures Questionnaire (CFQ) [46] and the Prospective and Retrospective Memory Questionnaire (PRMQ) [47]. Both scales were translated and validated in a sample of 295 Greek older adults (Older adults mean age = 69.9, SD = 3.6; Older-old adults mean age = 83.5, SD = 3.3). The CFQ shows sufficient structural validity (CFA: χ^2 (106, N = 449) = 260.46, p = .011, CFI = .985, SRMR = .036, RMSEA = .023) as well as internal consistency (Cronbach’s α = 0.93). On the other hand, the PRMQ also shows sufficient structural validity (CFA: χ^2 (88, N = 464) = 186.14, p < .001, CFI = .959, SRMR = .035, RMSEA = .049) and internal consistency (Cronbach’s α = .84, for Self-Rated Memory; α = .84, for Self-Rated Prospective Memory; and α = .79, for Self-Rated Retrospective Memory).

The Subjective Cognitive Decline Questionnaire (SCD-Q) is a 24-item scale that was validated in a cohort of 794 Spanish speakers to assess self-perceived change in several cognitive domains in older adults over the preceding two years [37]. The scale has a self and informant parts, each consisting of the same 24 items. The response options are dichotomous (yes/no) and the total score for each part of the questionnaire ranged from 0 to 24 points. The authors report sufficient internal consistency for the self (Cronbach's $\alpha = 0.90$) and Informant parts (Cronbach's $\alpha = 0.93$). Structural validity of the SCD-Q was investigated in the original study as well as another included study conducted in Spain, both using EFA [37,42] and therefore, both studies were judged to have "indeterminate" quality of structural validity.

The Cognitive Change Index (CCI) is a 20-item scale, developed and validated in a sample of 267 older adults in the USA [38]. It has a self and informant's parts consisting of the same questions. The items are rated on a 5-point Likert scale ranging from 1 = no change or normal ability, 2 = minimal change or slight/occasional problem, 3 = some change or mild problem, 4 = clearly noticeable change or moderate problem, to 5 = much worse or severe problem. The authors report sufficient internal consistency (Cronbach α: self = 0.96, informant = 0.98). No structural validity analysis was reported. Therefore, internal consistency could not be rated or considered sufficient.

The Cognitive Dysfunction Questionnaire (CDQ) is a 20-item questionnaire that was validated in a sample of 794 older adults in Sweden [30]. The questionnaire aims to assess changes in cognitive function over the preceding one year. The items are rated on a 5-point Likert scale ranging from very seldom = 1, seldom =2, sometimes = 3, often = 4, very often = 5. EFA was performed and the scale showed sufficient structural validity (The Kaiser-Meyer-Olkin measure of sampling adequacy = 0.95, Bartlett's test of sphericity: $v2 = 20254$, $p < 0.001$). Moreover, internal consistency was considered sufficient with a reported Cronbach's α of 0.90. Convergent validity was evaluated against another measure of self-report cognitive decline, the PRMQ [47], which was of sufficient quality ($r = 0.40$, $p < 0.001$). The same questionnaire was evaluated by the same first author to assess the structural validity of a refined version that has 20 more items using CFA. The reported results indicate sufficient structural validity of the refined version of the CDQ (S-B$\chi 2 = 558.5$, $df = 165$, $p < 0.000$, RMSEA = 0.046 (CI; 0.042–0.050), SRMR = 0.057, CFI = 0.98).

The Subjective Memory Complaints Questionnaire (SMCQ) is a 14-item scale that assess subjective memory decline [40]. The authors report developing and validating the questionnaire

in a sample of 1651 older adults in South Korea (mean age 74.3, SD = 8.2). The response options are either yes or no. The highest possible total score on the SMCQ is 14 points (SMCQ-T): 4 points for the judgment of global memory (SMCQ-G) and 10 points for everyday memory (SMCQ-E). The authored demonstrated that the SMCQ has sufficient structural validity by performing CFA. The reported goodness-of-fit index (GFI), comparative fit index (CFI), Tucker-Lewis index (TLI), and root mean square error of approximation (RMSEA) indices for model-fitting were 0.961, 0.929, 0.940 and 0.54, respectively. The internal consistency of the SMCQ was good and was considered to be sufficient (Cronbach's α: SMCQ-T = 0.864, SMCQ-G = 0.827, SMCQ-E = 0.694). The authors also report sufficient test-retest reliability of the SMCQ, SMCQ-G, and SMCQ-E (0.828, p = 0.001; 0.471, p = 0.03; and 0.836, p = 0.001, respectively).

Table 3: Characteristics of SCD PROMS in the included studies

First author (year)	***PROM***	***Domain***	***Target population***	***Reported purpose***	***Informant***	***Items***	***Response***	***Scoring***	***Mode of administration***	***Time to administer (min)***
Allison et al. (2019)	Spatial Navigation Questionnaire	Spatial navigation	Older adults	Screening	Yes	20	7-point Likert scale	NA	Self-administered: Electronic	5
Avila-Villanueva et al. (2016)	Everyday Memory Questionnaire	Forgetfulness of immediate information, executive functions, prospective memory, Forgetfulness of Common Objects, Spatial Orientation	Older adults	Discriminative	No	28	3-point Likert scale	0-56	Unspecified	Not reported
Chipi et al. (2018)	Cognitive Function Instrument	Memory, prospective memory, episodic memory, executive functions, spatial	Older adults	Diagnosis, follow-up	Yes	14	Yes; Maybe; No	0-14	Unspecified	Not reported

		orientation, social cognition								
Crook et al. (1992)	Memory Complaint Questionnaire (MAC-S)	Memory (facial recognition, spatial topographic memory, word and fact recall/semantic memory, general forgetfulness, everyday task-oriented memory, numeric recall, remote personal memory, and attention/concentration)	Older adults	Screening	No	49	5-point Likert scale	7-35	Unspecified	Not reported
Crowe et al. (2016)	Attitude Toward Intellectual Aging scale of the	Change in memory	Older adults	Screening	No	6	6-point Likert scale	Not reported	Unspecified	Not reported

	Personality in Intellectual Aging Contexts (PIC) Inventory (six items)									
Crowe et al. (2016)	Short version of Memory Functioning Questionnaire (MFQ)	Memory	Older adults	Screening	No	14	7-point Likert scale	Not reported	Unspecified	Not reported
Gifford et al. (2015)	SCD questions	global Memory functioning, temporal comparisons	Older adults	Screening	No	9	Yes/No (6 items), 3-point Likert scale (3 items)	Unclear	Self-administered: Mail-in	Not reported
Gilewski et al. (1990)	Memory Functioning Questionnaire (MFQ)	Memory	Older adults	Screening	No	64	7-point Likert scale	Unclear	Unspecified	Not reported

La Joie et al. (2016)	Cognitive Difficulties Scale	Retrospective and prospective memory, attention, language, orientation, praxis	Older adults	Screening	No	39	5-point Likert scale	Unclear	Unspecified	Not reported
Lubitz et al. (2018)	Complainer Profile Identification	Memory, attention, executive function	Older adults	Monitoring	No	17	5-points Likert scale	Unclear	Self-administered: Pen-and-paper; Electronic/Online	Not reported
Papaliagkas et al. (2017)	Cognitive Failures Questionnaire (CFQ)	General cognitive functions	Older adults	Screening	No	25	5-point Likert scale	Unclear	Unspecified	Not reported
Papaliagkas et al. (2017)	Prospective and retrospective memory questionnaire (PRMQ)	Prospective and retrospective memory	Older adults	Screening	No	16	5-point Likert scale	Unclear	Unspecified	Not reported
Rami et al. (2014)	The Subjective Cognitive	Memory, Language, Executive functions	Older adults	Diagnosis	Yes	24	Yes/No	0-24	Self-administered	Not reported

	Decline Questionnaire (SCD-Q)									
Rattanabannakit et al. (2016)	Cognitive Change Index (CCI)	Memory, executive function, language	Older adults	Screening	Yes	20	5-point Likert scale	Unclear	Self-administered: Pen-and-paper/Mail-in	Not reported
Valech et al. (2018)	The Subjective Cognitive Decline Questionnaire (SCD-Q)	Memory, Language, Executive functions	Older adults	Diagnosis	Yes	24	Yes/No	0-24	Self-administered: At home	Not reported
Vestergren et al. (2011)	Cognitive Dysfunction Questionnaire (CDQ)	Memory (Working memory, Semantic memory, Episodic memory, Procedural memory, Prospective memory), Global cognitive (spatial	Older adults	Screening	No	20	5-point scale: 1 to 5 (very seldom = 1, very often = 5)	Unclear	Self-administered: At home	Not reported

		navigation, temporal orientation)								
Vestergren et al. (2012)	Cognitive Dysfunction Questionnaire (CDQ): refined version	Memory (Working memory, Semantic memory, Episodic memory, Procedural memory, Prospective memory), Global cognitive (spatial navigation, temporal orientation) + Procedural actions, Semantic word knowledge, Face recognition, Temporal orientation, Spatial navigation, and Episodic memory	Older adults	Screening	No	40	5-point scale: 1 to 5 (very seldom = 1, very often = 5)	Unclear	Unspecified	Not reported
Youn et al. (2009)	Subjective Memory Complaints	Global memory	Older adults	Screening	No	14	Yes/No	14	Unspecified	Not reported

	Questionnaire (SMCQ)

Discussion

We conducted a systematic review to evaluate the reported measurement properties of SCD PROMs that are used to assess and detect SCD in older adults in the context of AD. We identified and included 16 studies that developed and/or validated 17 self-report measures that assess SCD. We examined the reported development procedure and the internal structure of the measures and provided a comprehensive evaluation of their risk of bias and methodological quality. Our findings suggest that currently available SCD PROMs do not address important psychometric properties.

SCD is an emerging construct that is being considered as one of the earliest clinical symptoms of AD [7,12]. Previous evidence shows that older adults expressing self-perceived decline in cognitive abilities show greater risk to develop AD dementia in late life [9]. SCD is commonly assessed using a single-item approach (e.g., "Do you feel that your memory is getting worse?") with a dichotomous response option (yes/no) [48–50]. This approach does not cover two important aspects of SCD. The first, self-perceived decline can affect other domains than memory. By asking about memory alone, potential perceived failures in other domains (e.g., executive function or language) may be missed. Secondly, it is important to ask about the time of onset and graduality of the subjective decline. A gradual perceived change in cognitive function over recent years is more likely to be an early manifestation of AD than persistent feeling of change that has been present for many years [7,51,52]. A self-report measure that aims to evaluate several cognitive functions (i.e., memory, executive functions, language, social cognition, etc.) would increase the chance of capturing early self-expressed changes in cognition. Another aspect to consider is the inclusion of an informant's report. The proposed diagnostic criteria for SCD by the SCD-I recommends including an informant's report of cognitive changes that are perceived by the older adult. While several SCD PROMs are currently used in research and clinical studies, the methodological quality of these measure varies greatly [14]. To the best of our knowledge, our study is the first systematic review to evaluate the psychometric properties of available self-reported questionnaire that are used to assess SCD in older adults.

Our findings suggest that several SCD PROMs show sufficient structural validity and internal consistency. However, despite this, we were not able to formulate a recommendation for which SCD measure is most adequate to use. This is due to several factors. First, none of the included studies conducted a content validity study. Content validity is the extent to which a measure truly captures the construct that it was developed to measure [16]. It is considered the most

important, yet most challenging aspect of a PROM development and validation process [17]. It involves a thorough procedure of asking patients and professionals to ensure that all items included in a measure are relevant to the construct under evaluation, are well comprehended by both the target population and professionals (e.g., health professionals or researchers), and are comprehensive enough to include all important aspects of the construct [16,17]. Because no content validity evaluation was available, and as recommended by the COSMIN guidelines, we could not evaluate the overall quality of the PROM nor provide an assessment of the confidence of collected evidence to present a recommended SCD PROM.

Secondly, only one study reported the administration time of the developed PROM (the spatial navigation questionnaire, average time of administration = 5 minutes) [25]. This questionnaire, however, evaluates only subjective change in only one cognition domain. The majority of the included studies also failed to specify the mode (e.g., pen-and paper versus electronic) and the proposed setting of administration (e.g., clinical setting versus at home). Without knowing how long each questionnaire takes or how it should be administered, it is difficult to infer the level of feasibility of the questionnaire at hand.

Some limitations of the present systematic review are worth mentioning. For inclusion in the systematic review, studies needed to have reported psychometric evaluation of questionnaires assessing SCD in older adults in the context of AD. This led to the exclusion of self-reported questionnaires that were developed to assess the construct of SCD in general and were developed or validated in other populations. Indeed, valuable insights can be gathered from these questionnaires, some of which may be well validated questionnaire that reliably assesses the same construct of interest [53]. However, including indirect evidence may introduce heterogeneity because participants in different studies would differ greatly in their sociodemographic and risk factors than those with or at risk of AD [53]. Moreover, our aim was to understand the current status of SCD self-reported questionnaire that are specific designed to assess SCD in related to AD. Therefore, the review team decided to only consider evidence that addressed and included population with or at risk of AD and that validated questionnaires for the sole purpose of identifying SCD in the context of AD. In addition, all identified 17 PROMs were developed and validated in high-income settings (i.e., European countries the USA, South Korea). This sheds light on the importance of further cross-cultural validation of SCD measures, not only in other languages but also more importantly, in low-and-middle-income settings as well.

In conclusion, the results of this systematic review highlight the need for questionnaires that address important measurement properties in order to reliably assess SCD in older adults. A well-validated measure that is also feasible can aid in identifying older adults at risk of AD. Early identification would not only assist in including the right population for clinical trials, but also allow people the opportunity to be followed-up closely and be offered meaningful intervention as early as possible.

Ethics approval

The systematic review did not require an ethical approval from the local ethics board.

Consent for publication

All co-authors revised and provided their consent to publish the final version of the manuscript.

Availability of data and material

Data is available upon reasonable request.

Competing interests

The authors do not have any competing interests to declare.

Funding

The systematic review was not funded.

Authors' contributions

AI formulated the research question, designed the study and wrote the protocol. AI also formulated the search strategy and conducted the database search. AI, MS and JR were the main reviewers of the abstract screening phase, full-text screening, data extraction, and risk of bias assessment. GP provided technical and methodological background and advice. EA and IG provided supervision to the review teams and were involved in the writing and revision process of the manuscript. All authors participated in the writing of the manuscript.

Acknowledgements

The authors would like to thank Dr. Marta Fadda for providing feedback on the final version of the manuscript.

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Appendix

- **Search strategy**

1. **MEDLINE/PubMed search:**

Search date: 03.06.2020. Search results = 43

(subjective[All Fields] AND ("cognitive dysfunction"[MeSH Terms] OR ("cognitive"[All Fields] AND "dysfunction"[All Fields]) OR "cognitive dysfunction"[All Fields] OR ("cognitive"[All Fields] AND "impairment"[All Fields]) OR "cognitive impairment"[All Fields])) AND (preclinical[All Fields] AND ("alzheimer disease"[MeSH Terms] OR ("alzheimer"[All Fields] AND "disease"[All Fields]) OR "alzheimer disease"[All Fields] OR "alzheimer"[All Fields]) AND "cognitive dysfunction"[MeSH Terms] OR ("cognitive"[All Fields] AND "dysfunction"[All Fields]) OR "cognitive dysfunction"[All Fields] OR ("mild"[All Fields] AND "cognitive"[All Fields] AND "impairment"[All Fields]) OR "mild cognitive impairment"[All Fields] AND ("alzheimer disease"[MeSH Terms] OR ("alzheimer"[All Fields] AND "disease"[All Fields]) OR "alzheimer disease"[All Fields] OR ("alzheimer's"[All Fields] AND "disease"[All Fields]) OR "alzheimer's disease"[All Fields]) AND ("dementia"[MeSH Terms] OR "dementia"[All Fields])) AND (("self report"[MeSH Terms] OR ("self"[All Fields] AND "report"[All Fields]) OR "self report"[All Fields] OR ("self"[All Fields] AND "reported"[All Fields]) OR "self reported"[All Fields]) AND ("surveys and questionnaires"[MeSH Terms] OR ("surveys"[All Fields] AND "questionnaires"[All Fields]) OR "surveys and questionnaires"[All Fields] OR "questionnaire"[All Fields])) AND ((instrumentation[sh] OR methods[sh] OR "psychometrics"[MeSH] OR psychometr*[tiab] OR clinimetr*[tw] OR clinometr*[tw] OR "outcome assessment (health care)"[MeSH] OR "outcome assessment"[tiab] OR "outcome measure*"[tw] OR "observer variation"[MeSH] OR "observer variation"[tiab] OR "Health Status Indicators"[Mesh] OR "reproducibility of results"[MeSH] OR reproducib*[tiab] OR "discriminant analysis"[MeSH] OR reliab*[tiab] OR unreliab*[tiab] OR valid*[tiab] OR "coefficient of variation"[tiab] OR coefficient[tiab] OR homogeneity[tiab] OR homogeneous[tiab] OR "internal consistency"[tiab] OR (cronbach*[tiab] AND (alpha[tiab] OR alphas[tiab])) OR (item[tiab] AND (correlation*[tiab] OR selection*[tiab] OR reduction*[tiab])) OR agreement[tw] OR precision[tw] OR imprecision[tw] OR "precise values"[tw] OR test-retest[tiab] OR (test[tiab] AND retest[tiab]) OR (reliab*[tiab] AND (test[tiab] OR retest[tiab])) OR stability[tiab] OR interrater[tiab] OR inter-rater[tiab] OR intrarater[tiab] OR intra-rater[tiab] OR intertester[tiab] OR inter-tester[tiab] OR intratester[tiab] OR intra-tester[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR intraobserver[tiab] OR intra-observer[tiab] OR intertechnician[tiab] OR inter-technician[tiab] OR

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2. Embase:

Search date: 27.05.2020. Search results = 212

'subjective' AND ('cognitive defect'/exp OR 'cognitive defect') AND ('psychometry'/exp OR 'psychometry') AND [english]/lim AND [embase]/lim AND [1982-2020]/py

3. PsycINFO:

Search date: 27.05.2020. Search results = 47

(((((((DE "Cognitive Impairment") OR (DE "Dementia")) OR (DE "Memory Disorders")) OR (DE "Neurocognitive Disorders")) AND (DE "Subjectivity")) AND (DE "Patient Reported Outcome Measures" OR DE "Self-Report")) AND (DE "Psychometrics" OR DE "Measurement" OR DE "Classical Test Theory" OR DE "Consistency (Measurement)" OR DE "Error of Measurement" OR DE "Factor Analysis" OR DE "Item Analysis (Test)" OR DE "Item Response Theory" OR DE "Measurement Invariance" OR DE "Measurement Models" OR DE "Multivariate Analysis" OR DE "Test Construction" OR DE "Test Reliability" OR DE "Test Sensitivity" OR DE "Test Specificity" OR DE "Test Validity" OR DE "Variability Measurement" OR DE "Conjoint Measurement" OR DE "Experimental Design" OR DE "Statistical Analysis" OR DE "Test Interpretation" OR DE "Test Revision" OR DE "Testing")

4. Pingree database

Search date: 29.05.2020. Search results = 9

subjective cognitive decline

5. Open Access Theses and Dissertations

Search date: 29.05.2020. Search results = 0

subjective cognitive decline AND alzheimer's disease AND self report AND psychometrics

6. WorldCat

Search date: 10.06.2020. Search results = 6

'kw:subjective cognitive decline kw:self report kw:psychometry kw:Alzheimer' > '1982..2020' >

7. Web of Science

Search date: 15.06.2020. Search results = 1

(ALL=Subjective cognitive decline AND ALL=Alzheimer AND ALL=self-report AND ALL=psychometr*) AND LANGUAGE: (English) Timespan: 1982-2020. Indexes: SCI-EXPANDED, SSCI, A&HCI, ESCI.

8. Scopus

Search date: 29.05.2020. Search results = 46

subjective AND cognitive AND decline AND alzheimer's AND disease AND self-report AND questionnaire AND psychometry AND (LIMIT-TO (LANGUAGE , "English"))

- **Supplementary tables**

Table S2: Reported results of the psychometric properties of the included SCD PROMs

	Psychometric properties				
First author (Year)	***Structural validity***	***Internal consistency (95%CI)***	***Test-retest reliability (95% CI)***	***Cross-cultural validity***	***Convergent validity***
Allison et al. (2019)	EFA - Uni, RMSEA = 0.76; ratio = 10.150	Subject: α = .0965 (0.953–0.974) Informant: α = 0.957 (0.942–0.970)	ICC: Subject = 0.838 (0.743–0.900) Informant = 0.723 (0.552–0.835)		
Avila-Villanueva et al. (2016)	EFA	NA (mentioned but no alpha reported)		Translation	
Chipi et al. (2018)		Subject: α = 0.77 (0.72–0.83) Informant-relatives: 0.77 (0.70–0.85) Informant-volunteers:0.72 (0.66-0.78)		Translation	
Crook et al. (1992)		α = 0.57	Unclear (= 0.67)		r = .41, p-value < 0.001
Crowe et al. (2016)		α = 0.81			
Crowe et al. (2016)		α = 0.92			
Gifford et al. (2015)	EFA, CFA	θ score range: Cognitively healthy participants = 20.12 - 0.90 participants with MCI = 0.34 - 0.83			
Gilewski et al. (1990)	EFA, CFA	α = 0.94, 0.94, 0.89, and 0.83 for each factor			
La Joie et al. (2016)	EFA			Translation	
Lubitz et al. (2018)	CFA: χ^2 (112) = 318.29, p < .001, CFI = .97, RMSEA = .05 (95% CI: .04–.06)	α = 0.87			

Papaliagkas et al. (2017)	CFA: χ^2 (106, N = 449) = 260.46, p = .011, CFI = .985, SRMR = .036, RMSEA = .023	α = 0.93		Translation	
Papaliagkas et al. (2017)	CFA: χ^2 (88, N = 464) = 186.14, p < .001, CFI = .959, SRMR = .035, RMSEA = .049	Self-Rated Memory α = .84 Self-Rated Prospective Memory α = .84 Self-Rated Retrospective Memory α = .79 (no CI was reported)		Translation	
Rami et al. (2014)	EFA: KMO value = 0.94; Bartlett's Test of Sphericity < 0.001	Subject α = 0.90 Informant α = 0.93			
Rattanabannakit et al. (2016)		Subject α = 0.96 Informant α = 0.98			
Valech et al. (2018)	EFA: KMO = 0.824 significant Bartlett's Test = 880.43; p < 0.0001)				
Vestergren et al. (2011)	EFA: KMO = 0.95 Bartlett's test of sphericity: v2 = 20254, p < 0.001	0.9			r = 0.40, p < 0.001
Vestergren et al. (2012)	CFA: S-Bχ^2 = 558.5, df = 165, p < 0.000, RMSEA = 0.046 (CI; 0.042–0.050), SRMR = 0.057, CFI = 0.98				
Youn et al. (2009)	GFI = 0.961, CFI = 0.929, TLI = 0.940, RMSEA = 0.54	SMCQ-T α = 0.864 SMCQ-G α = 0.827 SMCQ-E α = 0.694	SMCQ-T: 0.828, p = 0.001 SMCQ-G: 0.471, p = 0.03 SMCQ-E: 0.836, p = 0.001		

Abbreviations. α, Cronbach's alpha; CFI, comparative fit index; CFA, Confirmatory factor Analysis; CI,

confidence interval; df, degrees of freedom; EFA, Exploratory factor Analysis; GFI, goodness-of-fit index; ICC, Inter-Class Coefficient; KMO, Kaiser-Meyer-Olkin; r, Pearson's correlation coefficient, RMSEA, root mean square error of approximation; SRMR, Standardized Root Mean Square Residual; TLI, Tucker-Lewis index.

Table S3: Summary of the assessment rating for the quality of measurement properties of the included SD PROMs

	Psychometric properties				
First author (Year)	***Structural validity***	***Internal consistency: α (CI)***	***Test-retest reliability: ICC (CI)***	***Cross-cultural validity***	***Convergent validity***
Allison et al. (2019)	?	+	+		
Avila-Villanueva et al. (2016)	?	?		+	
Chipi et al. (2018)		+		+	
Crook et al. (1992)		-	?		+
Crowe et al. (2016)		+			
Crowe et al. (2016)		+			
Gifford et al. (2015)	+	+			
Gilewski et al. (1990)	+	+	-		
La Joie et al. (2016)	+			+	
Lubitz et al. (2018)	+	+			
Papaliagkas et al. (2017)	+	+		+	
Papaliagkas et al. (2017)	+	+		+	
Rami et al. (2014)	?	+			
Rattanabannakit et al. (2016)	-	?			
Valech et al. (2018)	?				
Vestergren et al. (2011)	+	+			+
Vestergren et al. (2012)	+				
Youn et al. (2009)	+	+			

Note. Each result per psychometric property is rated as either sufficient (+), insufficient (–), or indeterminate (?)

Chapter 5: The Italian version of the Short 10/66 Dementia Diagnostic Schedule: A validation study

Aliaa Ibnidris, Giovanni Piumatti, Fabio Carlevaro, Marta Fadda, Francesca Magno, Daniele Magistro, Emiliano Albanese

Manuscript published in BMJ Open:

Ibnidris A, Piumatti G, Carlevaro F, Fadda M, Magno F, Magistro D, Albanese E. Italian version of the short 10/66 dementia diagnostic schedule: a validation study. BMJ open. 2021 Jun 1;11(6):e045867.

Abstract

Objectives: To determine the criterion and concurrent validity of the Italian version of the short 10/66 Dementia Diagnostic Schedule and algorithm in a sample of Italian native speakers, older adults.

Design: A cross-sectional, validation study.

Setting: The study was conducted with older adults living in the community and in nursing homes in the Canton of Ticino, Switzerland and the Piedmont region in Italy between March and August 2019.

Participants: A convenience sample of 229 participants (69% females) were recruited. The eligibility criteria were being ≥ 60 years old and having an informant. The final sample included 74 participants (32%) with a previous clinical diagnosis of dementia and 155 (68%) cognitively healthy older adults.

Primary and secondary outcome measures: The short version of 10/66 Dementia Diagnostic Schedule consists of the Community Screening Instrument for Dementia (CSI'D), CERAD 10-word list learning task with delayed recall, and the depression scale EURO-D. Disability was measured using the World Health Organization Disability Assessment schedule (WHO-DAS II).

Results: The Italian version of the short 10/66 dementia diagnostic schedule showed fair sensitivity (87%), specificity (61%), and agreement with the clinical diagnosis of dementia (Kappa = 0.40, AUC = 0.74). Older adults with dementia living in nursing homes had higher disability scores (WHO-DAS II mean = 23.14, SE = 7.08) than those living in the community (WHO-DAS II mean = 7.08, SE = 0.66). WHO-DAS II was positively correlated with the short version of the 10/66 dementia diagnosis (β = 5.23, 95% CI = 2.05, 8.41).

Conclusions: In settings where lengthy diagnostic procedures are not feasible, the short 10/66 is a practical tool to identify dementia in older adults. Our findings extend evidence on the validity of the 10/66 dementia diagnostic algorithm to high-income countries, where epidemiological evidence on dementia and its impact is outdated.

Keywords: 10/66 diagnostic algorithm, criterion validity, concurrent validity, sensitivity, specificity, dementia diagnosis, nursing homes, older adults, Italian.

Strengths and limitations:

- Our study is the first to validate the short version of the 10/66 Dementia Diagnostic Schedule and algorithm to detect dementia in high-income settings, and in older adults living in the community and in nursing homes.
- We developed, piloted, tested and used innovative data capturing methods on mobile devices fully implemented in the electronic data collection system REDCap.
- We did not perform second-level assessment for the recruited participants who had a diagnosis of dementia which may have introduced differential verification bias.
- The specificity of the diagnostic algorithm in our study was lower than in previous studies. We used the same cut-offs for the sensitivity and specificity analysis of previous 10/66 studies. Adjusting the cut-offs for future epidemiological studies may lead to a better balance in the sensitivity and specificity of the short 10/66 dementia diagnostic algorithm, at the detriment of standardization of and reducing comparability across studies.
- Information bias cannot be excluded because the interviewers could not always be blind to the clinical diagnosis of the participants.

Introduction

Dementia is recognized by the World Health Organization (WHO) as a global public health priority (1), and because its occurrence increases exponentially with age, steep surges in the number of cases are expected in "graying" populations (2). The Italian-speaking regions in southern Switzerland and Italy have already world's high life expectancies of 85 (3) and 83 years (4), respectively. In these regions and worldwide, the population level needs associated with dementia are high and remain largely unmet. The WHO public health approach to dementia emphasizes the importance of increasing healthcare coverage, which is low not only at the community level, where up to 50% of people with dementia live (5), but also in nursing homes (6), and in both low and high-income countries.

High quality epidemiological studies are indispensable not only to measure the prevalence and impact of dementia, but also to monitor progress in the reduction of the diagnostic and healthcare coverage gaps (7) and can greatly contribute to advance our knowledge and understanding of dementia (8). However, traditional epidemiological studies into dementia have stagnated in the past 20 years in Europe (9). Mobile technologies (i.e., tablets and smartphones) can be used to engage with and recruit community-based samples, for data collection and management, and can contribute to making dementia ascertainment at the population level less time- and resource-consuming, and to make participation easier, more feasible and sustainable (8).

The 10/66 Dementia Research Group (DRG) has conducted extensive cross-country validation studies that confirmed the accuracy of the purposely developed algorithm for dementia diagnosis (10–12) and completed numerous surveys on dementia impact in several Low and Middle-Income countries (LMICs) (13). The 10/66 DRG has recently developed and validated a short dementia assessment schedule (14), which was successfully applied in the Trinidad national survey of ageing and cognition (15). The short-form schedule takes about 15 minutes with the participant and 10 minutes with an informant, and it provides the opportunity to conduct dementia studies in nationally representative samples in high-income countries as well. The aim of this study was to conduct an independent validation study of the short 10/66 diagnostic schedule and algorithm, and to assess the acceptability and feasibility of an all-electronic, web-based, and multi-lingual data collection platform fully consistent with the 10/66 instruments and data collection procedures.

Methods

We used the STARD reporting guidelines to report our study (16).

Study design

We identified two groups of older adults (≥ 60 years old) with and without a previously established diagnosis of dementia (the reference standard) in two separate sites. In both groups, we used an identical neuropsychological battery (the index test) to assess cognitive functions and to assign a diagnosis of dementia based on a probabilistic algorithm (described below).

Eligibility criteria

Eligible participants were older adults aged 60 years and above, living either in the community or in a nursing home, who also had an informant. An informant was defined as the person who is closest to and knows the participant best (e.g., spouse, relative or a carer of community-dwelling older adults). In the context of nursing homes, the informants were identified from the clinical staff i.e., the staff member that was caring for the participant. People with dementia were identified based on previous tests and clinical diagnosis made by a local specialist. We also included people with a clinical diagnosis of mild cognitive impairment (MCI).

Setting, location and dates

We conducted the study in two main settings, the community and nursing homes where older adults lived, and in two main Italian speaking locations, southern Switzerland (Ticino canton) and in northern Italy (Asti, Piedmont region), between March and August 2019.

Participants' recruitment and sampling strategy

This was a convenience sample, and participation was on voluntary basis. Based on previous evidence (14, 17), we calculated that a target sample size of 100 participants (50 people with dementia and 50 controls) was needed to attain a +/- 5% precision in the psychometric parameters estimations of the new measure. In the Swiss site, we recruited dementia patients from local memory clinics as well as geriatric, neurologic, and psychiatric services for older adults. Dementia diagnosis was established by specialists in the memory clinics and the other services, independently of the research team, and was based on the DSM-IV diagnostic criteria (18). Diagnosis of Mild Cognitive Impairment (MCI) due to Alzheimer Disease (AD) was also established in line with the NIA-AA criteria (AD-MCI) (19). The diagnostic procedure did not differ between centers. We matched the sample of clinically diagnosed cases with cognitively healthy controls who volunteered to participate. Cognitively healthy participants and their informants were

recruited through standard advertisement and word of mouth through local older adults' organizations and association, and interested participants contacted us directly.

In the Italian site, we followed a similar recruitment strategy for cognitively healthy, community-dwelling older adults and their informants through older adults' associations. However, we recruited all people with dementia from two nursing homes who had a diagnosis of dementia in their existing medical records. To facilitate and optimize both recruitment and data collection we selected nursing homes in which our research team had conducted previous studies and interventions. The clinical evaluation and diagnosis of dementia of nursing homes' participants was initially established by a general practitioner and was revised and confirmed by attending medical doctor in each nursing home before entering the study. Dementia was diagnosed based on the DSM-IV diagnostic criteria (18).

The study interviewers received standard instructions and training to evaluate the eligibility of participants before the conduction of the cognitive assessment interview. Participants in both sites were not asked to bring copies of their medical records to the interview when the 10/66 neuropsychological assessment was conducted. The local research teams had independent access to the clinical diagnosis, to all available and relevant clinical records, and could confirm diagnosis with a next of kin of the participant as needed. For all participants, we recorded their sociodemographic characteristics including age, gender, educational level and marital status. In participants with dementia, we confirmed information with the informant, and we recorded further information on dementia subtypes when available using the accessible records and clinical documentation.

Measurements

The index test was the previously developed and validated 10/66 Short Dementia Diagnostic Schedule and algorithm (14), which draws on the output scores of a composite neuropsychological assessment and a brief depressive symptoms scale, based on the following instruments:

1. The Community Screening Instrument for Dementia (CSI-D) consists of two parts, a participant (32 items) and an informant interview (26 items) (20). The CSI-D is a widely used dementia screening instrument based on a culturally unbiased, education-fair comprehensive cognitive assessment, combined with an information questionnaire about objective decline in cognitive functions and functional abilities (21). The total

cognitive assessment score (COGSCORE) ranges between 0 (cognitively impaired) and 32 (no cognitive impairment), while the informant's total score (RELSCORE) ranges between 12 (cognitive impairment) and 0 (no cognitive impairment).

2. The CERAD 10-word list learning task with delayed recall (22). consists of asking the participants to recall ten words that are read aloud at one second-pace per word. The number of words remembered gives a total score out up to 10 per trial. The immediate recall is the sum of three consecutive trials, and the delayed recall is the sum of number of words recalled after 5 minutes.
3. The EURO-D is a 12-item depression screening scale derived from the Geriatric Mental State examination (GMS) for mental disorders specific of older people (23). Each EURO-D item is scored 0 (symptom not present) or 1 (symptom present), and the total score ranges between 0 and 12.

The Italian version of the above-mentioned measures is available in the supplementary material. The English version of the questionnaires is publicly available on the 10/66 Dementia Research Group website (https://1066.alzint.org/resources.php). In addition, we used the short, 12-item version of the World Health Organization Disability Assessment schedule (WHO-DAS II) to assess disability in all participants. Participants are asked to rate any difficulties associated with health problems on a 1 (none) to 5 (extreme/cannot do) Likert scale, with higher scores indicating higher disability (24).

The Short 10/66 Dementia Diagnostic Algorithm

The 10/66 dementia case ascertainment methodology has been previously described and validated (12, 25). A short version of the 10/66 dementia diagnostic schedule was developed to allow dementia diagnosis in epidemiological studies in which the GMS interview is not possible and has been validated (14) using data from the 10/66 survey samples (26), and from a population-based study in Singapore (17). Furthermore, it has been successfully used in nation-wide surveys (15). We used the same procedures, cut-offs, regression coefficients, and statistical computations to assign a probabilistic dementia diagnosis to all participants, using the coefficients from the CSI-D, the modified CERAD 10-word list learning delayed recall score, and EURO-D scale (14). The data-processing algorithm is publicly available on the 10/66 Dementia Research Group website (https://1066.alzint.org/resources.php).

Translation

We followed the WHO protocol (27) for the Italian translation of the English version of the 10/66

data collection instruments. Two Italian mother tongue, experienced clinical neuropsychologists and fluent in English translated and independently back-translated all materials favoring conciseness and conceptual equivalence rather than literal translation. An expert panel formed of a geriatrician, a neurologist, and a psychiatrist, and three clinical neuropsychologists all working in local memory clinics, outpatients old age psychiatric services, and nursing homes discussed and resolved discrepancies and inadequate wording. The clinical neuropsychologists administered the instruments to five cognitively healthy older adults for pre-testing and discussed any potential difficulties with comprehension debriefing the interviews with the interviewees. Few minor translational improvements were made based on the summary of the problems encountered and were further discussed by the panel members to reach consensus.

Data collection and management

We imported the English original and Italian translated measures to Research Electronic Data Capture (REDCap) and conducted thorough checks and pilot testing that confirmed accuracy and seamless functioning. All study data were collected and managed using REDCap tools hosted in a secure server at Università della Svizzera italiana (USI) (28). REDCap is a secure, web-based application designed to support data capture and management for research studies, providing: 1) an intuitive interface for reliable and consistent data entry; 2) audit trails for tracking data manipulation and export procedures; and 3) automated export procedures for data downloads to common statistical packages. The interviewers used mobile devices (i.e. tablets and smartphones) to collect data in-person with both participants and informants, either online or with the dedicated REDCap app for offline data collection when internet connection was absent, weak or unstable. REDCap enables secure data collection and storage of data and personal information of participants on separate, remote servers (both hosted at USI). Before the beginning of the study, we confirmed that data collected in the field was seamlessly sent via the internet after encryption to and safely stored in the USI servers.

Finally, at the end of each interview we asked a set of questions to both participants and informants to explore the acceptability of the all-electronic data collection using mobile devices, and the feasibility of the interview, if it was perceived as too long and/or tiresome.

Training

We trained all interviewers for both sites using a standard training module based on the original 10/66 manual which was developed specifically for the short version of the 10/66 dementia diagnostic schedule (14), and which was previously used in community settings (15). The manual

covers the procedures to administer the cognitive tests (CSI-D and 10-word list learning task), and the Euro-D. The first session of the training aimed at introducing the interviewers to the cognitive assessment instruments and the theory behind them. The second session included practical activities to train the interviewers on administering the cognitive tests using REDCap on mobile devices. The practical session was conducted by two experienced neuropsychologists and the principal investigator (EA), an experienced neuro-epidemiologist and member of the 10/66 DRG since 2006. The practical training included a session with a simulated patient. A purposely trained professional actor played the role of the older adult with and without cognitive impairment. The practical training was followed by dedicated sessions of mock interviews between the interviewers that consisted of simulating the entire interview procedure, starting from obtaining signatures on paper copies of the informed consent to using mobile devices for data collection. The final session was dedicated to questions and answers, and to the standardization of data collection using study devised standard operating procedure (SOP) documents.

Interviews

In the Swiss site, interviews were conducted by four psychology postgraduate students and six junior psychologists from the local neurology and psychiatric services. In the Italian site, two postgraduate students in Health Sciences from the University of Turin conducted the interviews under the supervision of an experienced psychologist. In both sites, interviews with community-dwelling older adults (with or without dementia) and their informants took place at the participant's home. Prior to the conduction of the neuropsychological assessments, interviewers did not receive explicit information about the clinical diagnosis of the participant but were not blind to it, neither did they have access to the dementia diagnosis outcome based on the short 10/66 diagnostic algorithm during and after the data collection phase of the study.

Statistical analyses

We carried out descriptive statistics to explore clinical dementia diagnosis across sociodemographic characteristics. Similar to previous validation studies (17), we established the criterion validity of the short 10/66 dementia diagnostic algorithm and calculated its sensitivity, specificity, false positive value (FPV), false negative value (FNV), positive predictive value (PPV) and negative predictive value (NPV). We calculated all diagnostic accuracy statistic at 95% confidence interval (CI). In line with a previous study that validated the short 10/66 algorithm in a high-income setting (17), we test the agreement between the gold standard clinical diagnosis

and the 10/66 dementia diagnosis by calculating Cohen's kappa, percentage agreement, and Area Under the Receiver Operating Characteristics Curve (AUC) (see Supplementary material for statistical analysis). We repeated this analysis stratified by place of residence to explore differences in the accuracy of the short 10/66 diagnosis between community and nursing homes settings. Moreover, we explored the potential differential effect on diagnoses of age, gender, and education, comparing their distributions according to the clinical and 10/66 algorithmic dementia diagnosis. In the main analysis we considered participants with clinically diagnosed MCI to be not cognitively healthy and excluded participants with MCI in a sensitivity analysis.

In addition, we examined the concurrent validity of the short 10/66 dementia diagnosis with the WHO-DAS II, entering disability scores as the dependent variable in regression models adjusted for age, sex, educational level, and place of residence. We used Stata 15 for all statistical analyses (Stata Crop LP, College Station, TX, USA).

Patient and public involvement statement

We involved participants in the piloting phase of the study to explore potential difficulties in comprehending the translated questionnaires, and to enquire about the acceptability of the data collection procedures.

Results

Participants

Between March and August 2019, 244 eligible older adults completed the full set of instruments. 15 participants (6%) were excluded from the analysis because of missing values on at least one item across instruments. These participants did not differ from the rest of the sample in terms of age, gender, previous diagnosis of dementia or residency. The final analytic sample comprised of 229 participants.

Participants' characteristics

Table 1 reports the sample socio-demographic characteristics by clinical diagnosis of dementia. There were 74 (32.31%) previously diagnosed dementia cases, of which 24 cases were Alzheimer's disease dementia, 25 were vascular dementia, and 25 were of unspecified cause. We included 155 (67.69%) older adults who were classified as cognitively healthy based on the combination of clinical records and self-report of both participants and informants. The sample also included 22 participants with a clinical diagnosis of Mild Cognitive Impairment (MCI). Figure

1 and 2 provide a graphical representation of the frequency distributions to illustrate the performance of participants with and without dementia on the word-list recall and the CSI-D.

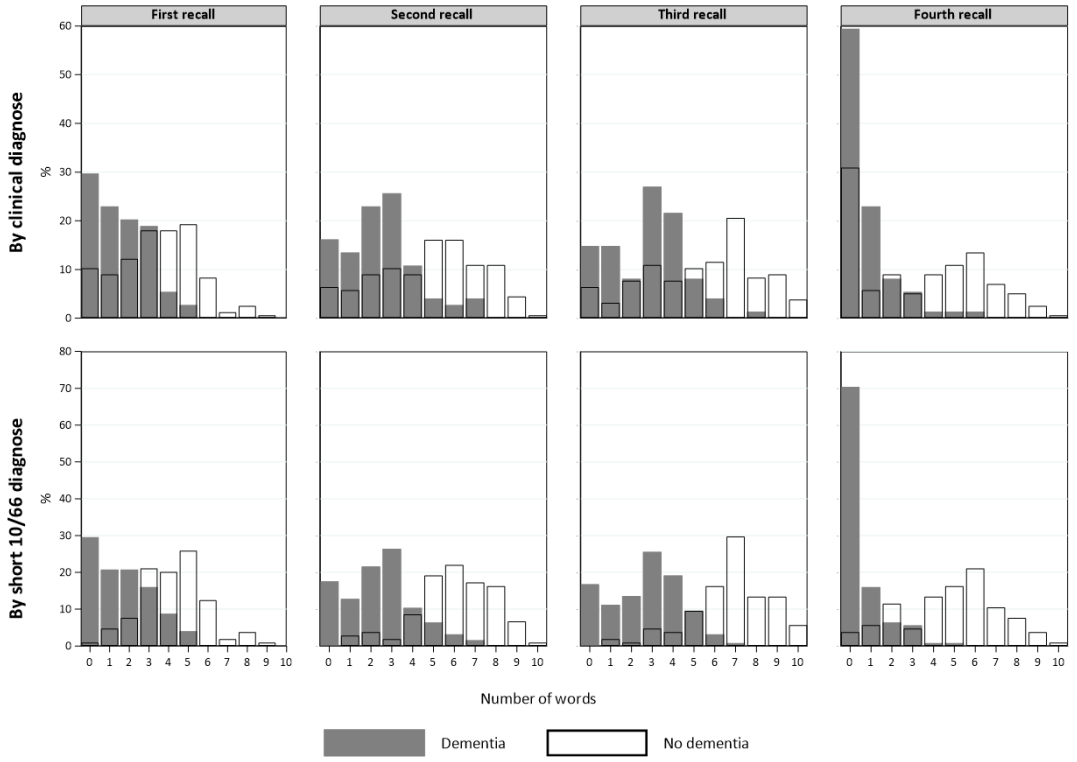

Figure 1: Distribution of word-list recall scores across trials by dementia diagnosis according to clinical or short 10/66 diagnosis

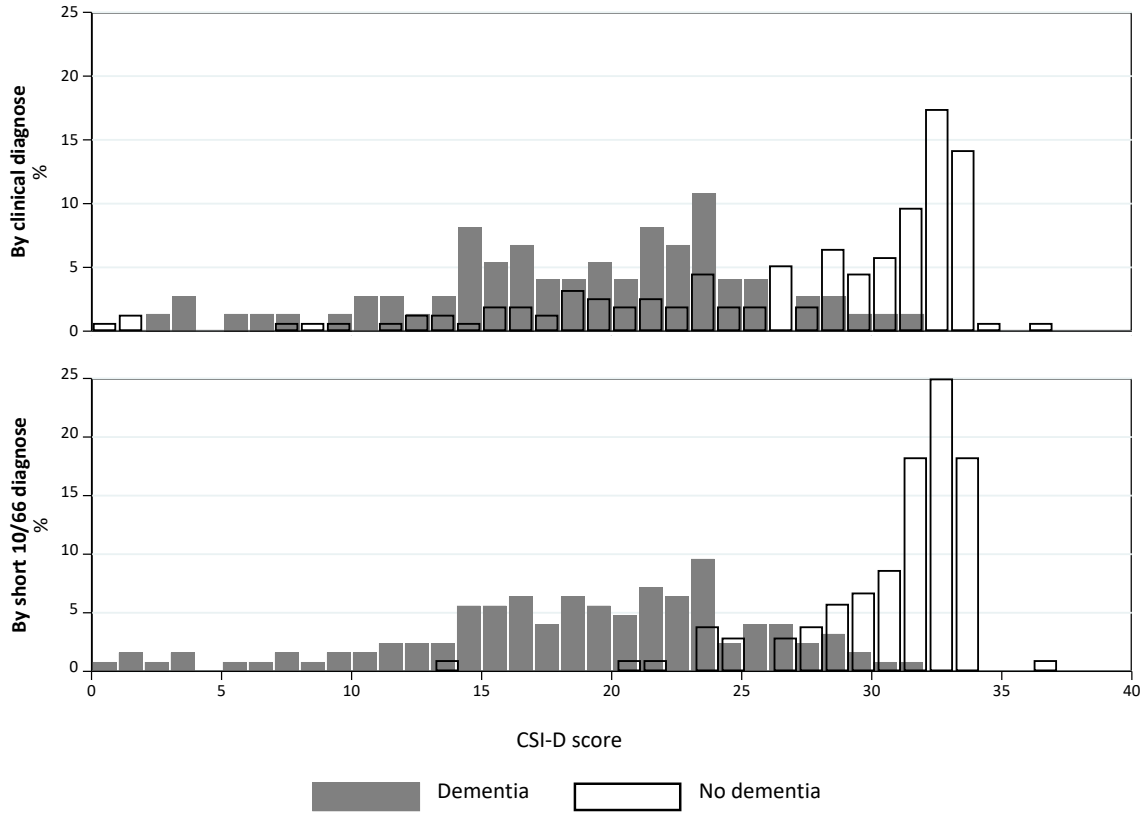

Figure 2: Distribution of CSI-D scores by dementia diagnosis according to clinical or short 10/66 diagnosis. CSI-D, Community Screening Instrument for Dementia

Frequency distributions were provided according to the clinical diagnoses as well as the 10/66 short diagnostic schedule. The histograms of both tests suggest that within the group of people with dementia, some participants have better performance than others which could, to some extent, be a proxy of the severity of dementia.

Table 1: Socio-demographic characteristics of 229 participants across the previous clinical dementia diagnosis. Values are frequencies (percentages)

	No dementia n = 155 (67.7%)	***Dementia[a] n = 74 (32.3%)***	***P value[b]***
Study site			<0.001
Italy (Asti)	41 (26.5)	40 (54.1)	
Switzerland (Ticino)	114 (73.6)	34 (46.0)	
Living conditions			<0.001
Community-dwelling	124 (80.0)	25 (33.8)	
Nursing home	31 (20.0)	49 (66.2)	
Age group (years)			<0.001
60-74	70 (45.2)	11 (14.9)	
75-84	51 (33.0)	28(37.9)	
85+	34 (21.9)	35 (47.3)	
Gender			0.369

Men	51 (32.9)	20 (27.0)	
Women	104 (67.1)	54 (73.0)	
Marital status			<0.001
Never married	11 (7.2)	10 (13.5)	
Married	83 (54.6)	21 (28.4)	
Widowed	15 (9.9)	4 (5.4)	
Divorced/separated	43 (28.3)	39 (52.7)	
Educational level			<0.001
None	8 (5.4)	7 (9.9)	
Primary	19 (12.9)	33 (47.9)	
Secondary	52 (35.4)	21 (29.6)	
Tertiary	68 (46.3)	9 (12.7)	

[a] Clinical diagnosis (excluding MCI participants).
[b] P-value based on Chi-square test.

Validity of the short 10/66 Dementia Diagnostic Schedule against clinical diagnosis and concurrent validity with WHO-DAS II

The diagnostic accuracy of the short 10/66 Dementia Diagnostic Schedule and algorithm is summarized in Table 2, against the clinical diagnosis. We explored the diagnostic accuracy statistics in cognitively impaired participants (dementia and MCI group) compared to the dementia group only. While the sensitivity was higher (87%), specificity was lower when people with MCI were excluded (61%), corresponding to a slightly lower proportion of false negatives, and a slightly higher proportion of false positives, respectively. Overall, the short 10/66 dementia diagnosis showed fair agreement with the clinical diagnosis (Kappa = 0.40). The algorithm also shows acceptable discriminatory ability (AUC = 0.74).

Table 2: Diagnostic accuracy of the short 10/66 Dementia Diagnostic Schedule and algorithm against clinical diagnosis of dementia, including and excluding MCI

	Clinical diagnosis (dementia and MCI group) (n = 96)	***Clinical diagnosis (dementia group only) (n = 74)***
Sensitivity	82% (73%, 89%)	87% (77%, 93%)
Specificity	65% (57%, 73%)	61% (53%, 68%)
FPV	35%	39%
FNV	18%	14%
PPV	63% (54%, 72%)	51% (42%, 60%)
NPV	84% (75%, 90%)	90% (83%, 95%)
% agreement	72% (67%, 78%)	69% (63%, 75%)

Kappa	0.458 (0.346, 0.569)	0.399 (0.293, 0.505)
AUC	0.74 (0.68, 0.79)	0.74 (0.68, 0.79)

MCI: Mild Cognitive Impairment. FPV: False Positive Values. FNV: False Negative Values. PPV: Positive Predictive Values. NPV: Negative Predictive Values. Kappa values: <0 = Less than chance agreement, 0.01–0.20 = slight agreement, 0.21–0.40 = fair agreement, 0.41–0.60 = moderate agreement, 0.61–0.80 = substantial agreement, 0.81–0.99 almost perfect agreement. AUC: Area Under the receiver operating characteristics Curve. 95% confidence intervals (Cis) are reported in parentheses.

In the sensitivity analysis, after exclusion of participants with MCI, the short 10/66 dementia diagnosis showed better accuracy in the community setting compared to nursing homes. Sensitivity was 96% and 81%, and specificity was 66% and 39%, respectively in the former and latter setting (table S1 in the supplementary material). Cross-tabulation of the 10/66 algorithm diagnosis by the previous clinical diagnosis is shown in table S2 in the supplementary material.

Those with dementia were older, with less education, and more likely men compared to those without dementia, and these distributions were non-differential between the clinical and the 10/66 algorithmic diagnostic approach, as shown in Figure 3.

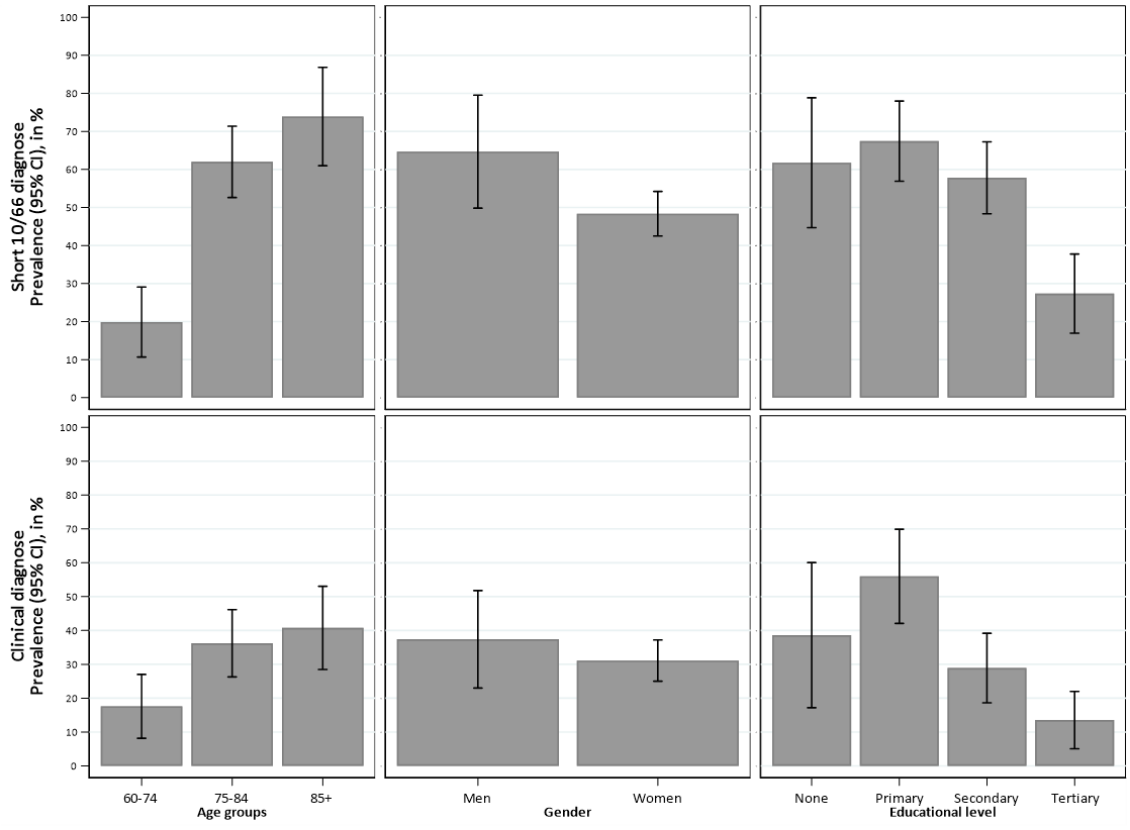

Figure 3: Dementia prevalence across age, gender and educational level according to the short version of the 10/66 diagnostic algorithm and the clinical diagnosis (note: prevalence and 95% CIs are from Poisson regressions with robust SEs, adjusted for age, gender and educational level

Compared to older adults who lived in the community (WHO-DAS II mean = 7.08, SE = 0.66),

disability scores were higher in those who lived in nursing homes (WHO-DAS II mean = 23.14, SE = 1.29). We found a positive correlation between the short 10/66 dementia diagnosis and the WHO-DAS II disability score, accounting for age, sex, educational level, and place of residence (i.e., community vs. nursing home) (β = 5.23, 95% CI = 2.05, 8.41).

Acceptability and feasibility of electronic data collection

Data collection using mobile devices was well accepted by the majority of participants (77%). 21% found it to be excellent and a significant improvement to traditional data collection. Only 2% preferred a traditional pen and paper questionnaire. Data collection, transmission, storage, and management in REDCap worked seamlessly, and proved to be feasible and efficient. Overall, the mean duration of the interview was 35.6 minutes (SD = 15.4). More specifically, on average, the interview lasted for 18.7 (SD = 6.5) minutes for the cognitive assessments, 8.7 (SD = 6.2) minutes for the Euro-D, and 8.8 (SD = 6.9) minutes for the WHO-DAS II questionnaire. Most participants (91 %) found the duration of the interview acceptable and not fatiguing, and only 4% of participants complained about the setting of the interview (i.e., too noisy or distracting, or lacking privacy).

Discussion

In this study, we investigated the criterion and concurrent validity of the short version of the 10/66 Dementia Diagnostic Schedule against the clinical diagnosis in an independent sample of older adults living in the community or in nursing homes. Our findings suggest that the short 10/66 schedule retains its criterion validity to identify dementia cases among older adults living in the community as well as in nursing homes, in two high-income countries. We also found that our innovative all-electronic data collection system implemented on portable devices was efficient, reliable, and highly accepted by older adults.

The 10/66 DRG has conducted numerous population-based studies into dementia, mainly in LMICs (13), with few notable exceptions including in Portugal (29) and Singapore (17). The 10/66 original diagnostic algorithm was validated in 15 countries for use in international epidemiologic research, providing strong support for the robustness and comparability of the epidemiological findings of the 10/66 surveys across continents (12). However, the 10/66 diagnostic algorithm required assessments were deemed too long to allow wide use, particularly in national censuses. Moreover, the duration of the original 10/66 interviews may pose constraints on the conduction of epidemiological studies in dementia, including in high-income countries due to the high costs of data collection. With this in mind, a short version of the 10/66 schedule was developed and

validated using data from the cross-sectional phase of the original 10/66 surveys (14). A similar approach was used in other settings, where epidemiological data on dementia prevalence had been previously collected (15, 17). Nevertheless, only one study from Singapore has been so far purposely designed and conducted to test the criterion validity of the short 10/66 schedule against a clinical diagnosis of dementia (17). This approach is standard and less prone to bias due to circularity, and it was used in the original validation of the full 10/66 dementia diagnostic algorithm (12). Neither the full nor the short version of the 10/66 diagnostic schedule have been validated or used in nursing homes, where up to 50% of residents may have dementia (30) and were a consensus diagnosis based on existing medical records is typically used to adjudicate dementia status (31). In addition, although electronic data collection with laptops was used in the 10/66 Cuban site by local physicians for the prevalence and incidence surveys (32), an all-electronic, online data collection and management system using mobile devices was not previously used across the 10/66 sites. Our findings on the high acceptability, feasibility and efficiency of this all-electronic, 10/66 fully compliant data collection system provides evidence on the robustness of the 10/66 DRG procedures using new technologies.

Our study extends evidence on the validity of the 10/66 methods and probabilistic dementia diagnostic approach and algorithm from LMICs to high-income countries (i.e., Switzerland and Italy), and to Italian language. Further, we found that the short 10/66 schedule has very good convergent validity with a standard measure of disability (WHO-DAS II), and acceptable criterion validity when compared to clinical diagnosis of dementia in older adults who live both in the community and in nursing homes. This may be important not only for epidemiological research, but also for monitoring and screening purposes, because dementia occurrence and impact in residential care facilities is significantly underestimated due to the lack of a standard, practical, and yet fairly valid approach to diagnosis. Multi-phase designs, in which screening tools are combined with in-depth assessments have been used on the ground of their apparent efficiency (33). Previous studies in Italy used a combination of routinely collected data complemented with assessments of cognitive function, functional activities and depressive symptoms (34, 35). Some studies included costly case finding procedures that combined neuroimaging, blood and urine testing to generate a probabilistic dementia diagnosis (36, 37). By using the short 10/66 schedule, we retain the assessment of cognitive functions, accounting for depressive symptoms and functional ability by combining instruments in a parsimonious ascertainment schedule (34–36). Moreover, the short 10/66 schedule, unlike previous approaches (35, 36), includes a structured informant interview as part of the assessment and case identification, which has shown to

improve both its sensitivity and specificity and further reduces education bias in diagnosis in participant's with or without dementia (12,14). Importantly, compared to DSM diagnostic criteria (18, 38), the 10/66 dementia diagnosis is significantly less prone to underreporting of social impairment and cognitive decline by informants, which tends to be high where dementia awareness is low (10). Although age and education differences between participants may have differentially impacted dementia ascertainment, both the short and the standard version of the 10/66 algorithm have similar sensitivity (94% in both) and specificity in low (93%, 94%) and high education (97%, 97%) groups, respectively (14). In addition, as mentioned above, the informant interview further reduces education bias.

Some limitations of our study are worth noting. Although the sensitivity was comparable and adequate (86.5%), the specificity was lower (60.6%) in our study compared to previous validation studies of the short 10/66 diagnostic algorithm (14, 17). We included older adults who live in nursing homes, and the ability of the short 10/66 algorithm to correctly identify people without dementia was somewhat lower than expected. However, the 10/66 algorithm was designed, validated for, and has been used in community samples (12, 14, 15). Moreover, in our study most dementia diagnoses against which we compared the accuracy of the short 10/66 diagnosis were made by specialists, and in highly specialized memory clinics. In these settings, differential diagnosis is often integrated with and informed by various kinds of biomarkers and structural and functional neuroimaging assessments. Diagnosis is then refined, and dementia may be excluded despite overt and objective cognitive and functional decline. Nonetheless, the algorithm's low specificity might imply that people without dementia could be erroneously identified as dementia cases. However, it is important to underline that the participants do not receive the results of the cognitive assessment at the end of the interview and a diagnosis of dementia should only be carried out by a trained medical professional based collectively on medical history and physical examination. Therefore, careful precautions should be applied in future studies, and communication of individual results to participants may be disclosed only upon approval of a competent research ethic body. In cases of a positive dementia ascertainment by the algorithm, and in order to improve the diagnostic procedure for future application of the algorithm, we propose to provide a pre-defined protocol to refer participants for further investigation by a clinician in case of being identified as a dementia case by the algorithm. Finally, the reported positive predictive value of the index test was not solely affected by specificity but also by the base rate of dementia in the present study sample.

Because the 10/66 diagnosis is syndromic and purposely symptoms- and needs-centered, we

maintain that our results provide empirical support for its construct validity despite the lower specificity. In the current study, we follow the same procedure and cut-offs for the specificity and sensitivity analysis of the 10/66 algorithm to allow for direct comparison with previous studies and findings (12, 14, 17). However, an adjustment to the original 10/66 cut-offs may be considered for a better balance in the sensitivity and specificity analyses of future studies, in which the test performance may be accounted for in prevalence calculations.

One of the strengths of our study is the inclusion of people with dementia whose severity of symptoms ranged from very mild to moderate based on their performance on the cognitive assessment of the 10/66 schedule (Figure 2 – 3). Yes, it is important to differentiate people with MCI from those with dementia in both the community and nursing home settings. In the sensitivity analysis in our study, the algorithm showed better accuracy when people with MCI were excluded. This adds confidence in our results on the relatively high sensitivity of the short 10/66 diagnostic algorithm because it is likely that the performance on cognitive tests of numerous participants with an existing clinical dementia diagnosis was only slightly below normative values. This is important also because the onset of dementia with, for example, psychological symptoms (including apathy) may precede cognitive disturbances and objective memory decline (39). Because dementia has an insidious progressive nature, and the diagnostic gap of dementia is likely high in Switzerland (6) and Italy (40), we cannot exclude with certainty that those whom we included as 'controls' may in fact already have dementia. That we did not perform a second-level clinical assessment for the recruited participants is another important limitation of our study. However, although this approach is standard and seemingly more robust, it may be affected by spectrum bias (41, 42). In other words, it is prone to an overestimation of the true performance of the 'index test' (i.e., the short 10/66 schedule) because certain cases are compared with certain non-cases. Studies performed on a population that lacks diagnostic uncertainty may produce a biased estimate of the 'new' test's performance relative to a study restricted to people for whom the test (our diagnostic algorithm) would be indicated. The ideal population should include only people with true diagnostic uncertainty, which was the case in our study. While our design and approach reduced the likelihood of spectrum bias, it is prone to differential verification bias due to the use of two different reference tests for at least some of our cases and controls (43). In fact, differential verification bias may explain why specificity was lower compared to previous studies. As said, while cases were more strictly defined, some of those classified and used in the analysis as 'controls' might have been already affected by dementia. The true number of false positives could be much lower (and thus specificity higher)

than what we found.

Training of interviewers and the relatively short duration of interviews with both older adults and informants suggest that the 'short' 10/66 schedule and diagnostic algorithm can be used in large scale, population-wide, nationally representative samples of older adults to ascertain dementia prevalence in the community and nursing homes in high-income countries, where epidemiologic research on dementia stagnate. Moreover, our results suggest that an electronic data collection system may facilitate the standardization and quality monitoring of data collection, without requiring data entry, and simplifying data cleaning and management. Because this could be integrated in routine electronic medical records systems, using the short 10/66 diagnostic approach may be promising beyond research purposes. Research is warranted, though, to explore whether this innovative data collection approach can contribute to reducing the current dementia diagnostic gap through an integration of its use not only at the primary care level and in general practitioners' clinics by purposely trained non-specialist health workers, but also in nursing homes.

Conclusion

The short 10/66 diagnostic schedule is a valid tool that is also practical, cost-effective, short to administer and highly acceptable also in a high-income setting, where epidemiological evidence on dementia is lacking or outdated. Our findings on the validity of the short 10/66 diagnostic schedule and the feasibility of electronic data collection may have positive implications for epidemiologic research in comparable settings. Moreover, they can contribute to conduct studies aimed at measuring the impact of dementia and contextually the gap in dementia diagnosis and care, and thus reduce the burden that dementia poses on those who are affected, their family, communities and society at large.

Acknowledgements

The authors thank all participants who volunteered their time to take part in the validation study. We also thank all interviewers in both study sites for their work in the data collection.

Contributors

DM, FM and FC contributed to the recruitment of participants and data collection. MF contributed to the preparation of ethical approvals and consent forms. Data analysis and interpretation was led by AI, GP and EA. AI and EA led the writing and revision of the manuscript. All authors were involved in the design and conduction of the study. All authors revised and

approved of the final manuscript.

Funding

The validation of the short version of the 10/66 Dementia Diagnostic Schedule in Switzerland was funded by Alzheimer Schweiz (no grant number was required as per standards of the funding body). The validation of the schedule in the Italian site was partially funded by a professorship grant (EA) from the Swiss School of Public Health. Additional costs in the Italian site were provided in kind by the local research collaborators.

Competing interests

None declared

Patient consent for publication

Not required.

Ethical approval

All participants and their informants provided written informed consent. Ethical approval was obtained in Switzerland from the Comitato Etico Cantonale (Project ID: 2017-02181 CE 3308), and Italy from the Ethical Review Board of Torino (Project ID 470621).

Provenance and peer review

Not commissioned, externally peer reviewed.

Data availability statement

Data are available upon reasonable request.

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Supplementary material

The Italian version of the Short 10/66 Dementia Diagnostic Schedule: A validation study

Table S1: Diagnostic accuracy of the short 10/66 Dementia Diagnostic Schedule and algorithm against clinical diagnosis of dementia by living conditions

	Community-dwelling	***Nursing home***
	Clinical diagnosis of dementia (n = 25)	***Clinical diagnosis of dementia (n = 49)***
Sensitivity	96% (80%, 100%)	82% (68%, 91%)
Specificity	66% (57%, 74%)	39% (22%, 58%)
FPV	34%	61%
FNV	4%	18%
PPV	36% (25%, 49%)	68% (54%, 79%)
NPV	99% (94%, 100%)	57% (34%, 78%)
Agreement	71% (64%, 79%)	65% (54%, 76%)
Kappa	0.376 (0.248, 0.503)	0.216 (-0.002, 0.431)
AUC	0.81 (0.75, 0.87)	0.60 (0.50, 0.71)

Table S2: Contingency table evaluating the accuracy of the short 10/66 Dementia Diagnostic Schedule and algorithm against the clinical diagnosis of dementia by living conditions. Values are frequencies (percentages)

	Total sample		***Community-dwelling***		***Nursing home***	
	Clinical diagnosis of dementia					
	Negative	***Positive***	***Negative***	***Positive***	***Negative***	***Positive***
Short 10/66 dementia diagnosis						
Negative	94 (90.4)	10 (9.6)	82 (98.8)	1 (1.2)	12 (57.1)	9 (42.9)
Positive	61 (48.8)	64 (51.2)	42 (63.6)	24 (36.4)	19 (32.2)	40 (67.8)
Total	155	74	124	25	31	49

STATISTICAL FRAMEWORK

Agreement assessment between the gold standard clinical diagnosis and the 10/66 dementia diagnosis

Our goal in this current paper is to test the agreement between the gold standard clinical diagnosis and the 10/66 dementia diagnosis. Reading from Abdin et al. (1), we calculated percentage of agreement and Cohen's kappa using the kappaetc command in Stata 15 (Stata Crop LP, College Station, TX, USA) developed by Klein (2). The first refers to a basic measure of agreement when two independent raters (in our case the clinical diagnosis vs. the short 10/66 diagnosis of dementia) classify n subjects into q predefined categories (in our case dementia case vs. healthy cases). The proportion of agreement p_o between the two raters can thus be defined as follows

$$p_o = \sum_{k=1}^{q} \frac{n_{kk}}{n}$$

where n_{kk} is the number of cases that both raters (or classifications as in our case) classified as k, and n is the total number of cases.

However, the percentage of agreement by itself does not account for the chance that certain cases may fall into one category at random due to the so-called chance agreement and not just because of their characteristics. Cohen's kappa on the other hand (3, 4), takes into account such a chance agreement p_e as follows

$$p_e = \sum_{k=1}^{q} \frac{n_{k.}}{n} \times \frac{n_{.k}}{n}$$

Where the chance-corrected k coefficient is defined as

$$k_{.} = \frac{p_o - p_e}{1 - p_e}$$

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Chapter 6: A systematic review and meta-analysis of dementia prevalence in seven developing countries: A STRiDE project

Nicolas Farina, Aliaa Ibnidris, Suvarna Alladi, Adelina Comas-Herrera, Emiliano Albanese, Sumaiyah Docrat, Cleusa P. Ferri, Emily Freeman, Ishtar Govia, Roxanne Jacobs, Claudia I. Astudillo-Garcia, Christine Musyimi, Tara Puspitarini Sani, Marguerite Schneider, Imelda Theresia, Yuda Turana, Martin Knapp, and Sube Banerjee.

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Manuscript published in Global Public Health:

Farina N, Ibnidris A, Alladi S, Comas-Herrera A, Albanese E, Docrat S, Ferri CP, Freeman E, Govia I, Jacobs R, Astudillo-Garcia CI, Musyimi C[i0], Sani T. P, Schneider M, Theresia I, Turana Y, Knapp M, Banerjee S, on behalf of the STRiDE team. A systematic review and meta-analysis of dementia prevalence in seven developing countries: A STRiDE project. Global Public Health. 2020 Dec 1;15(12):1878-93.

Abstract

The STRiDE project sets out to support the development of effective dementia policy in middle-income countries. As part of this it will generate new data about the prevalence of dementia for a group of countries (Brazil, India, Indonesia, Jamaica, Kenya, Mexico, and South Africa). This study aims to identify the current estimates of dementia prevalence in these countries and where the gaps lie in the current literature. A systematic review was completed on 30th April 2019 across electronic databases, identifying dementia prevalence literature originating from any of the seven countries. Four hundred and twenty-nine records were identified following de-duplication; 28 studies met the inclusion criteria and were included in the systematic review. Pooled estimates of dementia prevalence ranged from 2% to 9% based on DSM-IV criteria; these figures were generally higher in studies using other diagnostic criteria (e.g. the 10/66 algorithm). Available prevalence data varied between countries. Only Brazil, Mexico and India had data derived from studies judged as having a low risk of bias. Irrespective of country, studies often were not explicit in detailing the representativeness of their sample, or whether there was non-response bias. Further transparent and externally valid dementia prevalence research is needed across the STRiDE countries.

Keywords: middle-income, diagnostic criteria, older adults

Introduction

With population ageing, the number of people living with dementia is growing rapidly, especially in low- and middle-income countries (Prince, Guerchet, et al., 2013). Worldwide, an estimated 47 million people had dementia worldwide in 2015; this number is projected to increase to 66 million by 2030, and 131 million by 2050 (Prince et al., 2015). In low- and middle-income countries, the increase in numbers with dementia is happening within a context of health- and social-care systems that are generally unprepared for this challenge. Many low- and middle-income countries have very few data on dementia prevalence. One element of the STRiDE programme (STrengthening Responses to dementia In DEveloping countries, www.stride-dementia.org/) aims to fill this gap by generating new prevalence evidence in a subset of the seven STRiDE countries (Brazil, India, Indonesia, Jamaica, Kenya, Mexico, and South Africa). STRiDE is designed to support, perhaps to accelerate, the development of effective dementia policy and national planning in these seven countries, with the ultimate goal of improving dementia care, treatment and support systems so that people with dementia are able to live well. We chose the seven STRiDE counties on two criteria, the first was that they should represent a range of circumstances (population size, land mass sizes, different Gross Domestic Product sector compositions of agriculture, industry and service but all with 45% or higher reliance on the service sector) and needs, demonstrate different degrees of progress towards meeting the challenges presented by dementia, and are all on the list of Official Development Assistance (ODA) recipients. The second was pragmatic on the basis of existing research and policy links and willingness to participate.

Previous systematic reviews in this area tend to focus on single countries (e.g., Dong et al. 2007; Fagundes et al. 2011) or countries that are geographically close (e.g., Wu et al. 2013); this may prevent researchers from identifying patterns across developing countries. A notable exception is the World Alzheimer's Report 2015 (Prince et al., 2015). The novelty of our review lies in its deep dive into the data available in the seven STRiDE countries, including focused efforts to uncover a broader set of literature that may be more difficult to capture (e.g., inclusion of non-peer reviewed reports), whilst also being able to identify overarching themes between countries. Our primary aim was to obtain accurate, up-to-date estimates of dementia prevalence, in people aged over 60, across the seven STRiDE countries. We also aimed to appraise the design and methods of existing primary studies to formally assess their proneness to bias, so as to help design a harmonized STRiDE dementia prevalence study protocol. The review used a validated risk-of-bias instrument to identify strengths and weaknesses of previous studies.

Methods

This protocol was registered on PROSPERO (CRD42018089999) and adhered to the PRISMA guidelines.

Eligibility Criteria

We applied the inclusion and exclusion criteria originally used for the 2015 World Alzheimer's Report (Prince et al., 2015), with some adaptations aimed at increasing inclusiveness. Most notably, our review included non-peer reviewed publications and allowed for a broader range of diagnostic criteria to be applied for detecting dementia, recognising that diagnostic criteria that require clinical training may be prohibitive in low- and middle-income countries.

- *Inclusion Criteria*
    - Population-based studies of the prevalence of dementia among people aged 60 years and over.
    - No formal diagnostic standard was required, so long as it had face validity. For example, if the study did not use an internationally recognised diagnostic standard (e.g., DSM-IV), then the authors needed to provide evidence that the criteria used had the equivalent sensitivity and specificity. Face validity was determined first by reading the reported validity as presented by the identified full-texts, and then by reading any cited publications related to the diagnostic validity. If unclear about the validity based on the literature presented within the full-text, the research team would search for evidence of validity of the diagnostic tools and discuss between the two researchers.
    - Studies that independently reported data from at least one of the seven STRiDE countries.
- *Exclusion Criteria*
    - Studies in which diagnosis of dementia depended on accessing dementia care services.
    - Studies sampling from an out-of-date population (i.e., register compiled > 3 years prior to data collection)
    - Studies sampling from a specific care setting, or other unrepresentative healthcare population.

- Studies in which only the prevalence of specific dementia sub-types were reported.
- Studies restricted to young-onset dementia (<59 years old).

Information Sources

We used iterations of the syntax 'dementia AND (prevalence OR epidemiology)' (below) to search relevant databases (PubMed, SCOPUS, PsychINFO, SciELO, and WoS) using a combination of MeSH terms and text words, and relevant synonyms, spelling variations, and acronyms as appropriate. To identify grey literature, we used electronic databases such as Opengrey.eu and Google Scholar, and we hand-searched the references of those relevant studies identified. We contacted experts in each country, who are also part of the broader STRiDE team, to check for omissions and unpublished data. These experts were asked to identify and forward any known dementia prevalence literature (peer-reviewed or not). Experts were not asked to apply any eligibility criteria, which was undertaken by two of the authors (NF and AI) during the study selection process.

We adopted a comprehensive lateral search strategy, in which we explored citations from identified articles, but also previous reviews that explored this topic, for example the World Alzheimer Report 2015 (Prince et al., 2015). We also explored citation searches using the "Cited by" option on Google Scholar, and the "Related articles" option in PubMed.

For potentially relevant conference proceedings we contacted the corresponding author (where possible) to obtain access to the original data and information when needed. In addition, corresponding authors were contacted to obtain full-texts where not available online, or through our academic library systems.

Search Strategy

We adopted a broad yet specific search criteria, which we piloted before use. The search strategy included terms related to: 1) the health condition of interest (dementia), 2) Type of study (prevalence OR epidemiology) and 3) Countries of interest ("South Africa" OR Indonesia OR India OR Jamaica OR Mexico OR Brazil OR Kenya)

For the exact searches used for each database, see Appendix A.

Study Records

All search results were downloaded and entered into Mendeley, for automatic and manual de-duplication. The de-duplicated list of studies was then uploaded to a web platform (https://rayyan.qcri.org/) (Ouzzani et al., 2016), which allowed for titles and abstracts to be screened by two researchers independently.

Google Translate was used to translate any non-English language text, with language assistance from members of the broader multi-lingual STRiDE team from each country as needed.

Study Selection

At the screening stage, two researchers (NF and AI) independently examined titles and abstracts to see if they met inclusion criteria. In any cases of uncertainty, we included the study in the full-text phase (below). We collected the full-texts of all potentially eligible studies, and the two reviewers (NF and AI) independently established eligibility applying the full inclusion/exclusion criteria, tracking decisions using a pre-piloted form and dedicated table. During the shortlisting stage there was moderate agreement (κ=0.79). Discrepant decisions were discussed between NF and AI; if no consensus was reached then it was resolved through discussion with two senior researchers (SB and EA). In situations where there were multiple full-texts related to a single study (e.g., same data set), an original full-text was selected to be the primary source of information.

Data extraction

Data, defined as any information about (or deriving from) a study, were extracted from the full-texts of each included study using two sets of purposively designed, pre-piloted tables of: study design; characteristics of study delivery; main and secondary results; risk of bias; and study quality assessment. The extracted data were entered into an existing tool (The Joanna Briggs Institute, 2014), with additional items added to allow extraction of elements relevant to assessing risk of bias and study methodology specific to dementia prevalence (number of phases, dementia diagnostic criteria etc.). As the purpose of this review was to gain insight into the current state of the literature, including reporting styles, no efforts were made to contact authors for supplementary materials or clarifications outside of what was reported.

Data Items

For unweighted prevalence, we extracted either:

1) numerator and denominator,
2) prevalence and denominator,
3) prevalence and standard error, or
4) prevalence and 95% confidence intervals.

For weighted prevalence we extracted either:

1) weighted prevalence and weighted standard error, or
2) weighted prevalence and weighted 95% confidence intervals.

Studies were presented in different formats, either as a whole sample, gender-stratified, age-stratified, or a combination of them. We prioritised the extraction of whole sample raw prevalence data and extracted gender- and age-stratified prevalence data when available.

Descriptive information about the methodology and outcomes used in the included studies were extracted, such as sampling strategies, sample size, response rates and diagnostic criteria.

Outcomes and Prioritisation

The primary outcome of this systematic review was dementia prevalence.

Risk of Bias in Individual Studies

Risk of bias of the included studies was assessed using an existing tool for prevalence studies (Hoy et al., 2012). This has 10 domains, covering internal and external validity aspects of the studies. A single author (NF) judged each item (High vs Low Risk) based on predefined criteria. A second author (AI) reviewed the decisions, and any disagreements were discussed within the broader group. This tool was selected because it has been deemed as being easy to use, has good inter-rater agreement (κ =0.82) (Hoy et al., 2012) and has been adopted in previous prevalence-related systematic reviews (e.g., (Lundorff et al., 2017; Stolwijk et al., 2016)).

As per the guidance of the tool, any studies in which there was insufficient information to permit a judgement on an item was deemed as high risk. The final risk-of-bias rating of each study was selected based on the sum of decisions of each item. As the final risk-of-bias score has little guidance, we devised an algorithm to guide the decision-making process. Additional evidence of bias (e.g., abnormal prevalence rates) could be used as rationale to change the final risk-of-bias score. The criteria were:

- High risk of bias – Three or more items (≥75%) within the external validity domain OR four or more items (≥75%) within the internal validity domain being judged as having a high risk of bias.
- Low risk of bias – Fewer than two items judged as high risk within the external validity domain AND fewer than three items judged as high risk within the internal validity domain.
- Moderate risk of bias – All other scenarios.

The risk-of-bias tool was used for descriptive purposes and to formally explore sources of heterogeneity across studies. It is important to highlight that the scores only reflect information reported in each record and may not reflect the actual risk of bias of a study. Due to the nature of the tool, shorter reports are likely to have higher bias.

Summary Measures

Dementia prevalence (and 95% confidence intervals) was used as the summary measure.

Data synthesis

Descriptive data and risk of bias were reported for all included studies. A narrative synthesis of the findings was presented, grouped by country. Depending on the number of studies included in each country, data were synthesised using a series of meta-analyses to calculate pooled estimates of prevalence (double-arcsine) and 95% confidence intervals (CIs) in each of the countries using random effects models. A complementary set of heterogeneity statistics (Cochran's Q, tau^2, χ^2 and I^2) were reported between studies in each country where a meta-analysis was used (Higgins & Thompson, 2002; Huedo-Medina et al., 2006). We used existing categorisation to guide the interpretation of the heterogeneity (i.e., I^2 >75 indicates high heterogeneity) (Higgins et al., 2003). No efforts were made to reduce the heterogeneity reported using exploratory statistics. However, efforts were made to split the meta-analyses into subgroups (e.g., based on diagnostic criteria) whilst also potential *post hoc* explanations for heterogeneity between studies were considered.

Confidence in Cumulative Evidence

There are no standardised or widely adopted tools to assess confidence in cumulative evidence in prevalence studies, and therefore we did not describe this.

Results

Results of the search

Our search was completed on 30th April 2019. A total of 820 records were initially identified. Twenty-two records were also identified through lateral searches, and input from country-specific researchers of the STRiDE team. Following de-duplication there were 461 records remaining. Following the screening of the abstract and title, 365 records were deemed to not have met the inclusion criteria. We were unable to access three records (two conference proceedings, one thesis). The full-texts of 93 records were screened (Figure 1).

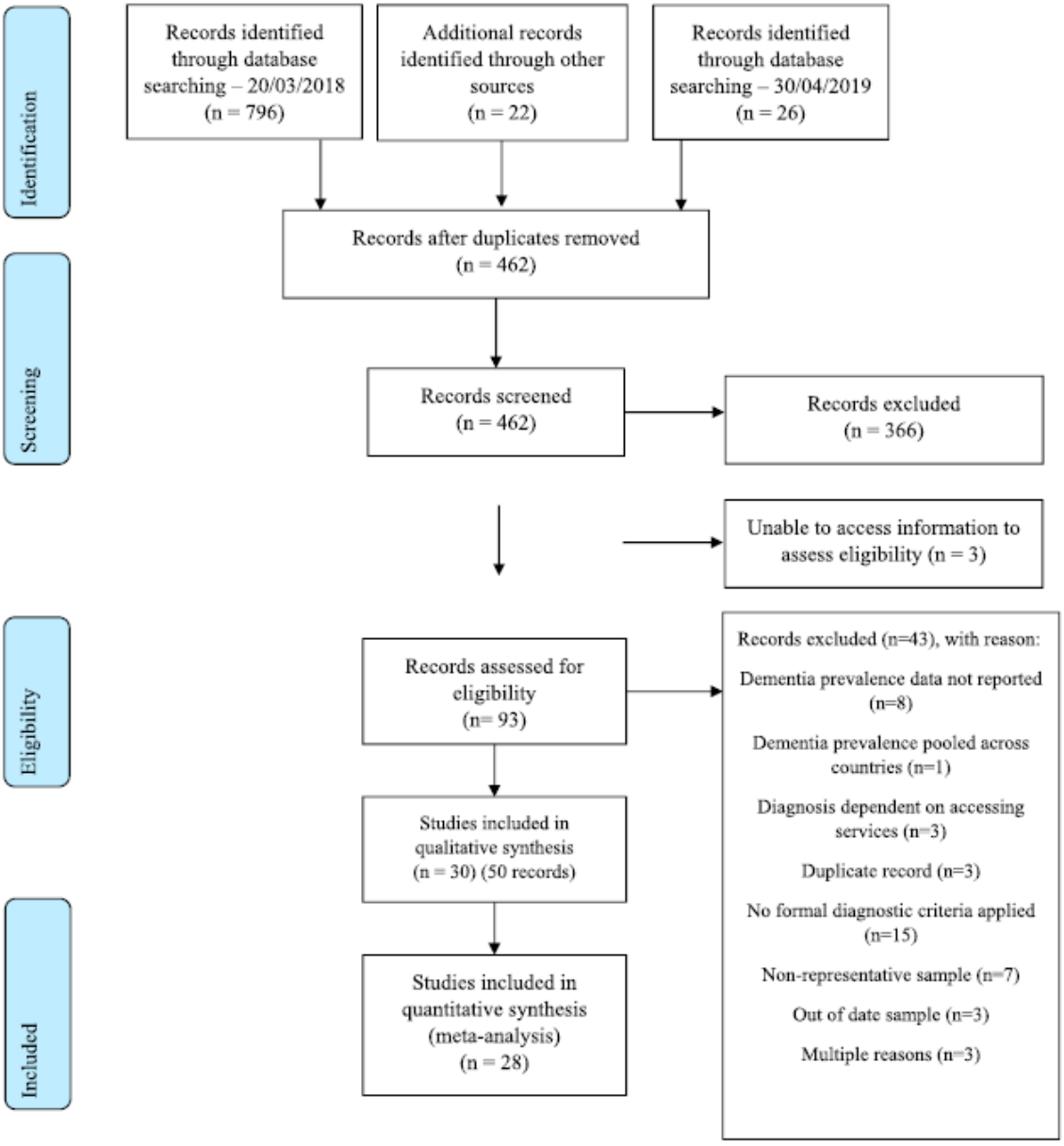

Figure 1: Flow chart of systematic review process.

Included Studies

A total of 30 studies (50 records) were included in this review. Seven studies were from Brazil, 16 from India, three from Mexico, two from Jamaica, and two from South Africa. (One study reported on multiple countries). There were no studies for Kenya or Indonesia that met the inclusion criteria.

Across the included studies, DSM-IV (and DSM-IV TR) was the most commonly used for dementia diagnosis. The most frequently adopted study design was a two-phase survey: screening followed by diagnosis. Identifying outcome measures captured in each study was difficult, due to variations in reporting style. There is considerable variation in the types and detail of measures used. There was a general tendency to capture domains of cognition, neuropsychiatric symptoms and function. Person-centred outcomes (e.g., quality of life) and carer-related information were generally lacking across studies. Importantly, there was a lack of transparency on the language format of the questionnaires, and whether they had been cross-culturally adapted for use within their country-specific context. Full descriptive details of the studies and their methodologies are presented in Appendix B.

Excluded Studies

A total of 43 records were excluded. Records were most frequently excluded because they did not apply an appropriate diagnostic criterion for dementia (n=15) or did not specifically report dementia prevalence data (n=8). See Appendix C for a list of excluded records.

Whilst there were a number of studies excluded from India, Brazil and Mexico, it is worth highlighting potentially relevant studies that did not meet our inclusion criteria from countries that are underrepresented in the literature more broadly (i.e., Kenya, Jamaica, Indonesia, and South Africa).

In Kenya, a monograph was identified which included the prevalence of dementia. However, it was excluded because it was unclear what diagnostic criteria were applied, and recruitment occurred, in part, within hospitals and institutions (Ndetei et al., 2013). This could account for why such a high percentage of the sample (44%) had 'probable dementia' (n=48) or a 'diagnosis of dementia' (n=61). In a more recent report, 15.9% (n=1,235) of participants were diagnosed with dementia (Mutiso, 2016); the report was excluded because it was unclear about the age of participants, how they were recruited, or what diagnostic criteria were utilised.

In Indonesia, a study (Hogervorst et al., 2011; Yesufu, 2009) was excluded because it appeared that the sampling frame was created 3 years prior to testing, whilst recruitment also seemed to be dependent on the sample having access to healthcare services. The authors reported that 4.1% of people over the age of 60 had possible dementia across urban and rural areas (Jakarta, Sumedang and Borobudur). Another study of people aged ≥ 60 living in Yogyakarta found that 20.1% of people were diagnosed with dementia (Suriastini et al., 2017). This study was excluded because we judged the diagnostic criteria lacked face validity.

Finally, in South Africa, an older study identified that 8.6% of older adults in Cape Town had dementia (Ben-Arie et al., 1983). However, this study was excluded because dementia was defined solely by MMSE score and was deemed to be non-representative due to only recruiting a Coloured [1] sample.

Risk of Bias of Included Studies

- *External Validity*

The most frequent item judged as having high risk of bias was related to whether the study target population was a close representation to the national population. Nearly all studies were limited to a specific geographical area, commonly urban areas. Even when authors attempted to recruit from a representative sample, there was a lack of explicit evidence that the sample closely represented the national population. Only one study was judged as of low risk in relation to the close representation item (Eldemire-Shearer et al., 2018).

Many studies were judged to have a high risk of bias regarding how closely representative the sample frame was to the target population (Banerjee et al., 2008; Caramelli et al., 2009; de Jager et al., 2017; Jacob et al., 2007; Llibre Rodriguez et al., 2008; Neita et al., 2014; Seby et al., 2011; Shaji et al., 1996, 2005; Tiwari et al., 2013; Van Der Poel et al., 2011; Vas et al., 2001), with studies failing to clearly report how they chose their sampling frame or selecting a frame out of convenience. Non-response bias was also frequently judged to constitute a high risk of bias, due to authors either not stating the study response rate or, when the response rate was low (<75%) whether there was any non-response bias (Banerjee et al., 2008, 2017; Bottino et al., 2008; Caramelli et al., 2009; Cesar et al., 2016; de Jager et al., 2017; Eldemire-Shearer et al., 2018; Gurukartick et al., 2016; Llibre Rodriguez et al., 2008; Lopes et al., 2012; Neita et al., 2014; Singh

[1] Coloureds is an official term to refer to a distinct ethnic group in South Africa.

et al., 2008; Velazquez-Brizuela et al., 2014).

For the random selection of participants within the frame, the majority of studies were judged to have a low risk of bias because either a census was utilised, or randomisation occurred.

- *Internal Validity*

Internal validity items across the studies were generally judged as having low risk of bias. The numerator and denominator item were occasionally judged as having high risk of bias because the authors did not report numerators and denominators sufficiently within the records, or the studies lacked clarity about why numbers in tables were not consistent.

- *Total*

Across the studies, only six were deemed to have low risk of bias: two in Brazil (Herrera et al., 2002; Scazufca et al., 2008), three in India (Chandra et al., 1998; Das et al., 2006; Rajkumar & Kumar, 1996), and one in Mexico (Cruz-Alcalá & Vázquez Castellanos, 2002). Thirteen studies were judged to have moderate risk of bias, and 10 studies were judged to have high risk of bias overall. Both Jamaica and South Africa did not have any studies that were deemed as low risk of bias. The risk of bias assessments were upgraded to 'high risk' in several studies (Caramelli et al., 2009; Cesar et al., 2016; Magalhães et al., 2008) with a high prevalence of dementia in their sample (>15%), indicating that these estimates would likely change with the addition of new data.

Prevalence of dementia

Reported below is the prevalence of dementia for each study split by country. Unless otherwise specified, prevalence rates are reported for samples aged ≥ 60, based on DSM-IV diagnostic criteria.

- *Brazil*

Seven studies from Brazil were included (Bottino et al., 2008; Caramelli et al., 2009; Cesar et al., 2016; Herrera et al., 2002; Lopes et al., 2012; Magalhães et al., 2008; Scazufca et al., 2008). Of the seven studies, five were conducted in the state of São Paulo.

Of the five studies in São Paulo state, four were urban and one urban and rural. The estimated dementia prevalence varied from across these. (i) Scazufca et al., (2008) reported 5.1% (4.1-6.0)

in those aged ≥ 65 years old (n=2072); (ii) Lopes et al., (2012) reported 5.9% (4.6-7.2) in Ribeirão Preto (n=1145); (iii) Bottino et al (2008) reported 6.8% (5.6-8.0) (n=1,563); and (iv) Herrera et al., (2002) reported 7.1% (6.0–8.5) amongst 1,656 older adults (≥ 65 years old) from the urban region of Catanduva. The study in urban and rural areas of Tremembé, Cesar et al (2016) reported an estimated prevalence of 17.5% (14.6-20.6) of older adults (n=630). This higher prevalence could be due to the bias introduced by having a modest response rate of the initial sample (56.9%).

From the two studies originating outside of São Paulo state, prevalence rates were substantially higher. In an urban and rural region of Caeté (Minas Gerais state), there was an estimated dementia prevalence of 27.5% (24.1-31.1), albeit within a sample of older adults aged over 75 years old (n=639) (Caramelli et al., 2009). In a rural area of Santo Estevão (Bahia state), there was an estimated prevalence of 49.6% (45.0-54.1), using the CAMDEX tool (Magalhães et al., 2008). It was unclear whether this was in accordance with DSM-IV criteria.

Across the studies there was a pooled prevalence of 14.3% (6.8-23.9). However, there was evidence of substantial heterogeneity, I^2= 99.14, χ^2 p < 0.001, tau^2 = 0.10. A large amount of heterogeneity was introduced through the diagnostic criteria used. Studies that used DSM-IV criteria had only moderate heterogeneity (I^2=64.6, χ^2 p = 0.04, tau^2 = 0.001), and had a pooled prevalence of 6.2% (5.2-7.3). See Figure 2.

- *India*

Fifteen studies were identified from India (Banerjee et al., 2008, 2017; Chandra et al., 1998; Das et al., 2006; Gurukartick et al., 2016; Jacob et al., 2007; Llibre Rodriguez et al., 2008; Mathuranath et al., 2010; Rajkumar & Kumar, 1996; Seby et al., 2011; Shaji et al., 1996, 2005; Singh et al., 2008; Tiwari et al., 2013; Vas et al., 2001).

Generally, dementia prevalence was estimated in urban settings, with Kolkata being the most common setting. In one such study, 2,720 participants in the urban region of Kolkata were surveyed, with an estimated dementia prevalence of 1.3% (0.9-1.7) (Banerjee et al., 2008). Similarly, 1.1% of older adults (n=8,542) were reported to have a diagnosis of dementia in Kolkata (Banerjee et al., 2017). In another study within Kolkata, there was a prevalence of 0.8% (0.6-1.1) in a sample of 5,430 older adults (Das et al., 2006). Outside of Kolkata, there have been several studies to explore the prevalence of dementia in other urban samples. Mathuranath and colleagues estimated the prevalence of dementia in Trivandrum (n=2,422) at 3.8% (Mathuranath et al., 2010). In Channai, an estimated prevalence of 2.7% was reported in those aged 65 and

over (n=1300) (Rajkumar & Kumar, 1996). However, a more recent study in Chennai (n=1005) estimated prevalence at 0.9% (0.3-1.5) in those aged 65 and above using DSM-IV criteria, though it was substantially higher using the 10/66 algorithm with an estimate of 7.5% (5.8-9.1) (Llibre Rodriguez et al., 2008). In Kochi, 2.9% aged 65 years and above (n=1934) were reported to be identified with having dementia (Shaji et al., 2005). In Mumbai, 6,041 older adults were surveyed, in which 1.6% were identified with having dementia (Vas et al., 2001). Whilst in an unnamed urban region in North Western India (n=1376), there was an estimated prevalence of 3.0% (2.6-4.3) (Singh et al., 2008), though other data were unavailable as we were only able to access a conference proceeding. The only study to have a somewhat higher prevalence was reported in the urban region of Wanowarie Bazaar (Seby et al., 2011). For those ≥ 65 years old, there was an estimated prevalence of 14.9%. Methodologically, there is no clear reason why this would be the case, though it could be attributed to the limited sample size (n=202) or the use of ICD-10 diagnostic criteria.

In the rural region of Tamil Nadu, there was an estimated prevalence of 0.8% (0.4-1.6) for those aged ≥ 65 (n=1,000) using the DSM-IV criteria but was 10.6% (8.8-12.7) using the education-adjusted 10/66 algorithm (Jacob et al., 2007). The AGECAT dementia prevalence rate was very high (63.47%), though this was not discussed within the article. In a rural region of Ballabgarh, there was an estimated prevalence of 1.4% of those aged ≥ of 65 years old (n=2715) (Chandra et al., 1998). In the Lucknow district 2.8% of older adults (n= 2,146) were estimated to have dementia (Tiwari et al., 2013). In the rural region of Villupuram District, there was an estimated prevalence of 3.1% in people 65 years old and above (n=1,304) (Gurukartick et al., 2016). The rural region of Thiruvaniyoor Panchayath (n=2,067) reported a prevalence of 3.2% based on the DSM-III-R (Shaji et al., 1996), whilst in Thiruporur (n=750), 3.5% of the same age group were reported to have dementia based on the AGECAT (Rajkumar & Kumar, 1996).

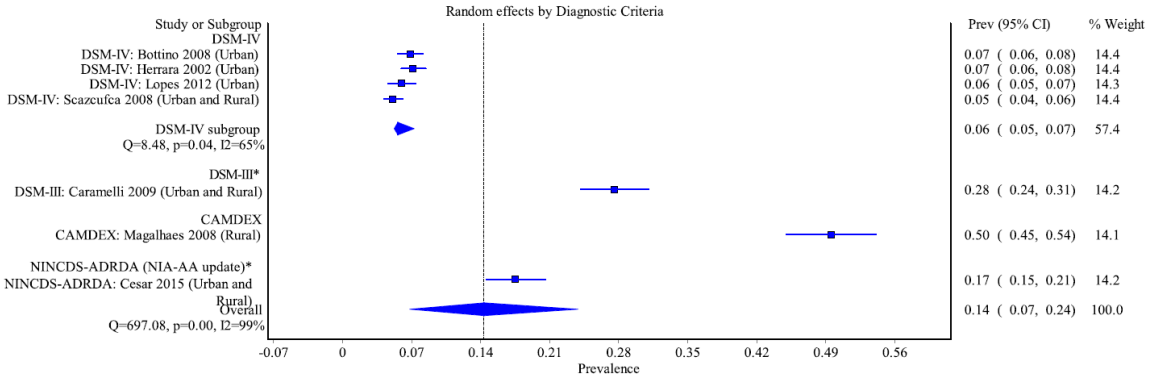

Figure 2: Dementia prevalence estimates within Brazil, split by diagnostic criteria.

The initial pooled prevalence was 4.4% (2.2 -7.2), with evidence of substantial heterogeneity between studies (I^2 = 99.4, Cochran's Q = 2868.67, χ^2 p = <0.0001, tau^2= 0.07). The diagnostic criteria appeared to contribute a portion of the heterogeneity reported. However, even within diagnostic criteria substantial heterogeneity was reported. Pooled prevalence ranged from 1.8% (1.3-2.4) based on the DSM-IV criteria, to 17.0% (0.0-66.0) based on the AGECAT. See Figure 3.

- *Indonesia*

There were no studies that met the inclusion criteria for this review. Please see "Excluded Studies".

- *Jamaica*

Two prevalence studies were identified from Jamaica (Eldemire-Shearer et al., 2018; Neita et al., 2014).

Neita and colleagues carried out a community survey of 200 older adults from two urban areas in Kingston, Jamaica (Neita et al., 2014). Dementia was diagnosed in 6.5% (3.4-10.4) based on DSM-IV criteria. In the study by Eldemire-Shearer and colleagues, a national survey of 2,782 people aged 60 years and above were recruited. A random sample of 301 participants (158 cases with MMSE < 20, 143 controls with MMSE>20) were subsequently assessed for dementia using the DSM-IV. Based on the raw data 11.4% (8.0-15.3) of participants had a diagnosis of dementia. The authors also noted that applying the anticipated number of cases of dementia in each group to the whole sample (n=2782), would yield a prevalence of 5.9%.

There was a pooled prevalence of 8.8% (4.6-14.2). There was some indication of moderate heterogeneity between the two studies (I^2 = 70.78, Cochran's Q = 3.42, χ^2 p = 0.06, tau^2= 0.01). See Figure 4.

- *Kenya*

There were no studies that met the inclusion criteria for this review. Please see "Excluded Studies".

- *Mexico*

Three studies were found to report dementia prevalence in Mexico (Cruz-Alcalá & Vázquez Castellanos, 2002; Llibre Rodriguez et al., 2008; Velazquez-Brizuela et al., 2014).

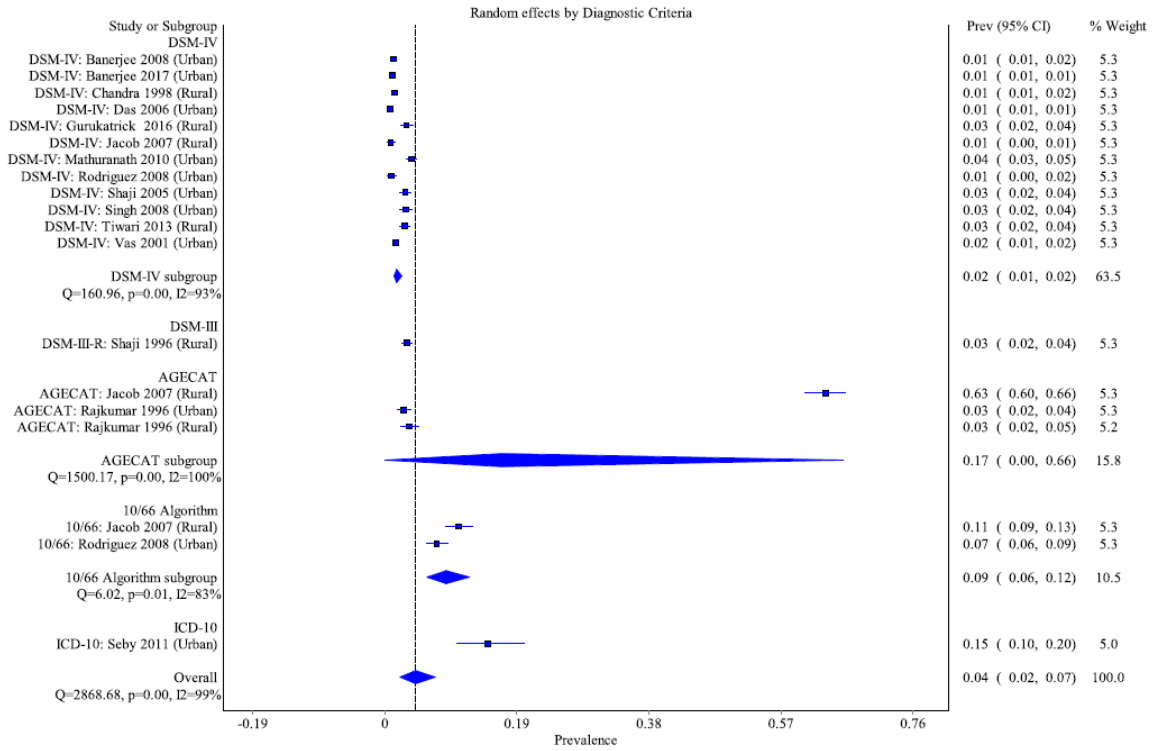

Figure 2: Dementia prevalence estimates within India, split by diagnostic criteria.

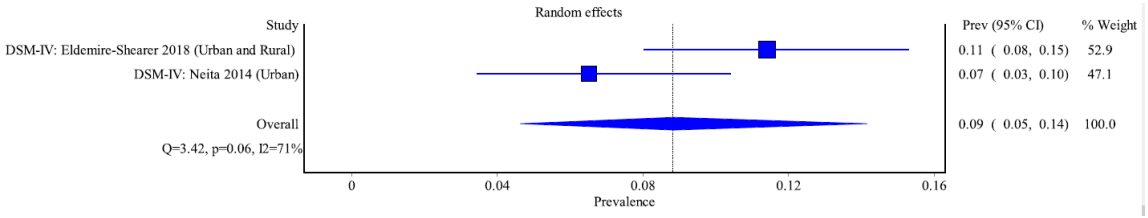

Figure 3:: Dementia prevalence estimates within Jamaica.

Within the urban region of Guadalajara, 9.5% (7.9-11.3) of people were diagnosed with dementia (Velazquez-Brizuela et al., 2014). In the 10/66 study (Llibre Rodriguez et al., 2008), participants aged 65 years and above were recruited from an urban (n=1,002) area of Mexico, with a dementia prevalence of 4.1% (2.8-5.3) using the DSM-IV criteria, and 8.6% (6.8-10.4) using the 10/66 algorithm. The only data derived from a rural area also came from the 10/66 study (Llibre Rodriguez et al., 2008), in which 2.2% (1.3-3.1) of the sample aged 65 years and above (n=1,000) were diagnosed with dementia based on the DSM-IV, but an estimated prevalence of 8.5% (6.7-10.3) using the 10/66 algorithm. A study from the urban region of Tepatitlan reported a prevalence of 0.33%, however this was across all ages of a larger cohort (n=9082), which did not provide a breakdown of these data (Cruz-Alcalá & Vázquez Castellanos, 2002). Due to insufficient information in this study did not be included in the pooled meta-analysis.

Overall, the pooled DSM-IV prevalence was 4.7% (1.2-9.5), with evidence of substantial heterogeneity between studies (I^2= 96.70, Cochran's Q = 60.53, X^2 p< 0.001, tau^2 = 0.03). Whilst pooled 10/66 algorithm prevalence was 8.4% (7.4-9.9). See Figure 5.

- *South Africa*

Two studies from South Africa were included in this review (de Jager et al., 2017; Van Der Poel et al., 2011). In the first study of 205 older adults (≥ 65 years) from central South Africa, authors identified a dementia prevalence of 6.4% using DSM-IV criteria. We were unable to extract numerators or denominators for the whole sample, or split by gender, age or combination of both. Similarly, the authors reported that the prevalence of dementia according to the 10/66 algorithm was "unusually high". The authors were unable to provide additional data at this stage.

In the second study (de Jager et al., 2017), 1,382 Xhosa-speaking community-dwelling older adults (≥ 60 years) were recruited from three catchment areas in an unnamed location within the Eastern Cape. The authors estimated that 7.6% (6.3-9.1) of participants had dementia, using the 10/66 short diagnostic schedule.

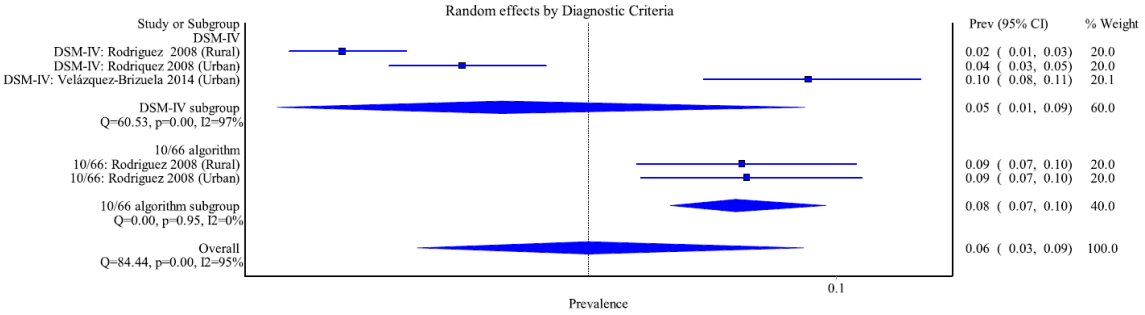

Figure 5: Dementia prevalence estimates within Mexico, split by diagnostic criteria.

Discussion

This systematic review set out to understand the prevalence of dementia across the seven STRiDE countries and the methodologies used to generate this evidence. Whilst there were no eligible studies from Indonesia and Kenya, 28 studies spanned the remaining STRiDE countries. India and Brazil had the largest number of studies included in this review.

Pooled meta-analyses within each country, based on DSM-IV, revealed that dementia prevalence rates ranged from 2% (India) to 9% (Jamaica). This is in line with global estimates of dementia, sitting at 5.2% (Prince et al., 2015). Due to the general absence of included studies and data outside of India, we did not pursue meta-analysis split by other potential factors (age, gender or

setting). It is likely that splitting the meta-analysis based on these factors would reduce some heterogeneity observed between studies, and that more heterogeneity might exist due to variation in study design, outcomes and diagnostic criteria. It should be noted that four studies introduced sizable heterogeneity into the meta-analyses, due to having small sample sizes and high prevalence rates (Caramelli et al., 2009; Cesar et al., 2016; Magalhães et al., 2008; Seby et al., 2011). Two of these studies (Magalhães et al., 2008; Seby et al., 2011) fell short of a sample size needed to estimate a true prevalence of 6% with a precision of ±2.1% (Prince et al., 2015).

The quality of studies included in this review was mixed, with a fifth (6/28) being judged as having a low risk of bias overall. Bias was commonly introduced through potential issues in external validity. Notably, the majority of studies adopted sampling techniques that minimise bias (e.g. random cluster sampling, all sectors within region, representative sectors); however, the authors did not explicitly state how representative their sampling frame was compared to the national picture. For example, prevalence studies in Brazil predominately originated in the southeast of the country. Another common item judged to have high risk of bias was the presence of non-response bias. Non-response can introduce a source of variation, and limit the representativeness of findings, with the reason for non-response (refusal, death/illness, moving home) affecting the characteristics and estimated prevalence of these non-response groups (Boersma et al., 2015). This could particularly be an issue in multiphase designs, as it can lead to underestimation of the prevalence of dementia and overestimation of precision (Prince, Bryce, et al., 2013). Two phase designs were most commonly adopted in studies included within this systematic review. Whilst language of diagnostic assessments was not of particular focus in this systematic review, it is also important to highlight the countries where language is strongly associated with specific ethnicities or regions, language may indirectly impact sample representativeness.

For inclusion in this review, studies were required to have a diagnostic criterion with face validity (consensus amongst authors). As such, there were a number of studies that were excluded because they used single cognitive impairment and/or functional tools to diagnose dementia. Among the included studies, DSM-IV criteria were frequently used to make a dementia diagnosis, which was reliant on hiring clinicians or utilising the CAMDEX toolkit. Within countries where a variety of diagnostic criteria were utilised, there was evidence that this introduced heterogeneity into the findings. This was evident in studies derived from the 10/66 group (Jacob et al., 2007; Llibre Rodriguez et al., 2008; Van Der Poel et al., 2011) which adopted multiple diagnostic criteria, and therefore produced multiple dementia prevalence rates. For example, the AGECAT

estimated a prevalence of 63.4%, the 10/66 algorithm (education-adjusted) estimated dementia prevalence at 10.6%, whilst the DSM-IV prevalence was 0.8% (Jacob et al., 2007). It is evident that diagnostic criteria employed are important determinants of prevalence estimates.

It should be noted that for a single study (de Jager et al. 2017) there was some discussion about its inclusion based on the diagnostic criteria used – the short version 10/66 algorithm. Despite being a relatively new diagnostic algorithm, recent evidence supports its validity across a number of settings (Abdin et al., 2017; Bernardo Seinhart et al., 2016; Stewart et al., 2016). For example, the short version 10/66 algorithm shows substantial agreement with clinical diagnosis of dementia (kappa = 0.70, AUC = 0.87) (Abdin et al., 2017). However, similar to the full 10/66 algorithm, the short version tends to estimate a higher rate of prevalence compared to the DSM-IV, which could be due to the DSM-IV dementia criterion underestimating dementia prevalence (Prince, 2009). Whilst the short version 10/66 algorithm (and the brief CSID from which it is derived) may appear to be less comprehensive compared to other methods for identifying dementia, it is important to recognise that there is an important place for algorithms that are both less time-intensive and do not require clinical training to administer.

A strength of this review was that we were able to capture all but two studies reported in the World Alzheimer's Report 2015 (Prince et al., 2015) despite having slightly different inclusion and exclusion criteria. We were also able to identify an additional 15 studies that were not identified in the World Alzheimer's Report 2015, partly because the search was more recent, but also because we enquired directly for studies within each country. This review is, however, limited in that it only covers the seven STRiDE countries, which prevents us making conclusions regarding the literature in other MICs. As highlighted within the section on risk of bias, another limitation of this systematic review is that it reflects data and information published (though not necessarily peer-reviewed), and therefore it may be that additional detail may exist but was not explicitly reported within the identified records.

Conclusions

There is substantial evidence of variability in terms of methodologies used to estimate dementia prevalence, making prevalence rates difficult to compare within and between countries. There is also wide variation within and between the countries in terms of risk of bias introduced by study designs (or how they are reported).

Acknowledgements

Thank you to all the members of the STRiDE teams who helped identify literature relating to this topic. The research is funded by the Research Council UK (RCUK) through its Global Research Challenges Fund. The funders had no direct input into the formulation or creation of the protocol, or the results and their interpretation.

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Appendices

Appendix A

Search strategy and associated hits

Scopus

• TITLE (dementia) AND TITLE-ABS (prevalence OR epidemiolog*) AND TITLE-ABS ("South Africa" OR indonesia OR india OR jamaica OR mexico OR brazil OR kenya)

• 127 hits, 20/03/18

• 4 hits, 30/04/19

PsycINFO

• ((TI(dementia)) AND (prevalence OR epidemiolog*) AND ("South Africa" OR indonesia OR india OR jamaica OR mexico OR brazil OR kenya))

• 172 hits, 20/03/18

• 2 hits, 30/04/19

Web of Science

• TI= (dementia) AND TS= (prevalence OR epidemiolog*) AND TS= ("South Africa" OR indonesia OR india OR jamaica OR mexico OR brazil OR kenya)

• 173 hits, 20/03/18

• 7 hits, 30/04/2019

Pubmed:

• ((dementia [Title] OR dementia [MeSH Terms]) AND (epidemiolog* [Title/Abstract] OR epidemiology [MeSH Terms] OR prevalence [MeSH Terms] OR prevalence[Title/Abstract])) AND ((“South Africa" [Title/Abstract] OR indonesia [Title/Abstract] OR india [Title/Abstract] OR jamaica [Title/Abstract] OR mexico [Title/Abstract] OR brazil [Title/Abstract] OR kenya[Title/Abstract]))

• 219 hits, 20/03/18

• 8 hits, 30/04/2019

SciELO:

• ((prevalence OR epidemiolog*) AND (mexico OR brazil OR jamaica)) AND (ti:(dementia))

• 23 hits, 20/03/18

• 2 hits, 30/5/18

Opengrey.eu

• Dementia AND prevalence

• 27 hits, 20/03/2018

• 0 hits, 30/05/2019

Google Scholar:

• allintitle: dementia prevalence "South Africa" OR indonesia OR india OR jamaica OR mexico OR brazil OR Kenya

• 55 hits, 20/03/18

• 3 hits, 30/04/2019

Appendix B

Description of included studies.

Author	Record ID	Sample size	Key Inclusion Criteria	# of phases	Setting	Sampling Frame	Participant Identification	Study measures	Language(s)	Diagnostic criteria
Brazil										
Bottino	13480301 13480300 15752111	1563	Aged ≥ 60	2	Urban	"A cluster random sampling of a population of individuals aged 60 years and over from three different socioeconomic classes (upper, middle and low) was used in Sao Paulo"	"…blocks of 10 domiciles were randomly chosen in each of the 90 selected census sectors."	• MMSE • FOME • IQCODE • BADL • CAMDEX • CAMCOG	NR	DSM-IV

Caramelli	15752121	639	Aged ≥ 75	3	Both (Caramelli,2009)	"Since a complete and updated list of these elderly individuals was notreadily available, an active search was undertaken. We contacted family health program agents from the municipal government and the municipality health department."; "As for institutionalized elderly, the two existing institutions in town were visited by the research team."	NR	• UPDRS-part III • MMSE • Brief Cognitive Screening Battery • Pfeffer Functional Activities Questionnaire • FAST • GDS • Mini International Neuropsychiatric Interview • Rey Auditory Verbal Learning Test • Naming and praxis tests from the CERAD protocol • Verbal Fluency Task (FAS)	NR	DSM-III (as cited within text)

								• FAB • Physical and Instrumental-Self Maintenance scale • CDR CSDD		

Cesar	13480321 N001 13280322 N003	630	Aged ≥ 60	1	Both	"According to IBGE there are 89 sectors (73 urban and 16 rural) in Tremembe´. Each census sector defined by IBGE is a territorial unit with identified physical limits in continuous areas, accounting for uniform households' numbers (usually 400 to 450 dwellers in each one). Twenty percent of the households with individuals aged 60 years or more were randomly selected from each of the municipality's census sectors, to obtain a homogenous representation of all regions and districts representing all socioeconomic and cultural levels."	"Twenty percent of the households with individuals aged 60 years or more were then randomly selected, from both urban and rural areas…"	• MMSE • Brief Cognitive Screening Battery • IQCODE • Pfeffer Functional Activities Questionnaire • ACE-R • MoCA • QMC22 • Verbal fluency test and clock drawing. • CSDD • PRIME-MD	NR	"Dementia was diagnosed based on clinical criteria updated by the National Institute on Aging according to criteria of McKhann et al for the diagnosis of all-cause dementia and recommended by the Brazilian Academy of Neurology."

Herrera	15752058	1656	Aged ≥ 65	3	Urban	"At the beginning of the study, the Brazilian Institute of Geography and Statistics had recently finished a door-to-door census of the city. From this census, we were informed about the domiciles, in each of the city's districts, where persons aged 65 years or more resided and how many lived in each house. According to these data, we estimated that about 6,800 possible subjects lived in 5,153 houses." "To investigate 1,700 persons, we selected every fourth address from each subdistrict list of addresses, so as to screen 25% of the domiciles." "To know if institutionalization of patients with dementia was a common practice in the community, which would interfere with the prevalence rate, all nursing home residents aged 65 years or more were also included min the survey."	"To investigate 1,700 persons we selected every fourth address from each subdistrict list of addresses, so as to screen 25% of the domiciles… all nursing home residents aged 65 years or more were also included min the survey."	• MMSE • Pfeffer Functional Activities Questionnaire • Hachinski Ischemic Scale • CDR • Routine blood tests	Portuguese	DSM-IV

Lopes	13480416 13480414 13480413 13480379	1145	Aged ≥ 60	2	Urban	"The cluster-sampling strategy aimed to include representative people from different socioeconomic levels, selected from three census units from three different regions according to a socioeconomic "score" (based on income and schooling)."	"…the cluster-sampling strategy aimed to include representative people from different socioeconomic levels, selected from three census units from three different regions according to a socioeconomic "score" (based on income and schooling). This selection followed operational and population criteria, such as referral of positive cases, correspondence between the density of elderly people in the region and the census unit and socioeconomic rank."	• MMSE • FOME • IQCODE • BADL • CDR (see Lopes 2005) • ADL-IS (see Lopes 2005) • CAGE (see Lopes 2007)	Portug uese	CAMDEX (DSM- IV)
Magalhaes	15752146	466	Aged ≥ 60	1	Rural	"The studied population includes all individuals aged 60 or above living in Lagoa Pequena"	"The studied population includes all individuals aged 60 or above living in Lagoa Pequena"	• CAMDEX	Portuguese	CAMDEX

Scazufca	13480493 13480488 13480494 15752170 N010	2,072	Aged ≥ 65	1	Urban	The present investigation was carried out in the borough of Butanta, located on the west side of the city."	"All eligible subjects were invited to participate, regardless of whether or not other older adults"	• CSI-D • An adapted version of the CERAD • Geriatric Mental State • HAS-DDS • "a structured neurological assessment to ascertain the presence of lateralizing signs, parkinsonism, ataxia, apraxia and primitive "release" reflexes."	NR	DSM-IV
India										
Banerjee	8545180	53,907 (6,129 ≥ 50 years)	Aged ≥ 50	2	Urban	"The survey area comprised 4 adjacent municipal wards (wards 66, 67, 91 and 107) located in the southern part of the city"; "surveyof all the inhabitants of the survey area was conducted"	"…survey of all the inhabitants of the survey areawas conducted"	• Kolkata Cognitive TestBattery • GDS • EASI • CDR	NR	DSM-IV

Banerjee	13480294	17,584	Aged ≥ 50	2	Urban	"The survey was conducted on a stratified, randomly selected sampleof 100,802 subjects (53,209 men; 47,593 women). Municipal area of the city of Kolkata comprises 5200 smaller units known as National Sample Survey Organization blocks, with an average of 75–150 households per block. For purpose of our study, we divided the city into six sampling strata."; "From each stratum, multiple National Sample Survey Organization blocks(number proportionate to the population) were randomly selected."	"In each selected block, alternate houses were surveyed…"	• KCSB • GDS • Everyday Activities Scale of India • CDR	NR	DSM-IV

Chandra	13480326 13480447 15752072	5,126	Aged ≥ 55	2	Rural	"A total of 5,649 Ballabgarh residents were identified as being age 55 or older in the census database. Each of these individuals was visited at home by a project field worker."	"A total of 5,649 Ballabgarh residents were identified as being age 55 or older in the census database. Each of these individuals was visited at home by a project field worker."	• HMMSE • Immediate learning, delayed recall, and delayed recognition of a 10-item word list (adapted from the CERAD) • Verbal fluency • The Object Naming Test • Constructional praxis	Hindi	DSM-IV

Das	15752010 15752126 13480484	52,377 5,430 over the age of 60 (Das., 2008)	Aged ≥ 50	2	Urban	"Stratified random sampling was used for selecting the population. The KMC area was divided into six strata for the purpose of this study based on geographical location and type of dwellings. Each of this stratum acted as a sample frame."; "From each stratum, nearly equal number of blocks was selected by using statistical random number table. It was known that each NSSO block consisted of 100-150 households, and each household consisted of 4-5 members."	"We got the information of the total number of people living in each block and surveyed 50 per cent of the households of each block by visiting alternate houses."	• General screening questionnaire • HMMSE	Hindi, Bengali	DSM-IV

Gurukartick	13480366	1,304	Aged ≥ 65	2	Rural	"A list of all the villages in the study area and their population was obtained from the local Block Development Office of Thiruvennainallur."	"…systematic random sampling was done to select the households in each village. In the selected house, a respondent (≥65 years) and one primary caregiver were selected. If there was more than one elderly person in the house, then one respondent was chosen by a lottery method. If there was no elderly person in the selected house, then the next djacent house was selected."	• VSID-Patient version - Tool 1 • VSID-Informant version - Tool 2	NR	DSM-IV

Jacob	13480387 13480477	1,000	Aged > 65	2	Rural	"The surveillance system consists of a four-tier monitoring system. The block has been divided into regions with specific personnel in charge of the health of each region. The system involves the village health worker, the community health aide, the public health nurse and the doctor. "; "Data obtained by the surveillance system are computerized. The data for the whole block are collated and reviewed monthly by the entire health team consisting of the community health workers, health aides, community health nurses, doctors and other development staff."	"A list of residents aged over 60 years of age was retrieved from the computerized database. A door-to-door survey revealed a few additional elderly people who were living in the study area."	• GMS • CSID • Modified CERAD 10-word list learning task (Ganguli et al., 1996) • HAS-DDS • NPI • WHODAS II	Tamil	AGECAT 10/66 algorithm DSM-IV

Mathuranath	13480423 15752110	2,466	Aged ≥ 55	2	Urban	"Sampling frame consisted of 41920 subjects from four of the eight wards (administrative districts of the city corporation) of Trivandrum. Residents of these four wards provided a good admixture and faithful representation of the socio-economically and culturally diverse population of Trivandrum."	"The census information and the Election Commission's database identified 2932 individuals to be 55 years of age." All approached in a "door knocking survey"	• ACE • An IADL-E was specifically developed for the local elders (Mathuranath et al., 2005).	Malayalam	DSM-IV

Rajkumar	13480469 13480470	Rural: 750 Urban: 1,300	Aged ≥ 65	2	Both	Rural: “The sample of 750 people 60 years of age and over was drawn using the cluster sampling technique.” Urban: “Using the ultistage stratified random sampling technique, 1,300 individuals 65 years of age and older were selected.” (Electoral frame electoral frame)	Rural setting: “Door to door survey…All Elderly age 60 & > included” Urban setting: “Finally, using a simple random sampling procedure, people 65 years of age and older were selected from the electoral rolls sample size allotted to each parliamentary constituency was proportional to the population size and distributed between the selected divisions of each strata.”	• GMS	Tamil	AGECAT

Rodriguez	13480477 13243182 13480529	1,005	Aged ≥ 65	1	Urban	"Catchment area boundaries were precisely defined. Mapping was carried out to identify and locate all households, which were allocated household IDs. Households were enumerated to identify possible eligibles (aged 65 and over)."	"Households were enumerated to identify possible eligibles (aged 65 and over)."	• AGECAT • CSI-D COGSCORE • CSI-D RELSCORE • HAS-DDS • NEUROEX • NPI-Q • Self-report list of 12 common physical impairments • WHO-SAS II • Physical assessment • ZBI • Caregiver mental health (GHQ-20) • CAS • CSRI • Reproductive assessment • Blood tests	Tamil	10/66 algorithm DSM-IV

Seby	N010	202	Aged ≥ 65	2	Urban	"It is an urban area and the total adult population (18 years and above) of ward no six was 7239 as per the latest electoral rolls. This ward is divided into four parts or divisions, and this study was conducted in part II division of this ward. This particular area was chosen because it was already a field research area of the coordinating institute."	"The total number of the adult population (18 years and above) residing in this area was 1965, of which 218 persons were aged 65 years and above." All were approached	• GHQ-12 • MMSE • GDS-15 • CAGE questionnaire – alcohol problems	Hindi and English	ICD-10

Shaji	13480510	1,934	Aged ≥ 65	3	Urban	"The list of voters and the area map constituted the sampling frame. The Ernakulam constituency is divided into 178 parts, each of which has a population of 800–1000. For operational purposes, each part was designated as a cluster, and a cluster sampling technique was used."	"…in each [part] a door-to- door survey was conducted to identify residents aged 65 years and above."	• MMSE • CAMDEX Section B • CAMDEX Section H • The Socio-economic Status Scale – Urban (Kuppuswamy, 1976)	Malayalam	CAMDEX (DSM- IV)

Shaji	13480511	2,067	Aged ≥ 60	3	Rural	"The voters list and area map were taken from the administrative office and served as the survey frame. The study area was selected by considering its easy access by road, the stability of the population, and the cooperation of the rural administrative officials."	"A door to door survey was conducted in this area by surveyors to identify people aged 60 years or above…"	• MMSE • CAMDEX-Section B • CAMDEX-Section H	NR	DSM-III-R

Singh	13480516	1,376	Aged ≥ 60	N R	Urban	Cluster sampling.	NR	• MMSE	NR	DSM-IV

Tiwari	15752131	2,146	Aged ≥ 60	2	Rural	"The two rural revenue blocks- Malihabad and Bakshi Ka Talab of Lucknow district of the State of Uttar Pradesh in north India were randomly selected for the study location. There were 215 villages in these two rural blocks with approximate population of 4,52,598 and 300 to 500 houses in each village."	"Of these, 30 villages were randomly selected for the complete enumeration of the elderly aged 60 yr and above"	• Socio-economic status scale • HMMSE • SPAS • MDQ • SCAN • CAMDEX-R • Physical and Neurological Examination	Hindi	CAMDEX (DSM- IV and ICD-10)

Vas	13480548	24,488	Aged 40+	3	Urban	"The sample was determined from the electoral rolls of "H" Ward of the Municipal Corporation of Greater Mumbai Bombay)." "It has a population of approximately 151,000 persons and from these electoral rolls we identified 30,000 persons who were aged 40 or older in 1991 (the census year). Because the sample was selected from the electoral rolls, it included persons from all socioeconomic levels and different ethnic backgrounds."	All those on electoral roll (assumed).	• Modified Sandoz Clinical Assessmen t Geriatric Scale • MMSE • HMMSE • CAMDEX-A or H • CAMCOG • CDR	Hindi and Marat hi	DSM-IV
Jamaica										
Eldemire-Shearer	157520466	2,943	Aged ≥ 60	2	Both	"…four parishes in Jamaica. Theseparishes are representative of the national population (based on age, gender and geographic distribution)." (Mitchell-Fearon et al.,2014)"	"…with each of the 35clusters having 76 participants."	• MMSE • "The 1989 structured, pre-coded, paper-based questionnair e. The epidemiology of ageing in Jamaica [unpublished doctoral thesis]."	NR	DSM-IV

Neita	13480438 13480439	200	Aged ≥ 60	2	Urban	"…low- and middle- income urban communities of August Town and Mona Heights"	"…100 participants each were randomly selected…"	• MMSE	NR	DSM-IV-TR
Mexico										

Rodriguez	13480477 13243182 13480529	Urban: 1,002 Rural: 1,000	Aged ≥ 65	1	Both	"Catchment area boundaries were precisely defined. Mapping was carried out to identify and locate all households, which were allocated household IDs. Households were enumerated to identify possible eligibles (aged 65 and over)."	"Households were enumerated to identify possible eligibles (aged 65 and over)."	• AGECAT • CSI-D • HAS-DDS • NEUROEX • NPI-Q • Self-report list of 12 common physical impairments • WHO-DAS II • Physical assessment • ZBI • Caregiver mental health (GHQ-20) • Caregiver Activity Survey • CSRI • Reproductive assessment • Blood tests	Ibero-American Spanish	1066 algorithm DSM-IV

Cruz-Alcala	N016	9,082	Not reported	2	Urban	"The city was divided into 37 conglomerates, from which, by chance, 28 of them were selected." "In each conglomerate one out of every four dwellings was systematically selected, to obtain an average of 71 per conglomerate."	"…one out of every four dwellings was systematically selected, to obtain an average of 71 per conglomerate " [translated]	• "a questionnaire designed to detect suspects of neurological diseases was applied"	Spanish	DSM-IV

Velazquez Brizuelu	13480552 N015	1,142	Aged ≥ 60	2	Urban	"The study was conducted in the metropolitan area of Guadalajara (GMA), Mexico, which includes the city of Guadalajara and its surrounding municipalities: El Salto, Tlajomulco, Tlaquepaque, Tonala, and Zapopan. The six municipalities of GMA are subdivided into 14 urban basic geostatistical areas (UGEA)."	"Locating the block, we proceed at the southwest corner clockwise until we find an adult 60 years or more."	• MMSE • GDS • Katz Index	Spanish	DSM-IV
South Africa										
Van DerPoel	113480542	205	Aged ≥ 65	NR	NR	NR	NR	• "10/66 Dementia Research Group's core minimum data set"	Sesotho	DSM-IV 10/66 algorithm
De Jager	13480339	1,382	Aged ≥ 60	1	Rural	"The study area clinic catchment areas with primary health clinics ineach area and a government hospital"	NR	• CSID • EURO-D	isiXhosa	Brief 10/66 algorithm

ACE/ACE-R = Addenbrooke's Cognition Examination – Revised, AGECAT = Automated Geriatric Examination for Computer Assisted Taxonomy, B-ADL = Bayer Activities of Daily Living Scale, CAMCOG = Cambridge Cognition Examination, CAMDEX/CAMDEX-R = Cambridge Mental Disorders of the Elderly Examination and revised version, CAS = Caregiver Activity Survey, CSID = Community Screening Instrument for Dementia, CDR = Clinical Dementia Rating , CSDD = Cornell Scale for Depression in Dementia, CERAD = Consortium Establish a Registry for Alzheimer's Disease, CSRI = Client Service Receipt Inventory, DSM-IV = Diagnostic Statistical Manual – version 4, EASI = Everyday Abilities Scale for India, FAB = Frontal Assessment Battery, FAST = Functional Assessment, Staging, FOME = Fuld Object Memory Evaluation, GDS = Geriatric Depression Scale, GHQ-20 = General Health Questionnaire – 20, GMS = Geriatric Mental Status schedule, HMMSE = Hindi Mini-Mental State Examination, HAS-DDS = History and Aetiology Schedule – Dementia Diagnosis and Subtype, IADL-E = Instrumental Activities of Daily Living Scale for the Elderly, IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly, KCSB = Kolkata Cognitive Screening Battery, MDQ = Mood Disorder Questionnaire, MDRS = Mattis Dementia Rating Scale, MINI = Mini International Neuropsychiatric Interview, MMSE = Mini-mental state examination, MoCA = Montreal Cognitive Assessment, NPI-Q = Neuropsychiatric Inventory Questionnaire, NR = Not reported/unclear, PRIME-MD = Primary Care Evaluation of Mental Disorders, QMC = Questionnaire of Cognitive Change, SCAN = Schedule for Clinical Assessment in Neuropsychiatry, SPAS = Survey Psychiatry Assessment Schedule (SPAS), UPDRS = Unified Parkinson's Disease Rating Scale, VSID = Vellore Screening Instrument for Dementia WHODAS-II = World Health Organisation Disability Assessment Scale II, ZBI = Zarit Burden Inventory.

Appendix C

List of excluded studies, alongside rationale.

First author, Year	RecordID	Country	Reason	Evidence
Non-Specific				
Andreasen2014	13480291	-	Dementia prevalence pooled across countries	-
Prince 2009	8545171	-	Narrative article	-
Rodriguez 2008	13480478	-	Duplicate	Identified as a duplicate upon accessing the full-text (13480477)
Shaji 2010	15752154	-	Review article	-
Brazil				
Barbosa2009	N002	Brazil	Non-representativesample	"were having been a client of thehealth care plan for at least 12 months"
Bendetti2008	N022	Brazil	No formal diagnosticcriteria (with face validity) applied.	"To analyze dementia, theclassification used was "does not present dementia" (<2points) and "presents dementia" (≥ 3 points)."
Burla 2013	15752113	Brazil	Review article	-
Burla 2013	15752008	Brazil	Duplicate	Identified as duplicate upon accessing full-text (15752113)
Caixeta2004	13480313	Brazil	Diagnosis dependenton accessing service	"We evaluated 70 demented patients, consecutively attended in three different care settings: a public psychiatric outpatient clinic, a private memory clinic and the university outpatient dementia ambulatory"
Caldas 2012	15752175	Brazil	No formal diagnostic criteria (with face validity) applied.	"Mean total score on the LCT was 26.3±4.1; this value is above the cut-off proposed for the screening of dementia for this instrument (22 points). Mean total score on the MMSE was 23.4±3.6, oscillating between the case/no case classification proposed by Almeida, in 1998"
Laks 2005	N021	Brazil	No dementia prevalence data reported	Only the MMSE and the Pfeffer Functional Activities Questionnaire scores reported.

Lopes 2007	N004	Brazil	No dementia prevalence data reported	"The instruments for detecting cognitive and functional impairment (CFI)"
Lourenco 2014	15752013	Brazil	Diagnosis dependent on accessing service	"847 elderly individuals derived from a sample stratified by gender and age, who were clients of a Brazilian private health plan"
Meguro 2001	13480428	Brazil	Non-representative sample	"…elderly Japanese immigrants living in Brazil were examined"
Ramos- Cerqueira 2005	N006	Brazil	Non-representative sample	"All individuals aged 65 and older, residents in the urban area of Piraju, a town in Sao Paulo State, Brazil, routinely seen by CHWs [Community Health Workers], were included in the present study."
Ribeiro 2011	N007	Brazil	Non-representative sample	"were having been a client of the health care plan for at least 12 months"
Scazufca 2009	15752089	Brazil	No dementia prevalence data reported	No prevalence data reported. Secondary analysis
Suemoto 2017	15752102	Brazil	Non-representative sample	Participants required an autopsy. Participants were excluded if "Subjects with severe chronic conditions that might damage cognitive function prior to death by interfering in brain homeostasis. These conditions include severe heart failure, chronic kidney failure and brain metastasis"
Vianna 1991	13480557	Brazil	No formal diagnostic criteria (with face validity) applied.	"The IMC [Informação, Memória e Concentração] was adapted from Hachinski et al. and tested in previous work (Viana et al.) regarding specificity and sensitivity, with results indicated that this test is an adequate instrument in the detection of dementia in the elderly" (Translation)
Veras	N020	Brazil	No dementia prevalence reported	The "prevalence of cognitive impairment" is reported only.
Yamada 2002	13480562	Brazil	Non-representative sample	"The epidemiological study was done in 2000 for the Japanese-Brazilian population in Campo Grande in Brazil."
India				
Poddar2011	13480452	India	No formal diagnostic criteria (with face validity) applied.	"a cut-off score of ≤23 was taken to screen the dementia cases"
Raina2008	13480468	India	No formal diagnosticcriteria (with face validity) applied.	"The clinical evaluation was carriedout by a neurologist with the help oftwo public health specialists. An individual was confirmed as a case of dementia only after the clinical evaluation which also

				included a revisit to cognitive screen scores (BMSE)."
Riana 2008	13480467	India	Non-representative sample. No formal diagnostic criteria (with face validity) applied.	"The prevalence cohort consisted of 200 individuals aged 60 years and above residing in the Mishriwala migrant community cluster of Jammu city". "An MMSE score below 24 (out of a possible score of 30) was evaluated for clinical diagnosis. This scoring was performed to establish the presence or absence of a dementia syndrome, stage of severity and the likely cause."
Riana 2010	13480465	India	No formal diagnostic criteria (with face validity) applied.	"The clinical evaluation established the presence or absense of a dementia syndrome, its stage of severity, likely cause and estimated date of onset….using a standardized diagnostic protocol"
Riana 2013	13480464	India	No formal diagnostic criteria (with face validity) applied.	"The clinical assessment of dementia involved a careful detailed clinical history to determine the precise features of intellectual loss if any. The subjects were examined for three categories of symptoms: (1) cognitive or intellectual, (2) functional and (3) psychiatric or behavioral. An individual was confirmed as a case of dementia only after clinical evaluation. The clinical evaluation also included the use of cognitive screen scores (BMSE)."
Riana 2014	13480463	India	No formal diagnostic criteria (with face validity) applied.	“The clinical assessment of dementia involved a careful detailed clinical history to determine the precise features of intellectual loss if any. The subjects were examined for three categories of symptoms: 1. Cognitive or intellectual, 2. Functional, and, 3. Psychiatric or behavioural”
Saldanha 2010	13480487	India	Out of date sample pool	"…based on 2001 census data" "total study period of study extended from July 2005-September 2007."
Shaji 2005	13480507	India	Duplicate	Identified as a duplicate upon accessing the full-text (13480510)
Singh 2008	13480516	India	No formal diagnostic criteria (with face validity) applied.	"Cognitive deficits were assessed by a separate questionnaire prepared by a psychologist, based on existing questionnaires used in developed countries. The questionnaire examined memory function, intelligence, cognition, and behaviors of daily life common among this population"

Indonesia				
Hogervorst2011	13480375	Indonesia	Out of date samplepool	"All were over 56 years of age and were covered by the local health districts around Borobudur. Some were survivors of our earlier study (Hogervorst, 2008) conducted in 2006. Of these, an estimated 80% could still be contacted for follow- up from Borobudur and Salam districts after the 3 year follow-up in2009. Follow-up data are discussed in another paper, as this paper concerns the rolling cohort data collected in 2009, which also included novel participants who were over 56 years of age in 2009."
Suriastini 2017	N013	Indonesia	No formal diagnostic criteria (with face validity) applied.	“Subjects were diagnosed with dementia when 1. MMSE score was below the normative value after being adjusted for age and education level (see Supplementary 1); 2. Unable to perform one activity in IADL; and 3. AD8 score equal to or higher than 2.”
Yefusa 2009	N009	Indonesia	Non-representative sample	“A convenience sample of 298 elderly was included after giving informed consent These participants were attending the local community health centers, or were visited at the institute in which they lived (n=49) or at home (n=1)”

Jamaica				
Waldron2015	N018	Jamaica	Dementia prevalencenot reported	“More than one fifth (21.2%, n = 591) of older adults had mild cognitive impairment and more thanone tenth (11.0%, n = 307) had severe impairment. The majority (67.7%, n = 1884) of older adults had no cognitive impairment.”
Eldemire1996	N017	Jamaica	Dementia prevalencenot reported	“A community based study using the Folstein minimental screening tool identified 2.3% of theover-60 population as severely impaired and 11.8% as questionable.”
Kenya				
Mutiso2016	N014	Kenya	Age of participants. No formal diagnostic criteria (with face validity) applied. Non-representative sample.	It is unclear the age of the sample. No ages were reported. It is unclearthe diagnostic criteria used to diagnose dementia. It is unclear whether participants were a representative sample.
Ndetei 2013	N005	Kenya	No formal diagnostic criteria applied	No clear evidence of diagnostic criteria applied. However, The Community Screening Interview for Dementia was used.
Mexico				
Acosta-Castillo2017	13480273	Mexico	No formal diagnosticcriteria (with face validity) applied.	"We developed a dementia algorithm based on: 1) cognitive performance evaluated with the MiniCog, and semantic verbal fluency, and 2) information about the basic and instrumental activitiesof daily life." Note: Unclear validity of algorithm.
Alanís- Niño 2008	N019	Mexico	No formal diagnosticcriteria (with face validity) applied.	*“[The MMSE] is the most used scale in studies epidemiological studies to assess deterioration cognitive and dementia in the Hispanic population. Several studies show that it has a good sensitivity and specificity to identifycognitive impairment It has been used to diagnose dementia, although it's important to consider the patient's education”* (Translation)
Cruz-Alcala2002	N011	Mexico	No formal diagnosticcriteria (with face validity) applied	“*Once identified people suspected ofEpilepsy, Vascular Disease Cerebral, Dementia or Parkinson's was validated or discarded the* diagnosis by reviewing clinical files or with a new interview at home.” (Translation)
Meji- Arango 2011	13480430	Mexico	No formal diagnostic criteria (with face validity) applied.	“Based on cut-points for the two instruments all individuals assessed with the CCCE and the IQCODE were combined in two global groups: cognitive normal and cognitive impaired. Groups were further classified based on functional performance. Those

				who received help with one or more basic activities of daily living (BADLs) and/or two or more instrumental activities of daily living (IADLs) were considered functionally impaired and those who didn't need help in any activity or needed help only in one IADL were considered functionally normal. Four groups were identified: 1) Subjects without cognitive impairment and functionally normal were the normal group 2) Subjects functionally impaired and with normal cognition were named the FINCI group (for the first letters of functional impairment not cognitively impaired). 3) Subjects with cognitive impairment and no functional impairment were the CIND (for the first letters of cognitive impaired no dementia). 4) Subjects with both cognitive and functional impairment were the Dementia group."
Sanchez- Arenas 2014	15752178	Mexico	Diagnosis dependent on accessing service	Sample only included those "registered with Mexican Institute of Social Security"
South Africa				
Ben-Arie1983	N012	SouthAfrica	No formal diagnosticcriteria applied. Non-representative sample	Diagnosis based on "cognitive impairment" and "social impairment". The sample was composed of "150 randomly selected Coloured persons aged 65 years or more"

Risk of bias

Country	Study		External Validity				Internal Validity						Summary
	Author	ID	1. Close Representation	2. True or Close Representation	3. Random Selection	4. Non-response bias minimal	5. Directly from the subjects	6. Acceptable case definition	7. Reliability and validity	8. Same mode of data collection	9. Length of the shortest prevalence period	10. numerator and denominator	11. Summary
Brazil	Bottino	13480301	H	L	L	H	L	L	L	L	L	L	M
Brazil	Caramelli	15752121	H	H	H	H	L	L	L	L	L	L	H (!)
Brazil	Cesar	13480321	H	L	L	H	L	L	L	L	L	L	H (!)
Brazil	Herrera	15752058	H	L	L	L	L	L	L	L	L	L	L
Brazil	Lopes	13480416	H	L	H	H	L	L	L	L	L	L	H
Brazil	Magalhaes	15752146	H	L	L	L	L	H	L	L	L	L	H (!)
Brazil	Scazufca	13480493	H	L	L	L	L	L	L	L	L	L	L

India	Banerjee	8545180	H	H	L	H	L	L	L	L	L	L	H
India	Banerjee	13480294	H	L	L	H	L	L	L	L	L	L	M
India	Chandra	13480326	H	L	L	L	L	L	L	L	L	L	L
India	Das	15752010	H	L	L	L	L	L	L	L	L	H	L
India	Gurukartick	13480366	H	L	L	H	L	L	L	L	L	L	M
India	Jacob	13480387*	H	H	L	L	L	L	L	L	L	L	M
India	Mathuranath	13480423	H	L	L	L	L	L	L	L	L	L	M
India	Rajkumar	13480469	H	L	L	L	L	L	L	L	L	L	L
India	Rodriguez	13480477*	H	H	L	H	L	L	L	L	L	L	H
India	Seby	N010	H	H	L	L	L	L	L	L	L	L	M
India	Shaji	13480510	H	H	L	L	L	L	L	L	L	L	M
India	Shaji	13480511	H	H	L	L	L	L	L	L	L	L	M
India	Singh	13480516	H	L	H	H	L	L	L	L	L	H	H

India	Tiwari	15752131	H	H	L	L	L	L	L	L	L	L	M
India	Vas	13480548	H	H	L	L	L	L	L	L	L	H	M
Jamaica	Eldemire-Shearer	157520466	L	L	H	H	L	L	L	L	L	L	M
Jamaica	Neita	13480438	H	H	L	H	L	L	L	L	L	L	H
Mexico	Rodriguez	13480477*	H	H	L	L	L	L	L	L	L	H	M
Mexico	Cruz Alcala	N016	H	L	L	L	L	L	H	L	L	H	L
Mexico	Velázquez-Brizuela	13480552	H	L	L	H	L	L	L	L	L	L	M
South Africa	Van der Poel	113480542*	H	H	H	L	H	L	H	L	L	H	H
South Africa	De Jaegar	13480339	H	H	H	H	L	L	L	L	L	L	H
* The study is part of the 10/66 group, (!) = Studies with a very high dementia prevalence rate >15%.													

Chapter 7: Participants' Comprehension of the Informed Consent in an Epidemiological Study on Dementia Prevalence: A Qualitative Study

Ilaria Falvo, Maddalena Fiordelli, Rebecca Amati, Aliaa Ibnidris, Emiliano Albanese and Marta Fadda

Manuscript published in Frontiers in Psychiatry:

Falvo I, Fiordelli M, Amati R, Ibnidris A, Albanese E, Fadda M. Participants' Comprehension of the Informed Consent in an Epidemiological Study on Dementia Prevalence: A Qualitative Study. Frontiers in psychiatry. 2021 Apr 7;12:405.

Abstract

Aim: In the absence of an effective treatment, informed participation in dementia research can hardly be underestimated. However, although informed consent is key in biomedical research, it may become a barrier to participation. Whether informed consent may cause confusion and contribute to unfair participant selection in dementia research is not known. In preparation of a future epidemiological study on the prevalence and impact of dementia in Switzerland, we aimed to conduct a qualitative study to explore participants' comprehension of the purpose of informed consent form and process shortly after participation in the pilot and validation study that preceded the large-scale survey.

Methods: We conducted a qualitative study with 22 participants of the validation phase of an epidemiological study on the prevalence and impact of dementia in Switzerland to capture their understanding of both the nature and the content of the informed consent form and process. Participants were older adults (65 years or more) eligible for a dementia epidemiological study and their informant (a person who could provide information on their health and cognition). None of the participants reported to be suffering from dementia at the time of the interview.

Results: We found that participants held inaccurate and potentially trust-threatening beliefs regarding the scope of the informed consent. Participants identified contradictory contextual, formal and content needs that are difficult to be fulfilled and misperceived the clinical and research settings in terms of informed consent procedures.

Conclusions: Participants and their proxies should be informed about both the scope of the informed consent process, and the content of the informed consent document in a focused, age-appropriate manner, while dispelling confusion about the purpose of research.

Keywords: informed consent, autonomy, ethics, epidemiology, dementia, qualitative study, Switzerland

Introduction

Contrary to mild cognitive impairment (MCI), the stage between the expected cognitive decline of normal aging and the more serious decline of dementia, dementia is a neurodegenerative syndrome characterized by progressive impairment in cognitive functions, including memory, reasoning, attention, and language (1). Dementia may be caused by different diseases and traumas primarily or secondarily affecting the brain, such as Alzheimer's disease or stroke (1). While consciousness may not be affected, dementia alters behavior and the ability to perform everyday activities (1). The most common form of dementia is Alzheimer's disease (60–70% of cases), a "primary degenerative cerebral disease of unknown etiology with characteristic neuropathological and neurochemical features" (1). Other major forms include vascular dementia, dementia with Lewy bodies, and a group of diseases that contribute to frontotemporal dementia (1). In the absence of an effective treatment, conducting both therapeutic and nontherapeutic research on dementia is crucial for prevention, and to reduce the burden on dementia on those who are affected, their family, and caregivers (2, 3). Dementia research is at the core of the seventh action area of the World Health Organization (WHO) Global action plan on the public health response to dementia (2), which highlights the importance of collecting up-to-date epidemiological data. The potential benefits of epidemiological research include obtaining new information about dementia etiology, diagnosis, and treatment, and about dementia costs, and the cost-effectiveness and use of healthcare (4). Researchers should promote and sustain high study participation rates among individuals both with and without dementia. Scarce participation can contribute to reduce both internal and external validity, thus limiting the generalizability of study findings (5). Factors that may contribute to older adults' exclusion from research include the complexity of the study design or ethical reasons (6–8), or to refusal to participate in research due to fear, concerns, or lack of trust (9–12). Moreover, evidence suggests that the informed consent process may also pose a potential barrier to participation in research among this age group (13, 14). Informed consent is a cornerstone of research in human subjects (15) and, seeking to uphold the ethical values of participants' autonomy and their protection from harm, it represents one of its main requirements (16). However, studies have shown that the patient information sheet and declaration of consent might be a source of confusion among study participants. Participants may not understand the information presented during the informed consent procedure because the language is too complex, forms are excessively long, information is scant or of low quality, or the context where it is provided is not optimal (17–20). Three essential conditions must be fulfilled for informed consent to be valid, regardless of age: subjects should decide whether to participate freely

without any coercion, they should receive sufficient clear, understandable, and usable information about the study, and be competent to understand such information and think rationally upon it (21). These conditions may be more difficult to meet at older ages (22). In particular, studies found that old age adversely affected recall of information offered in the informed consent form (23) and was associated to reduced understanding of informed consent information (24, 25). Only competent individuals can give informed consent for research; and even among them, it may be difficult or even impossible for those made vulnerable by sickness or dependency (26). Cognitive impairment may further limit the ability to actively participate in the process, even when consent is provided by a proxy or legal representative (27, 28). In many instances, the decision-making capacity is only partially impaired but declines during the course of a research project (13). Other factors, such as level of education and income, may introduce additional inherent vulnerabilities among eligible study participants (24, 29). Finally, older participants may not understand the purpose of the informed consent for cultural reasons (30). In preparation of a future epidemiological study on the prevalence and impact of dementia in Switzerland, we aimed to conduct a qualitative study to explore participants' comprehension of the purpose of informed consent form and process shortly after participation in the pilot and validation study that preceded the large-scale survey. Specific objectives included exploring the meaning participants attributed to the informed consent process, their perceived barriers to accessing and understanding the informed consent form, and their preferences regarding the informed consent document's format and content.

Materials and methods

Study Design

The present study constituted a qualitative follow-up investigation to a validation study conducted between March 2019 and October 2019 with 160 subjects in the Canton of Ticino, Switzerland. The validation study aimed at confirming the validity of the instruments to be employed in a soon-to-be study to assess the prevalence and impact of dementia in Switzerland. Inclusion criteria were being 65 or older for older adult participants, while there were no age restrictions for being an informant. All participants had to be resident in the Canton of Ticino, Switzerland. Each participant was also asked to identify a proxy, or "informant" i.e., a person who knew the participant well and could answer questions on his/her health. Of the 320 participants of the validation study (i.e., subjects and their informants), 35 agreed to be re-contacted for future studies and provided their personal contact information (e-mail address or telephone number). They were contacted by a member of the research team (RA) up to three

times, who invited them to participate in an interview on their participation experience in the validation study. We informed prospective participants about the nature and scope of the present study and provided the necessary ethical safeguards (e.g., anonymity and confidentiality of the data, right to withdraw at any time, etc.). Recruitment lasted from December 2019 through January 2020. This article follows the COREQ (COnsolidated criteria for Reporting Qualitative research) Checklist (31). The study was reviewed and approved by the Ethics Committee of the Canton of Ticino. The ethics committee waived the requirement of written informed consent for participation.

Data Collection

Interviews were conducted in Italian between December 2019 and January 2020 by a member of the research team (RA, female, PhD) who has extensive experience in qualitative research and was employed as a postdoctoral researcher at the time of data collection. The interview setting was either the participant's home or the University building, according to participants' preferences. The interview resembled an in-depth conversation with open questions, where participants were invited to freely express their personal thoughts. Interview questions were developed ad hoc for this study and elicited the meaning participants attributed to the informed consent process, their perceived barriers to accessing and understanding the information sheet and declaration of consent form, and their preferences regarding the document's format and content, including their opinion on using visual aids such as a video to support the informed consent process. Other questions elicited participants' motivation to participate in research and their preferences regarding the return of individual-specific and general study findings, which are the object of separate analysis. Interviews followed Holstein and Gubrium's "active interview" model, where interviewer and interviewee are conceptualized as equal and coactive in the production of knowledge (32). We adopted a flexible interview style, whereby participants were free to interrupt the interview whenever desired. Each interview lasted approximately one 1 hour, was tape and video recorded (as materials would be later used to develop a campaign to boost participation rates in the epidemiological study), and transcribed verbatim. While one team member conducted and transcribed the interviews, a second team member double-checked all transcriptions to guarantee a correct documentation of the data collected. Data collection was driven by data saturation, which happened when not novel insights could be extracted from the data. This condition was reached after 11 interviews. We collected data on participants' sociodemographic characteristics such as age, gender, occupation, and district of residence.

Data Analysis

To identify the most significant and meaningful responses from the sample, two coders (IF and MF) performed an inductive thematic analysis of the 19 transcripts based on Braun and Clarke's six-step approach (33). The two coders read all transcripts to familiarize themselves with the content, highlighting important quotes, identifying different labels, and organizing them in hierarchical order. Subsequently, we identified relationships between labels, highlighting thematic convergences and divergences. Discussion occurred between each stage of the analysis process and disagreement was resolved through discussion. Analysis of the transcripts was conducted in the original language (Italian) using NVivo12 by QSR software.

Results

Socio-Demographic Characteristics of Study Participants

The final sample included 22 individuals (11 women), including three couples who asked to be interviewed together. Those interviewed individually included 10 older adults who were eligible for the validation study as "participants,", and 6 six informants who, at the time of the interview, were caring for a family member affected by dementia. One couple was composed of two friends, who were both older adults eligible for the validation study as participants. One was a couple of spouses, who were both older adults eligible for the validation study as both participants and informants (of each other). One was a couple of spouses composed of a participant and his informant. None of the participants reported to be suffering from dementia at the time of the interview. Among the informants, 2 two were daughters/sons and 7 seven were spouses of an actual dementia patient or an older adult eligible for the validation study. The average age was 71 years (SD = 9.3; range = 45 - −86). In terms of educational level, most participants either had completed high school (n = 10) or had a University degree (n = 8), were retired and resident in the Lugano district. See Table 1 for an overview of participants' socio-demographic characteristics.

Themes Extracted From Participants'

- *Reports*

In general, participants identified a number of barriers to their comprehension of the informed consent form, including graphical and linguistic ones, and suggested ways to facilitate both the process of obtaining consent and their understanding of the informed consent document. The thematic analysis resulted in three themes related to the meaning attributed to the informed

consent process. From the participant perspective, the informed consent process does not ensure full protection of study subjects. In addition, participants identified contradictory aspects. Finally, participants suggested that research and clinical informed consent is the same, they do not understand what research is.

- *Between Failed Protection and Trust*

Participants' attached meaning to the informed consent process centered around two main positions. According to the first position, as the following participant reported, the informed consent form is a document is something to be looked at with suspicion, as it is mainly created to ensure protection of the study team, but not of participants.

"Clearly the person who wrote it, wrote it in favor of the person doing the research. He did not put himself in the participant's shoes. . . But this is the game of the parties" (Participant 2, older adult).

Participants reported to be aware that a PI may want to employ the informed consent form as a tool for protecting the study team from possible legal consequences.

"In certain situations, informed consent is just a formality. . . Something to download. . . But it is also understandable, now with all the lawsuits they receive in the hospital" (Participant 3, older adult).

A second position is defended by some participants who argued that the informed consent did not represent a barrier in their decision to consent to the study. They trusted the interviewer, the study team, and the University and, therefore, they also trusted the document. As two participants reported:

"Because I think you have no interest in cheating on people. (. . .) I signed certain things. When the probability to be deceived is greater, much greater, then yes! But here, I went on trust" (Participant 17, older adult).

"There may be cases of people who may not understand and just sign because they trust you" (Participant 7, older adult and informant).

In particular, as the following participant explained, interpersonal contact with the interviewer or the study team replaced the function of the informed consent:

"Honestly, we went on trust because the lady called us on the phone, we heard her voice, she

arrived here, we drank a coffee, we did all this. . . ” (Participant 15, older adult).

- *Contradictory Needs That Are Challenging to Fulfill*

The second thematic category explored the sample’s perceived challenges related to accessing and understanding the informed consent. When we asked participants for their suggestions on how to improve both the informed consent process and the informed consent form, their reports were partly contradictory. Participants reported they would like to receive comprehensive information on the study, but at the same time they expressed their preference for a document which is as short as possible as they did not have enough time to read it. In particular, they reported that the informed consent form should always mention how anonymity, privacy, data protection, non-disclosure of data, information, and freedom to leave the study at any time are ensured.

“Those who participate want to be anonymized, indeed they demand it. . . This is the first point and on this you have to reassure them. The second point is the use of this information toward the participant himself, because in short it is like when I give my blood for testing or for other patients, I take it for granted that other people need it, I take for granted that it is examined, but I desire to stay anonymous. Respect, if unpleasant things are discovered, that I would like to be informed” (Participant 2, older adult).

“Giving the possibility and indicating at the end of the text that one can withdraw consent could be a guarantee and reassure those who participate” (Participant 18, older adult).

Participants also reported that the document should contain information on the study aim(s), study rationale, study process, and a section in which it is possible to provide consent to the return of individual-specific results. But, at the same time, this information should be provided in few words. For example, one participant stated:

“But if you could summarize it so that you could read it, it would be better. . . It should be summed up in four lines if you could (. . .). You have to say in four words, in a schematic way, what the study aim is, how you will develop the results, if you want to have the results or not. These, I think, are the information which you have to provide” (Participant 5, informant).

They added that the form should be written in a simple language and important information should be placed on the first page so that participants can have access to it as soon as they start reading the document.

“Shorter is better, it is very simple. If it follows your rules, it becomes difficult, but the fact is: shorter is better” (Participant 17, older adult).

Participants emphasized that not enough time is devoted to read the informed consent form, partly because of lack of it and partly because people do not like reading.

“Look, if I read it, I did it as I am reading this, very quickly, one line every four to do it quickly” (Participant 7, older adult and informant).

“But I also know that people do not like reading. You can talk with any insurer. . . People refuse, they do not have time and then it is also difficult to understand” (Participant 2, older adult).

In addition, participants wished to obtain information as soon as possible to have time to read it at home, and at the same time they wanted to meet someone who provides the information. When asked when it would be the most appropriate moment to offer the informed consent form or its visual aids, all participants agreed on doing so as soon as possible. Participants suggested the possibility to have the document delivered at home before the first study meeting to have more time to read it carefully and reflect.

“When you have to sign something, you need to have time to read it and to think about it, so you could send it at home as soon as possible” (Participant 17, older adult).

“In my opinion, it would be more useful to send it a few days before the interview so that someone will read it at home and be able to say either yes, I do it, or I do not do it” (Participant 7, older adult and informant).

At the same time, participants reported that they wanted to be supported by the researcher during the informed consent process. Participants were aware of the time and resources required by this process, but they understood that the benefits that could derive would compensate for the investment. As two participants explained:

“I mean, you should have a person to explain what you are signing. . . Nobody did it and nobody does it because it is expensive and a waste of energy” (Participant 7, older adult and informant).

“I think that it is still important. . . Yes, the meeting to explain well. I know it is a matter of time, but you have to realize that time is also money, time is the best result” (Participant 15, older adult).

- *A Blurred Line Between Research and Clinical Settings*

The interviewer clearly stated that the interview was about the informed consent process that happened as part of the validation study and not just any informed consent process that happens either in research or when we visit hospitals. Despite this, when we asked participants what they thought the scope of the informed consent was, a position embraced by many was that it is a mandatory document that necessarily needs to be signed in order to participate in research, similarly to situations in which they are asked to sign it in order to receive medical treatment. Participants reported to be aware of the fact that, if they failed to sign it, they would be excluded from the study, and perceived this instrument as a rigid, non-flexible tool to be accepted without any discussion or agreement.

"If I do not sign it, you do not do anything. I go home and the story is over. . . Right?" (Participant 18, older adult)

"No (I did not read it). It is like when you go to the hospital, there is always this informed consent to be signed. It is a rule, it is mandatory." (Participant 2, older adult).

As the following participant reported, the informed consent is seen as a customary procedure, something you "just have to do" and for which there is no alternative. Again, the participant made a parallel with the clinical setting.

"When you need to undergo a surgery at the hospital, they ask you sign something before (laughing). I had to sign it for my brother in the hospital after he had a bike accident. . . And I said to myself: —Sign, which is the alternative? If I do not sign, you will do nothing. . . " (Participant 3, older adult).

Other highlighted that not enough time is allowed to patients to carefully go through the document before undergoing a medical procedure or treatment. "I saw it in the hospital, you give it to the patient offhandedly and say:—Yes, yes, sign and go" (Participant 19, older adult).

Discussion

The aim of this study was to explore, in view of an epidemiological study on dementia, participants' comprehension of the informed consent form and process. We explored the meaning participants attributed to the informed consent process, their perceived barriers to accessing and understanding the informed consent form, and their preferences regarding the informed consent document's format and content. We found that participants held inaccurate

and potentially trust-threatening beliefs regarding the scope of the informed consent. Participants identified contradictory contextual, formal and content needs that are difficult to be fulfilled and misperceived the clinical and research settings in terms of informed consent procedures. A first finding is that participants were aware that the information sheet and declaration of consent have both legal and ethical foundations (34). Some argued that, from a legal point of view, their declaration of consent mainly serves the study team as a form of protection from possible lawsuits, while others viewed the informed consent process and document as a minor practice that is safeguarded by their trust in the study team and in the institution promoting the study. These findings expand our understanding of study participants' beliefs regarding informed consent. A previous investigation of the patient's awareness and understanding of the legal nature of informed consent in the clinical context found that 75% of patients falsely believed that it was a legal requirement (35). However, previous studies exploring participants' understanding of informed consent in the research setting started from the assumption that participants understand the intrinsic purpose of the informed consent process and rather focus on the comprehension of the different components of informed consent (36). The importance of discussing the ethical and legal role of the informed consent with participants has never been explicitly mentioned. Practices such as informed consent are meant to ensure the protection of future research subjects and their exercise of autonomy, but also to restore public trust in biomedical research (37). Lack of trust can severely endanger the whole biomedical research enterprise (38). Inaccurate beliefs regarding the purpose of informed consent may erode trust in investigators and research, and ultimately constitute a barrier to participation (39). A second finding is that participants were aware that their understanding of study-related information and informed consent process may be impaired by lack of sufficient time, and graphic and content variables related to the information sheet and declaration of consent. For this reason, they reported a preference for a timely and short document and, at the same time, for comprehensive and interpersonal explanations regarding the study. These needs are difficult to meet simultaneously. This finding is echoed by previous evidence showing that elderly participants may require more time to mentally process information than do younger participants (21). Studies also found that elderly participants consenting to study participation needed more time to make a decision compared to those who decided not to participate (40). Impaired eyesight and visual acuity that accompany the aging process may influence the subject's ability to perceive information in a written form (27, 41). Studies showed that years of education and level of reading might also affect older participants' ability to comprehend the content of informed consent forms (19, 25, 27). However, the fact that our sample was highly

educated partly contradicts this finding, suggesting that even participants with many years of education may need simplified informed consent forms and interpersonal support. Several studies have been conducted to improve participant understanding of the informed consent, but mixed evidence is available on their effectiveness (42). For example, the effectiveness of providing shorter informed consent form or using multimedia on improving participants' understanding is still questioned (43–46). Systematic comparisons of the literature found that enhanced consent forms (with increased readability) and extended person-to-person interactions and discussions were the two most effective strategies in improving participant understanding (44, 47). In light of our study results, the success of the latter strategy does not surprise. Our participants recognized that a committed and supportive presence of the investigator is an important element that facilitates a truly informed consent (34), suggesting that the manner and context in which information is conveyed is as important as the information itself. A third finding was that participants viewed the informed consent process as a customary procedure for which there is no alternative, highlighting a conceptual blurring of the line between the research and medical/clinical treatment contexts. In this sense, they reported to feel compelled to sign the informed consent for the validation study without questions, in line with their experience in the medical care setting. Concerns about the boundaries between research and standard clinical care are not new. For the past forty 40 years, bioethics scholarship and research ethics guidelines have argued that informed consent to participate in research should include clarification of the differences between these two activities (48–54). In line with our findings, previous studies have found that some research participants do not appreciate important differences between clinical research and treatment, a phenomenon called "therapeutic misconception" (TM) (55, 56). Study participants who are unaware of study design implications, especially random assignment to a control or comparison group, may believe that they are assigned a medication based on what is best for them, personally. Not adequately appreciating the purpose and methods of research studies might compromise these participants' ability to evaluate risks and benefits of study participation (57). Our study results expand the evidence on the phenomenon of TM in psychiatric research (58), suggesting that such misconception may not only occur in the clinical research context but also in epidemiological study settings. Our results have a number of practical implications. Our study reiterates that presenting study information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice and ultimately question the validity of the informed consent procedure among older participants (50). As other initiatives have suggested, it is of paramount

importance to define an effective informed consent process, train research staff on best practice to inform prospective study participants and obtain consent and improve the informed consent document (51). This should be presented as a tool first and foremost aiming at protecting their health. Participants should also be informed that, for an ethics committee, approval of an informed consent is mandatory.

Limitations

Some limitations of this study are worth noting. First, we cannot exclude possible selection bias because participants had already taken part in a previous validation study. Their positive attitude and proneness to research participation may be related to the opinions expressed about the consent form and process. However, this might have given them a chance to reflect upon the informed consent before being interviewed, enriching their reports during the interview. Second, due to the face-to-face nature of the interview and the presence of a video-maker, social desirability bias may also have occurred. Nonetheless, the interviews setting was informal, and the interviewer adopted a nonjudgmental approach during the interview, and we offered participants to choose their preferred place to be interviewed. Third, many of the answers of the participants involved ""trust"" as a significant element of the informed consent process. In this sense, there are two variations of the interview setting that may have influenced participants' trust in the interviewer: (1) the interview being conducted alone vs. with a partner, i.e., a person of trust (in this case, the presence of participant's partner might facilitate the relationship with the interviewer); (2) interview conducted at the University vs. at home (in this case, a familiar, trustful environment might facilitate the establishment of rapport with the interviewer). While the variation of the interview setting might have influenced the interview results, we always ensured that both interviews conducted alone and at the University took place in a warm, non-judgmental environment. International guidelines suggest that, for responsible epidemiologic research practice to take place, participants should be well- informed about the study and what is asked from them, and they should all sign an informed consent form before any study-related procedures are initiated (59, 60). As potential participants of epidemiological studies into dementia are likely to be part of vulnerable groups (due to their older age, possible cognitive decline, and presence of co-morbidities) (13), it is crucial that this document is prepared with care, using methods developed in consultation with them and their proxies, and taking into account their beliefs, needs and capacities (12). This can be best done by combining both quantitative and qualitative research approaches when engaging potential participants and their proxies. For example, investigators may ask for a stepwise consent procedure, where

comprehension, risk and inconvenience scores can be obtained before and after the study procedures by asking closed-ended questions about the study's essentials (61). Other proven methods include the use of large print and simplified language, a storybook, and a videotape (62). While providing information to participants and their proxies on the study's main elements, investigators should also clarify and disclose the scope of the informed consent process, including its ethical and legal foundations. This should be done in a focused, locally appropriate manner and within a continuous informed-consent framework, ensuring application of the best competency assessment instruments and dispelling confusion about the scope of research (63, 64). This is likely to result in high levels of comprehension, information retention and, ultimately, and participation rate. To prevent exploitation of human subjects and build true collaborative research partnerships with prospective and actual participants, researchers conducting epidemiological research must consider the plethora of ethical challenges posed by the informed consent process and document for older participants. Failing to do so will result in this instrument becoming a source of discrimination and an obstacle to not only participation but to the real exercise of participants' autonomy, which this tool is indeed designed to protect and sustain.

Data availability statement

The datasets generated during and/or analyzed during the current study are not publicly available due privacy reasons but data summaries are available from the corresponding author on reasonable request. Requests to access the datasets should be directed to Marta Fadda (marta.fadda@usi.ch).

Ethics statement

The study was reviewed and approved by Comitato Etico del Canton Ticino. The ethics committee waived the requirement of written informed consent for participation.

Author contributions

RA made all the contacts with the participants and conducted the interviews. MF and IF led the analytic process and analyzed the data. RA, MF, and EA contributed to the study design. MF verified the findings of the analysis. All authors contributed to writing the paper.

Funding

This study is part of a larger project (SwissDEM), which was funded by the Swiss National Science Foundation (Grant no. 320030_184794). The present study was financed with the Institute of

Public Health corporate funding.

Acknowledgments

We thank all participants who devoted their time to participate in this study.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.656822/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary Material

Appendix 1. Interview grid

Participation to the validation study	
Participation experience	How was your experience of participating in the validation study? What did it mean for you to participate in the validation study? What do you remember from participating? What was the purpose of the study? How did you feel during participation? After participating in the validation study, what expectations did you have concerning the next phases of the project?
Motivation to participate	What motivated you to participate in the validation study? Why do you think other people participate? Why do you think other people do not participate? Would you participate if you received an invitation to participate in an epidemiological study on the prevalence of dementia in Switzerland? (If participant answers "yes" to the previous question) Let us pretend I am one of your friends. Unlike you, I do not want to participate. What would you tell me to convince me?
Barriers to participation	Is there anything or someone who made you hesitate with respect to participation? Was there anything or anyone who pushed you to participate? In your opinion, what should we do to ensure a high response rate to the epidemiological study?
Return of study results	
General opinion on the return of study results	Overall, what do you think about the fact that researchers communicate the study results to participants? What do you think of the fact that researchers report the results of the tests you have been administered?
Understanding of the type(s) of study results	What types of results would you be interested to know?
Preferences regarding the communication of study results	How would you like the results to be communicated to you, if you agreed to receive them (in writing, verbally)?
Preferences regarding who to involve in the communication of the study results	Whom would you want to be informed of your results, if you agreed on their return?
Preferences regarding when to communicate the study results	When would you like to be informed of the results, if you agreed on their return?
Feelings associated with the return of study results	What feelings come to your mind if you think about having the results communicated to you?
Informed consent	
General opinion on informed consent	When you participated in the validation study, do you remember if you signed a document? If so, what do you remember regarding the document you signed? In general, what do you think about the fact that study participants give their consent to the return of study results?

Preferences regarding informed consent procedures	How would you like to provide your consent regarding the return of study results?
Preferences regarding who to involve in the informed consent form	Think about the individuals you want to be informed of your study results. Would you include these individuals in the consent?
Preferences regarding when to provide informed consent on the return of study results	When would you like to give your consent regarding the communication of the results?
Meaning of informed consent process	What do you think informed consent is meant for? What is its scope?
Perceived barriers	Was there anything that prevented you from understanding the information sheet and declaration of consent form?
Preferences regarding the document's format and content	Is there anything you would change regarding the document's format and content? What do you think about using visual aids such as a video to support the informed consent process?

Other questions	
Dementia-related challenges	In your opinion, what are the biggest challenges in relation to dementia and Alzheimer's disease? What and whom should researchers invest on? What do you expect from research, in general?

Chapter 8: Returning individual-specific results of a dementia prevalence study: insights from prospective participants living in Switzerland

Marta Fadda, Maddalena Fiordelli, Rebecca Amati, Ilaria Flavio, Aliaa Ibnidris, Samia Hurst, Emiliano Albanese

Manuscript published in:

Fadda M, Fiordelli M, Amati R, Falvo I, Ibnidris A, Hurst S, Albanese E. Returning individual-specific results of a dementia prevalence study: insights from prospective participants living in Switzerland. International journal of geriatric psychiatry. 2021 Jan;36(1):207-14.

Abstract

Objectives: To explore prospective participants' preferences regarding the return of their individual-specific results from a dementia prevalence study (a probabilistic diagnosis of dementia).

Methods/Design: We conducted a qualitative study with 22 individuals aged 45 to 86 and resident in the Canton of Ticino (Switzerland). Participants had previously joined the validation phase of an epidemiological study into dementia and its impact.

Results: We found that individuals welcome the return of their individual-specific results, provided these meet a number of validity, clinical, and personal utility criteria. They justify researchers' duty to return study findings with the principles of beneficence (e.g., providing information that can help participants' medical decision-making) and justice (e.g., acknowledging participants' efforts to help research by sharing their personal information). Furthermore, individuals anticipate societal benefits of the return of individual specific study findings, including improved interpersonal relationships among individuals and decreased dementia-related stigma.

Conclusions: Our findings suggest that researchers should address the return of individual-specific study results early on during study design and involve prospective participants in identifying both the conditions under which results should be offered and the perceived individual and societal benefits returning can have.

Keywords: Dementia, epidemiology, individual-specific results, older adults, qualitative research, Switzerland

Introduction

Dementia research and innovation correspond to the seventh action area of the World Health Organization (WHO) Global action plan on the public health response to dementia (1) Advancing research is considered an urgent and crucial matter, in order to not only decrease dementia incidence but also improve the lives of patients, their families, and caregivers (1, 2). Epidemiological research is one of the plan's priorities (3, 4) Epidemiological data can provide information on the prevalence and incidence of the disease but also its impact, including the direct and indirect costs. Effective progress in this area also depends on the promotion of participation in research. In fact, the well-known obsolescence of dementia-related epidemiological data in Europe (5) is due to a decrease in participation rates in epidemiological studies over the past 30 years, which has witnessed an even steeper decline in more recent years (6, 7). The success of population studies depends on the voluntary participation of individuals who donate their time and their personal health information, often accepting a certain degree of risks to their welfare. Therefore, researchers should take into account legitimate expectations of individuals to receive some personal gain from participation, such as research results or information on their health (8). Evidence suggests that current dementia research ethics policies and norms are not aligned with participants' preferences and may hinder equitable opportunities to take part in epidemiological research (9, 10). Among the reasons to participate in DNA biobank studies, expectations of personal benefit through health information are prominent (11-13). Willingness to participate is higher when participants are offered a chance to know their individual-specific results. Consensus statements indicate that the return of research results should occur when the findings are clinically relevant (14-17). Recently, scholars have highlighted the urgent need for guidance in related decision-making contexts, such as when to provide family members with access to health-related data of dementia patients and how to manage the return of individual results from dementia research (18). Lack of clarity on how to meaningfully interpret positive results in a clinical sense, coupled with fears of causing anxiety or depression to subjects have so far prevented most investigators from disclosing individual-specific research results to dementia research participants (19-22). However, little has been done to address such issues in dementia epidemiological research. We conducted a qualitative study to explore preferences regarding and understanding of the return of individual-specific results, in view of an epidemiological study into dementia and its impact, whose primary outcome is prevalence of dementia based on a probabilistic dementia diagnosis.

Methods

Study design

This article presents a follow-up investigation of a validation study conducted between March and October 2019 with 160 dyads in the Canton of Ticino, Switzerland. Each dyad consisted of an old person (aged +65 years) and his/her informant (i.e., a carer, spouse, or child). Therefore, in the original study, the number of informants was equal to the number of older adults (n = 80 in each group). In the present investigation, we conducted semi-structured, in-depth interviews with a sample of the validation study's participants. We included both participants and their informants to generate a more comprehensive understanding of their attitudes, thoughts, and preferences regarding the return of individual-specific results (23).

Study participants

Inclusion criteria for participants were age (being 65 or older) and place of residence (Ticino). Informants had to be older than 18 years. In the informed consent for the validation study, participants gave permission to be contacted for a follow-up interview. No individual-specific results were offered in the validation study. Of the 320 participants of the validation study (160 dyads), 35 individuals provided their contact details and were contacted by a member of the research team (RA), who provided a description of the present study, and reference to its ethical safeguards. We offered no financial incentives for participation. Recruitment lasted between December 2019 and January 2020.

Data collection

The interviews were conducted in Italian and face-to-face by a member of the RA between December 2019 and January 2020, either at the participant's home or the University, according to participants' preferences. Three couples requested to be interviewed together. In these cases, both participants took turn to answer to all questions posed by the interviewer, resulting in two answers for each question, which were analyzed independently. The interview guide was designed to foster an in-depth conversation and consisted of preset open-ended questions formulated to elicit their preferences on what, how, to whom, and when research results (both general and individual specific) should be returned. A second set of open-ended questions explored participants' perspectives on why results should be returned. These include personal views and interpretation of the nature and value of the return of the results, personal justification in favor or against the return, and anticipated feelings (see Appendix 1 for the interview grid). Participants were asked to imagine that they might be receiving information on

whether they are likely to have dementia or not. We followed Holstein and Gubrium's "active interview" model, which conceptualizes the interviewer and interviewee as equal, collaborative partners in the social production of meaning around a given research topic (24). After permission from participants, we digitally video-recorded all interviews. One member of the RA transcribed them verbatim, while a second member (IF) cross-checked the recorded interviews to guarantee accurate documentation of the discussion. To determine the point of data saturation, we relied on the concept based on thematic redundancy, or inductive thematic saturation (25, 26). In this model, which relates to the emergence of new codes or themes, saturation is confined to the level of analysis and data collection is interrupted when no novel insights can be extracted from the data (26). We reached saturation of the data after the 11th interview. We collected data on participants' sociodemographic characteristics at the end of each interview.

Data analysis

Two members of the RA (MF* and IF) independently performed an inductive thematic analysis of the 19 transcripts. We followed the six-stage comprehensive thematic analysis approach developed by Braun and Clarke (27). The key phases of the coding process include familiarizing with the content of the transcripts, highlighting meaningful quotes regardless of their length, condensing them under a number of labels, organizing the generated labels hierarchically, creating relationships between them, and identifying remarkable quotations to represent thematic similarities, differences, and contradictions. This method allows to unveil themes that may not have been covered by established theory (28, 29). To validate the results, comparisons between the two coders took place multiple times in-between each of the above-mentioned phases, so that themes, labels, and quotations were constantly discussed, and interpretation discrepancies resolved through dialog and reference to the transcripts. We performed the analysis with the qualitative research software NVivo.30 No translation of the transcripts was needed, as the analysis was conducted in the original language. This article follows the Standards for Reporting Qualitative Research (SRQR) (31).

Results

Participants' characteristics

The final sample included 22 participants (11 women), including three couples that requested to be interviewed together. The mean age was 71 years (SD = 9.3; range = 45-86). Most participants had completed secondary school (n = 11), were retired (n = 17), and resident in urban districts (n = 13; see Table 1 for an overview of participants' sociodemographic characteristics).

Preferences regarding the return

A clear difference between aggregated and individual results emerged from the interviews. All participants welcomed the return of the overall study findings, with most of them reporting that they would like to be informed also on intermediate results and not only final ones. Reasons included a desire to be regularly updated on the study, know better what they are contributing to and what investigators have discovered. A small minority expressed a preference for a public disclosure of the aggregate results rather than individual-specific ones, which would allow them to receive peer support from other individuals who are experiencing the same situations and emotions. The focus of this article will be on individual-specific results. Most participants were in favor of the return of their individual-specific results. The majority stated that they expected them, even though they favored different approaches to disclosure. Most (n = 12) reported that they would not be afraid of the disclosure and had a strong desire to know their personal results. Four participants also reported anticipated fear with respect to the disclosure but declared that they would nevertheless prefer to know the results in order to act. Finally, two participants reported they would be afraid and prefer not to know, stating they would not be able to psychologically manage a risk of dementia. Preferences on how results should be returned varied across participants, and according to the type of results. Most participants stated that they would accept their results being communicated via email, postal letter, or phone call in case they were negative (no risk of dementia), but agreed that, in case of positive results, a face-to-face meeting with the investigator would be more appropriate. With regards to whom they would like their individual-specific results to be shared with, most mentioned their spouse and children. Only those reporting a positive relationship with their family doctor would share their results with him/her and a few reported that they would like themselves to be the only recipients of the results. In terms of timing, all reported that disclosure should happen as soon as possible if results were positive.

Understanding of the nature of the return

We categorize participants' understanding of the nature of the return of research findings around three broad themes: (a) a matter of transparency; (b) a matter of reciprocity; and (c) a matter of relationship.

A matter of transparency

The majority of participants reported that researchers have a moral duty to return individual-specific results based on transparency towards study participants. “(Return of study results) must

be agreed in a very clear way. (…) We should be grateful to those who warn us or make us aware of some problems, no? (…) I find it very positive when someone, even a friend, makes us aware or points out to some deficiencies. I believe that this, if a person reasons in an objective way, is fair and it is something that must happen". (P2, 80, male, university, older adult). Some participants recognized that researchers should be transparent on results that may have clinical utility. "If there were general indications… to understand if there is a beginning of an aging process that is not really healthy like Alzheimer's, like dementia...". (P16, 67, female, secondary school, older adult). or, as the following caregiver reported, that may reduce uncertainty. "(…) When you enter this problem, anything will give you joy, because it's just so hard to go on". (P1, 73, male, secondary school, informant). Two participants also noted that results could not only prompt him/her to seek help but also have an important impact on reducing the stigma and isolation associated with dementia and improve relationships with friends and family members. "Well, it helps… that is, if I know what I have, what is happening, I can ask for help where they can give it to me, I can talk about it with my friends, they will understand me better, I will no longer see those looks like <<What is it? What are you doing?>> It will be a much more open and sincere relationship with others, rather than denying, having to hide and not wanting to accept… I think I should invest much more energy on talking about it openly rather than in hiding and camouflaging everything, so that I can channel my energy to help me deal with the situation". (P6, 69, female, university, older adult).

A matter of reciprocity

Most participants reported that researchers have a moral duty to return study results because this satisfies a principle of reciprocity or mutual exchange. Participants share something with researchers and should, therefore, receive something back. Moreover, failing reciprocity would hinder participation in future, similar studies. "(…) someone gives you (something)… A company gives you a small amount, (you should say) at least a 'thank you'. If you do not do it, you lose. Therefore, there needs to be this exchange. If you give me 20 francs for my association, I at least must thank you. Thank you for being close to our association. But if I do not do anything, next time you will say <<what do these guys want again?>>". (P1, 73, male, secondary school, informant). In addition, a restricted number of participants reported that the principle of reciprocity is not absolute but should be balanced against the validity and the actionability of the results. They reported to be aware of the limitations of the test (in terms of diagnostic uncertainty) which would require a follow-up with further examinations. "I think it is a matter of *do ut des*. I mean, we as participants have consecrated time and commitment to answer these

questionnaires. Even if this scares us off, we surely also expect a non-binding answer, with all the necessary precautions, possibly with a recommendation to see one's family doctor or discuss the results that have emerged… therefore, my opinion would be that it would be an act of courtesy from your side" (P2, 80, male, university, older adult). Despite recognizing the duty to return study results, one participant noted that the scope of a study is to generalize knowledge and not to identify deficits in single individuals. According to this participant, offering options to communicate results should not be framed as an incentive to participation, as this risks to represent a source of exploitation of those participants who would join the study only to know about their results. "I have some doubts regarding the fact that you are the one piloting the participant, because participants decide to join your initiative in order to provide information and allow your study to have solid basis, they do not come to you to be helped basically, therefore I do not believe that you should assume a guiding role on that towards participants". (P2, 80, male, university, older adult).

A matter of relationship

Almost all participants reported that, for optimal disclosure, it is central that researchers establish a personal relationship with participants early on during recruitment. "Now I speak very personally: this experience has shown me that what really matters is contact with the person". (P16, 67, female, secondary school, older adult). For this participant, it is important that contact is not only personal, but also open and that meetings can be scheduled in a flexible fashion. "If you would like to come, gladly, that would certainly make us glad… but perhaps your visit, after (doing) certain things, we can always meet, that is very nice, gladly. It's interesting so that it doesn't stay a hybrid thing. Exactly the contact with the other part who is working, that is nice. (…) I am always open in any moments… As we did it today: 'we have this thing here', we meet… 'we have these results here, we would be pleased to come' and then we meet". (P1, 73, male, secondary school, informant). For the following participant, meetings with the RA should be nonjudgmental and should constitute an opportunity to express one's problems. "It would be nice for those who are interested to personally meet, to express their problems". (P13, 77, male, secondary, informant). Half of the participants reported their desire to maintain a relationship with the study team also after the interview is concluded and the results are disclosed. Participants recognized that results can potentially reveal a risk of dementia which can be difficult to manage from a both behavioral and psychological point of view. "Research (should invest) on individuals (…) as politicians always do when they want to get votes, they are all there, and after that they disappear. You are abandoned". (P1, 73, male, secondary school, informant).

For this reason, participants reported that they would like to receive the researchers' support, which they described in two main ways. About a quarter of participants expressed a desire to receive remote or face-to-face personal feedback on how their individual specific results are different compared to the average, and advice on whom to consult and how to mitigate the risk. “If it hadn't gone so well it would be important to understand how to move in the future, what kind of measures, what kind of solutions I should take”. (P12, 74, female, university, older adult). A restricted number of participants reported a preference for a face-to-face, empathic consultation. “If I had to go back to what I experienced with that biopsy (performed not in the context of the present study), I would probably not do it again, but this is not due to the biopsy itself but rather to the lack of emotional support, and for me emotional support is fundamental. (P16, 67, female, secondary school, older adult).

Discussion

The goal of this study was to explore participants' preferences regarding the return of their individual-specific results in a prospective study on dementia prevalence. We found that the return of individual specific results should repose on two main principles, transparency and reciprocity, and be dialogic. Investigators should disclose anything that could inform health-related decision-making, and the benefits that may derive from individual uses of participants' information should be mutual. Next, participants reported that investigators should assess the validity, clinical utility, and actionability of study findings prior to offering their return. Finally, return should occur in the context of a personal, open, and supportive relationship with the investigator. The idea of justifying the return of research findings with the arguments on transparency and reciprocity is not new to the literature. In the context of genomics, studies found that participants have several health-related and personal reasons for wanting individual research results, and researchers recognize that the highest benefit is helping treat or prevent disease (32-37). In the biobanking context, providing participants with their individual-specific study results that are valid and with potential clinical utility, is perceived by both researchers and participants as a means of demonstrating respect and gratitude for their contributions (38-40). Studies have shown that provision of such information may lead to greater trust, accountability and engagement in research, which is, in turn, a strong predictor of research participation (8). Finally, the obligation to respect participants' ownership of the information they provided—and thus offer “return” rather than “disclosure”—is consistent with the shift towards participant engagement (41). Traditionally, epidemiologists strive to maximize the potential benefits of research by communicating results to study participants in a timely fashion (42). This study

expands the current interpretation of the principle of beneficence in epidemiological research (42). Our results indicate that the return of study results can also contribute to reducing stigma, through improved awareness and understanding of dementia at a collective level. This is consistent with the pivotal role of dementia awareness of the WHO public health response to dementia (1). Our findings on the dialogic context that is necessary for the return of study results are in line with previous investigations on the implications of a dementia diagnosis and its communication with patients and family members. In the clinical context, studies highlighted the difficulties in the communication process with patients (43), the necessity to understand what the diagnosis means to them (including the impact of disclosure) (44), and the value of peer support for people with dementia and their carers as a postdiagnostic intervention (45). Our findings suggest that, in the epidemiological context, return of study findings should occur within an optimal relationship with the investigator, one that does not fade after results are disclosed. If results suggest an increased risk of dementia, investigators should have a role in helping them to manage this risk by offering emotional support and medical advice.

People might frame data ownership as private property, thus perceiving that data belong first and foremost to themselves (46). This could explain the expectation that researchers strictly adhere to a principle of transparency. Furthermore, individuals contributing to research with their health-related information often do so because they are curious about themselves (11-13). Frustration and loss may result when investigators take but do not share. This explains why participants argued for a principle of reciprocity. As in the clinical context, study participants are aware of the potential difficulties in understanding and managing dementia-related results and the impact of their disclosure on different levels, including potentially on health costs (44, 45). In Switzerland, private health insurance is compulsory for all residents, and a diagnosis of dementia may lead to additional costs for individuals related to copay for clinical assessments and exams. However, dementia treatments and most care and nonpharmacological interventions are fully covered by health insurance after a clinical diagnosis made by a specialist. In addition, a dementia diagnosis has no direct impact or implications for fitness-to-drive assessments and license.

Nonetheless, it is likely that participants may expect that interpersonal contact with the investigator is established early on and maintained throughout the entire study to discuss the implications of both negative (i.e., no dementia) and positive results (47) Based on our results, implications are to be noted for both theory and practice. In terms of theory, our results enrich our understanding of the conditions under which disclosure of individual-specific study results

should occur. To respect the ethical principle of nonmaleficence, and thus prevent participants' exposure to unnecessary risks, investigators have an obligation to take into account the test validity, results' actionability and significance, and their personal and clinical utility (48). Our findings add that, when such criteria are taken into account, the interpersonal component of the disclosure should be integrated. In terms of practice, investigators should discuss the issue of the return of research findings early on during study design and address it with the study team. Since the return of individual-specific research results necessarily requires the diversion of some resources from the primary goal of the research (49,50) investigators could consider the option to elicit prospective participants' views on such issue, especially in research contexts when this has not previously been done or when employing innovative screening and diagnostic tools. When a positive decision is made on offering study results, some requirements should be met. Investigators should include a section in the informed consent form that solicits participants' preferences for whether or not they wish to receive individual results and offers options regarding how any identified results will be returned. Investigators should also include a section where participants can identify a proxy to receive the results if they do not wish or are unable to receive them. Finally, investigators are urged to establish a direct, long-lasting link with participants. The present study is not without limitations. First, we cannot exclude possible selection bias, as participants were part of a previous study. However, this can be seen as an advantage as they may have already reflected upon the issue of the return of research findings. Second, participants might have answered the interviewer's questions in a manner that would be viewed favorably, introducing social desirability bias. To reduce this, the interviewer adopted techniques such as nominative questions and employed a nonjudgmental approach. Third, each interview was videotaped by a video-maker. To reduce this contextual bias, the video-maker was trained to limit intrusiveness and participants could choose where they would feel more at ease to be interviewed. Fourth, being dementia a sensitive topic to embark on, this may have had an effect on study participants in terms of difficult emotions and impaired openness. To mitigate this information bias, we established rapport with study participants by telephone before data collection and fostered reciprocal trust through dialog. Finally, the language (i.e., Italian) and nationality (i.e., Swiss) of the participants may limit the generalization of our findings, which should be interpreted and applied cautiously to populations of other geographic and linguistic regions.

Conclusions

We found that, in the context of a dementia prevalence study, participants expect their rights

both to know and not to know their results to be respected, provided the meaning and potential clinical implications of study findings have been previously assessed and clarified. Considering the implications of the issue of result disclosure for decision to participate and the representativeness of dementia epidemiological study samples, investigators should offer participants an ample set of options on the return of their individual-specific results. Epidemiologists' primary roles are the design and conduct of scientific research and the public health application of scientific knowledge (42). This includes the reporting of results not only to the scientific community and society but also to research participants (42). However, it is not clear if this applies to aggregate or individual-specific results. A tradeoff between anonymising data and being able to provide individual specific results may exist and should be adequately accounted for. Since formal guidance is lacking, we call for evidence-based guidelines on how to assess the duty to return individual-specific results in dementia epidemiological research. Finally, ethics committees should support the development of plans to return individual research results, and additionally assess whether they were developed in alignment with prospective participants' needs, preferences, and values.

Acknowledgements

We are grateful to all study participants for their valuable input. This study is part of a larger project (SwissDEM), which is funded by the Swiss National Science Foundation (Grant no. 320030_184794). The present study was financed with the SNSF grant and with the Institute of Public Health corporate funding.

Conflict of interest

The authors declare no conflicts of interest.

Data availability statement

Due to the sensitivity of the information provided by participants, data are only available upon request.

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Appendix

Interview grid

Participation to the validation study	
Participation experience	How was your experience of participating in the validation study? What did it mean for you to participate in the validation study? What do you remember from participating? What was the purpose of the study? How did you feel during participation? After participating in the validation study, what expectations did you have concerning the next phases of the project?

Motivation to participate	What motivated you to participate in the validation study? Why do you think other people participate? Why do you think other people do not participate? Would you participate if you received an invitation to participate in an epidemiological study on the prevalence of dementia in Switzerland? [If participant answers "yes" to the previous question] Let us pretend I am one of your friends. Unlike you, I do not want to participate. What would you tell me to convince me?
Barriers to participation	Is there anything or someone who made you hesitate with respect to participation? Was there anything or anyone who pushed you to participate? In your opinion, what should we do to ensure a high response rate to the epidemiological study?
Return of study results	
General opinion on the return of study results	Overall, what do you think about the fact that researchers communicate the study results to participants? What do you think of the fact that researchers report the results of the tests you have been administered?
Understanding of the type(s) of study results	What types of results would you be interested to know?
Preferences regarding the communication of study results	How would you like the results to be communicated to you, if you agreed to receive them (in writing, verbally)?
Preferences regarding who to involve in the communication of the study results	Whom would you want to be informed of your results, if you agreed on their return?
Preferences regarding when to communicate the study results	When would you like to be informed of the results, if you agreed on their return?
Feelings associated with the return of study results	What feelings come to your mind if you think about having the results communicated to you?
Informed consent	
General opinion on informed consent	When you participated in the validation study, do you remember if you signed a document? If so, what do you remember regarding the document you signed? In general, what do you think about the fact that study participants give their consent to the return of study results?
Preferences regarding informed consent procedures	How would you like to provide your consent regarding the return of study results?
Preferences regarding who to involve in the informed consent form	Think about the individuals you want to be informed of your study results. Would you include these individuals in the consent?

Preferences regarding when to provide informed consent on the return of study results	When would you like to give your consent regarding the communication of the results?

Other questions	
Dementia-related challenges	In your opinion, what are the biggest challenges in relation to dementia and Alzheimer's disease? What and whom should researchers invest on? What do you expect from research, in general?

Chapter 9: Discussion

Aliaa Ibnidris

Key findings

Chapter 3 key findings: Genetic risk factors of AD and their association with intrinsic functional connectivity

In chapter 3, we presented the main findings of an explanatory analysis of PRS of AD and functional connectivity at rest of certain brain regions that are implicated in AD. Our main objective was to look at the association between of higher PRS and modulation of functional connectivity at rest as well as its impact on cognitive performance in cognitively healthy adults. Our findings do not show significant association between PRS and functional connectivity of the PCC and medial temporal lobe structures. We also investigated the effect of high PRS on cognitive performance. Our findings suggest that higher PRS in older male participants (older than 60 years) is associated with lower performance in verbal fluency tests (semantic and phonemic parts). While our connectivity results were non-significant, we argued that other risk factors may be implicated in addition to genetic disposition in determining the risk of AD in late life. It is important to consider that the expression of a phenotype (i.e., clinical symptoms of AD) is not the sole product of genetic disposition and that interaction between genes and the environment is a critical aspect to consider (1). Our findings prompt further investigation of the impact of genetics in combination with other sociodemographic factors such as level of education, family history of AD, and smoking status.

Chapter 4 key findings: Assessment of SCD in older adults at risk of AD

In chapter 4, we examined scale development, another important aspect in cognitive and neuropsychological assessment research. Because timely detection of AD is critical for prevention and meaningful intervention, it is essential to identify and validate feasible, early detection biomarkers and methods. On the other hand, while biomarkers can advance disease diagnosis, the majority of AD cases, whether at the MCI or dementia stage, is still mainly assessed and diagnosed clinically. Subjective decline in cognitive functions may be one of the very early clinical symptoms of AD (2). In a systematic review, we evaluated the measurement properties of available questionnaires used to assess SCD in both research and clinical settings. Our aim was to enable the recommendation of an SCD questionnaire that is well developed, valid and reliable. Although some of SCD questionnaires showed sufficient structural validity or reliability, none of

the identified questionnaires evaluated the content validity of the developed instrument. Demonstrating construct validity is the most important psychometric property in scale development (3–5). Our findings indicate the lack of properly developed and validated SCD questionnaires and emphasize the need for such instruments. A reliable and valid SCD questionnaire will facilitate the identification of older adults at risk of MCI or AD dementia and allow for more timely intervention.

Chapter 5 key findings: Validation of a brief dementia diagnostic schedule

Chapter 5 presented the findings of the validation study of the brief 10/66 Dementia Diagnostic schedule and algorithm. In this study, we investigated the criterion and concurrent validity of the short version of the 10/66 Dementia Diagnostic Schedule and algorithm (6–8) to detect dementia in 229 older adults in Switzerland and Italy living either in the community or in nursing homes. We validated the short version of the 10/66 Dementia Diagnostic Schedule (9) against the gold standard of dementia clinical diagnosis. The schedule was translated and back translated into the Italian and was administered using an electronic data collection software with mobile devices. The data collection methodology was widely acceptable by participants and was preferred to the traditional pen-and paper data collection. Sensitivity of the schedule was 87% while specificity was 61%. Despite the lower specificity, our findings suggest that the short schedule is still a valid and practical tool to identify dementia cases among older adults residing in the community and in nursing homes.

Chapter 6 key findings: Epidemiological evidence of dementia in LMICs

We presented our results on the up-to-date prevalence estimates of dementia in LMICs in chapter 6. In preparation for a large-scale dementia prevalence study in two of the seven countries in the STRiDE project (South Africa and Indonesia), we conducted a systematic review and meta-analysis to provide the current estimates of dementia prevalence in the seven STRiDE countries. We identified and included 28 studies that met the inclusion criteria in the systematic review and meta-analysis. Our results indicated that the pooled estimates of dementia prevalence ranged from 2% (India) to 9% (Jamaica) (10). The prevalence figures were generally higher in studies using the 10/66 compared to the DSM 5 dementia diagnostic criteria. The available prevalence data varied between countries. The majority of studies were judged as having a high risk of bias. The exception were Brazil, Mexico and India. For all included studies, information regarding the representativeness of the sample was not explicitly detailed.

Chapter 7-8 key findings: qualitative study on the understanding of older adults in dementia research on informed consent and return of research results

In chapter 7 and 8 we presented two publications based on data from a qualitative study with 22 participants during the validation phase of the short version of the 10/66 dementia diagnostic schedule. We aimed to explore the participants' understanding of what informed consent entails. Participants were older adults (≥ 65 years) with an informant who is usually someone who knows the participant best and can provide information on their current cognitive status and general health. Our findings from the publication presented in chapter 7 indicate that participants had harmful views regarding the scope of informed consent. Moreover, participants held inaccurate perceptions regarding informed consent procedures in clinical and research settings. clinical and research settings in terms of informed consent procedures. Key findings presented in chapter 8 regarding the preference in return of research results show that individuals welcome the return of their individual-specific results, as long as the results meet a set of identified clinical and personal utility criteria. Furthermore, participants expressed that they expect societal benefits of the return of individual specific study findings such as decreased dementia-related stigma.

Limitations

There are a number of limitations to the present dissertation that should be mentioned. The main limitation is the potential heterogeneity of the included studies in the dissertation. The dissertation investigates six main questions in AD and AD dementia research, spanning from exploring the implications of genetic disposition on functional connectivity of the brain, the assessment of available scales to assess SCD, to validating diagnostic schedules and dementia epidemiology. Each research question required a specific methodology and study design to be examined in depth. This doctoral thesis applies the approach of population neuroscience to demonstrate that neuroscience research is enriched when combined with population-health research. Ultimately, the aim of neuroscientific research is to bring solutions to clinical problems that are faced in day-to-day clinical practice. We argue that this is in fact a strength and that the reported studies in Chapter 3 to 8 were carefully designed to assess each question at hand to the best feasible methodological quality.

Other limitations are detailed in the respective chapters. In chapter 3, our main findings conclude that, regardless of age, a high PRS does not seem to have an association with dysfunction in global cognition, memory, or executive functions as measured by psychometrically valid

neuropsychological tests. In this study, a major limitation was that we did not compare the group of cognitively healthy adults to a group of patients with MCI or AD. Such comparison may have enabled us to better understand the potential similarities as well as differences in the effect of genetic variants on the alteration of functional connectivity. Another important limitation is that we analyzed a cohort of 139 participants at a cross-sectional point in time. Therefore, we could not determine the long-term effect of their genetic risk as indicated by a PRS on the modulation of functional connectivity of the PCC as well as their cognitive status. This, however, provides an opportunity for future investigation to follow up on the same cohort of participants to see whether some of them may demonstrate further disruption of the PCC functional connectivity and/or develop cognitive decline and progress to MCI or AD.

Chapter 4 presents the main findings of a systematic review to evaluate the psychometric properties of self-reported questionnaires used to assess SCD in older adults. This chapter introduces extensive work that was conducted with the aim to ultimately be able to recommend a psychometrically valid questionnaire that is feasible for use in clinical and research settings. The main limitation of this systematic review is that we only included studies that reported developing or validating self-reported questionnaires developed in the context of assessing SCD in preclinical AD. This may have led to the dismissal of existing SCD questionnaires that are in fact well-developed. Nonetheless, by excluding indirect evidence of questionnaires developed to assess SCD in other diseases (e.g., depression or schizophrenia) we reduced the potential heterogeneity of the included studies and increased the confidence in the gathered evidence (11).

In chapter 5, we aimed to validate a brief dementia diagnostic schedule to detect dementia in the community and in long-term residential care facilities such as nursing homes. Our study design to collect dementia diagnosis from the community as well as from nursing homes relied on the presence of dementia diagnosis in previously obtained medical records. Clinical assessments and diagnosis of all participants were neither feasible nor fundable in both the study sites. Moreover, previous studies aiming to determine dementia diagnosis in similar settings included a dementia staging scale such as the Clinical Dementia Rating (CDR), which is not part of the 10/66 schedule (12–14). Nonetheless, we provided information on the cognitive performance of the two main instruments of the schedule to demonstrate the severity of cognitive impairment as a proxy for severity of dementia. We found that, although the sensitivity of the short schedule was adequate (86.5%), the specificity was lower than expected (60.6%) in our study than what was found in previous validation studies of the short 10/66 diagnostic

algorithm (15,16). Most likely the inclusion of older adults from nursing homes settings may have contributed to the observed lower specificity. Participants from nursing homes who may have developed dementia after their admission into the nursing home are unknowingly overlooked as dementia patients, because care is informed by needs assessments rather than diagnosis in this setting. Misclassification bias likely occurred, with several true dementia cases classified as cognitively healthy because of the lack of a clinical diagnosis. This may have also occurred in community dwelling older adults, and the effect of the dementia diagnostic gap is potentially more relevant in cross-sectional compared to longitudinal studies. Consequently, false positives are likely fewer than what the specificity would suggest. Importantly, the results of the diagnostic schedule and algorithm were not communicated to participants at the end of the interview, and all participants were informed that a diagnosis of dementia should only be made after thorough examination by a trained medical professional.

In chapter 6, the systematic review and meta-analysis looked at previous prevalence studies of dementia in seven LMICs only (India, Indonesia, Kenya, South Africa, Mexico, Brazil, and Jamaica). While this may seem restricted to a limited number of countries, we argue that we investigated previous epidemiological evidence in seven representative countries within three regions. The included countries are representative in their respective regions in terms of population characteristics, age distribution, and the availability of information and services for dementia and older adults. In addition, it is important to emphasize that the systematic review was conducted in a preliminary phase to prepare and inform a large-scale epidemiological study on the prevalence and impact of dementia in LMICs. It was part of and functional to a large dementia research program. The findings or the systematic review, combined with existing needs led to the decision to conduct a prevalence study in two of the STRiDE countries, South Africa and in Indonesia.

Finally, the main limitation of the qualitative study (chapters 7 and 8), is that we included participants from an existing pool of recruited individuals for the validation study of the dementia diagnostic schedule. This may have introduced selection bias. However, because the same participants had time between the recruitment for the validation study and the qualitative study, they may have had a chance to reflect on the process and purpose of informed consent before being interviewed. This may have ultimately enriched their reports during the interview for the validation study. Secondly because the nature of the interview setup (e.g., the presence of video-maker), social desirability bias may have affected the responses of the participants leading them to give favourable answers. Nonetheless, to minimize this potential bias, the

interviews were conducted in an informal way and the interviewer adopted a non-judgmental approach.

Implications of findings and recommendations for future research

Bringing together the reported evidence from each of the conducted studies, we presented some implications and suggested directions for further research. Our findings in chapter 3 on the influence of genetic risk factors for AD on functional disruption in the brain highlight the importance for further research into identifying not only which variants lead to an increased risk of developing AD, but also what triggers the expression of clinical symptoms. While DNA genotyping, PRS calculation, and functional neuroimaging are becoming more readily available, their use remains mostly limited to research purposes. Therefore, future efforts to translate this into routine clinical practice are warranted. On the other hand, assessing clinical symptoms using properly developed and validated questionnaires is much more accessible and could provide a valuable alternative to more costly biomarkers to identify people at risk of AD. Here, SCD is a viable candidate that can be used to screen older adults both in the general population as well as for recruitment to clinical trials on disease-modifying. Our findings from chapter 4 highlights further research needs to develop a psychometrically valid and reliable questionnaire to assess SCD. We further recommend the cross-cultural validation of such a questionnaire, not only in different languages and cultures, but also in high, to middle, to low-income settings where responses and the understanding of self-expressed cognitive decline may differ between ethnicities, age groups, and socioeconomic levels in any given society.

In chapter 5 and 6 we examined the status and current need for innovative tools to diagnose dementia that would in turn facilitate the conduction of large-scale epidemiological studies on dementia prevalence and impact. Findings in chapter 5 highlight how using practical diagnostic tools could improve dementia identification and care provision for older adults living in the community and in nursing homes. Epidemiological evidence on dementia occurrence in high-income settings is outdated and it is extremely scarce in LMICs. Such evidence is indispensable to understand the nature of the condition, to characterize needs, and to identify barriers. Updated prevalence figures are needed to inform policy decisions, and to address the needs of people with dementia. Yet, the design and conduction of epidemiological studies has stagnated for the past 30 years (17). We first validated the short version of the 10/66 Dementia Diagnostic Schedule in two HICs in older adults in the community and in nursing home. An important implication of our results calls for precaution in using the short schedule in future studies.

Communicating individual results to participants is only advised upon approval of the relevant research ethics board. For future research, we propose to provide a pre-defined protocol that addresses practical and beneficial procedures for participants for further investigation by a clinician in case of being identified as a dementia case by the algorithm.

By demonstrating the acceptable sensitivity (87%) and specificity (61%) of the short schedule, we extend the evidence of the schedule's criterion validity, not only to high-income settings but also to diagnosing dementia in community-dwelling older adults and those living in long-term residential care settings. Our findings have an immediate practical implication because the validated short schedule and algorithm of the 10/66, along with data cleaning steps, the developed electronic data collection system and the Standard Operating Procedures (SOPs) that were put together during the validation phase in Switzerland, have been transferred to research collaborators in the STRiDE project to apply in a planned large-scale dementia prevalence study in two LMICs in Africa (South Africa) and Asia (Indonesia). This is a great example of north-south collaboration and demonstrable transfer of knowledge that would enrich data on dementia prevalence across continents and in diverse settings. Finally, our findings from the qualitative study have several practical implications. We demonstrated that participants may hold beliefs that could hinder their participation in research and that researchers should take into account the expected benefits of participants from the return of individual-specific research results. Our results indicate that it is extremely importance to put together an effective informed consent process, ensure proper training of the research team on the process of sharing study purposes and obtaining informed consent from participants.

Closing remarks

The set of publications that make up this PhD thesis presents an attempt to apply the approach of population neuroscience to explore different angles in AD and dementia research. The main aim was to investigate different problems and research questions in Alzheimer's disease and dementia. To that end, we deployed different research methodologies and approaches and aimed to apply the best methodological quality in the preparation, conduction, and reporting of each study. This PhD thesis falls squarely within the perimeter of population neuroscience, and can be regarded as one of the first structured research endeavours that met the ambition of blending, with reason, the methods and techniques of neuroscience and epidemiological disciplines and approaches, to "serve precision medicine and population health" (18).

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Chapter 10: Methodological contributions

This chapter presents the details of my methodological contributions to each of the presented chapters of this thesis. This is written in the first person, in order to provide the reader with a better idea of my exact role.

Contribution to the exploratory analysis of the relationship between PRS and intrinsic functional connectivity and cognitive functions (Chapter 3)

As the first and corresponding author of this manuscript, I was in charge of the conception of the research question and hypothesis as well as data cleaning and statistical analysis. I also took care of the write-up of the manuscript while coordinating with the co-authors in writing sections related to their contribution to the study. The study was conducted as part of my research visit to Goethe University – Frankfurt (GUF) between November 2020 and October 2021. Throughout the visit and working on the project, I was working closely and under the supervision of Dr. Silke Matura, head of the AG mHealth and Lifestyle Modifications lab at the department of Psychiatry and Psychotherapy at GUF. This manuscript has been submitted to Frontiers in Aging Neuroscience before the final defence of the PhD thesis and I will be the main author to take care of the peer-review process.

Contribution to the systematic review to evaluate the psychometric properties of SCD PROMs (Chapter 4)

As the first and corresponding author I conceptualized and managed the entire process of the systematic review. This work was carried out as a collaboration with two reviewers from the University of the West Indies and active members of the STRiDE project in Jamaica. Throughout the study, I managed the team of reviewers (MS and JR, besides myself) from start to finish. I was responsible for finalising the piloting of the search strategy, conducting the search in major medical databases, collecting and exporting records to the screening software, as well as preparing the data extraction and risk of bias tools. I was also responsible of the write-up of the manuscript. The manuscript has been submitted to BMC Systematic Reviews before the final defence of the PhD thesis and I will be in charge managing the peer-review process.

Contribution to the validation study of the Italian version of the brief 10/66 Dementia Diagnostic Schedule and Algorithm (Chapter 5)

As the first and corresponding author of this manuscript, I was in charge of the conception of the research question and hypothesis. I was also responsible of the write-up of the manuscript. The validation study was conducted as a collaboration between our research team at the Università della Svizzera italiana in Switzerland and the research team from the University of Turin in Italy. Throughout the writing and submission process, I was coordinating the role and contribution of the co-authors as well as the peer-review process. The manuscript is published at BMJ Open (http://dx.doi.org/10.1136/bmjopen-2020-045867).

Contribution to the systematic review to estimate the prevalence of dementia in LMICs (Chapter 6)

I was the second reviewer and second author of this published systematic review and meta-analysis. As the second reviewer, I contributed to the piloting of the search strategy, screening of titles and abstracts, screening the full-texts, data extraction, and risk of bias assessment. I also contributed to the meta-analysis and writing up of the methods and results sections during a research visit to the Brighton and Sussex Medical School to work on this part with the first reviewer and author, Dr. Nicolas Farina. The manuscript is published at Global Publish Health (https://doi.org/10.1080/17441692.2020.1792527).

Contribution to publications on the qualitative study on informed consents and return of individuals-specific research results (Chapter 7-8)

For the two published manuscripts on the qualitative study reported in chapter 7 and 8, I contributed to the revision of the final draft of the manuscript. I also provided further feedback and comments during the peer-review process. Both manuscripts have been published in high-quality, peer reviewed journals and can be accessed through the following links: Chapter 7: http://doi:10.3389/fpsyt.2021.656822; Chapter 8: http://doi:10.1002/gps.5416.