Longitudinal Patterns and Predictors of Cognitive Impairment Classification Stability

by

Cynthia McDowell

B.A., Simon Fraser University, 2017

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I acknowledge and respect the Lək ʷəŋən peoples on whose traditional territory the university stands and the Songhees, Esquimalt and W̱SÁNEĆ peoples whose historical relationships with the land continue to this day.

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Abstract

Introduction: Classifications such as Mild Cognitive Impairment (MCI) and Cognitive Impairment, No Dementia (CIND) are thought to represent the transitory, pre-clinical phase of dementia. However, increasing research demonstrates that MCI and CIND represent nonlinear and unstable entities that do not always lead to imminent dementia. Despite an increase in research examining patterns and predictors of cognitive impairment classification stability, this concept is still poorly understood, and the research remains limited. The present study was designed to address the existing limitations within the literature by utilizing a longitudinal repeated measures design to gain a more thorough understanding of CIND classification stability patterns, as well as identify predictors of future stability. **Objectives:** The objectives were to i) explore patterns of longitudinal stability in cognitive status across multiple assessments, and ii) investigate whether select baseline variables could predict 6-year cognitive status stability patterns. **Methods:** Participants included 259 older adults from Project MIND, a six-year longitudinal repeated measures design in which participants were classified as either Normal Cognition (NC) or CIND at each assessment. A latent transition analysis approach was adapted in order to identify and characterize transitions in CIND status across annual assessments. Participants were classified as either Stable NC, Stable CIND, Progressers, Reverters, or Fluctuaters. Multinomial logistic regression was then employed to test whether baseline predictors were associated with cognitive status stability patterns. **Results:** The sample demonstrated high rates of reversion and fluctuation in CIND status across years of study. Additionally, premorbid IQ, total number of medications, presence of arthritis, and CIND severity at baseline were all significantly associated with select CIND stability outcomes. **Conclusion:** CIND status was unstable for several years following baseline assessment, and

factors such as cognitive reserve may delay or protect against demonstrable cognitive impairment. Further, considering cognitive impairment severity (i.e., single versus multidomain impairment) at the time of initial classification may improve CIND classifications. Continued research on CIND stability is recommended to improve classification methodology and provide a framework for future identification and prevention.

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Introduction

Despite the growing prevalence rates and associated health care costs, dementia remains the only disease within the top ten causes of death without a steadfast method of prevention or cure (Pike et al., 2021). As dementia is characterized by substantial and irreversible neurological damage, early detection and prevention is paramount. Accordingly, dementia prevention research has spurred an increase in studies aimed at capturing the transitory, pre-clinical phase of dementia. Diagnostic criteria for various cognitive impairment classifications, such as Mild Cognitive Impairment (MCI) and Cognitive Impairment, No Dementia (CIND) have been developed in order to describe this state between normal cognition (NC) and dementia, in which cognitive decline is present beyond what is expected of normal aging but does not yet meet a dementia diagnosis (Petersen, 2004; Welstead et al., 2021). Such classifications are characterized by objective deficits in cognitive abilities that do not impact functional independence (Canevelli et al., 2017; Moradi et al., 2021). Notably, impaired objective test performance *and* a subjective complaint of cognitive decline is typically required for an MCI classification, whereas CIND classifications typically require impaired test performance *or* a subjective complaint (Plassman et al., 2011). Nevertheless, the criteria defining MCI and CIND have become synonymous over time, with each frequently classified using cognitive test performance in addition to a self or informant complaint. It is estimated that approximately 10-20% of individuals over the age of 65 experience MCI/CIND (Katayama et al., 2020; Makino et al., 2021), however long-term outcomes following classifications are heterogeneous.

Although originally conceptualized as diagnostic tools to identify those at risk of developing dementia, MCI and CIND represent nonlinear and unstable entities that do not always lead to imminent dementia. Indeed, these classifications are controversial and many individuals with MCI/CIND will not progress. In a meta-analysis consisting of 41 studies, Mitchell and Shiri-Feshki (2009) reported that only 5-10% of individuals classified with MCI convert to dementia, even after a 10-year follow-up. The researchers further reported that the annual conversion rate from MCI specifically to Alzheimer's disease (AD) is approximately 7%, and even fewer – approximately 2% – convert to vascular dementia. However, annual progression rates of MCI to dementia may differ depending on whether the sample is community-based (4-15%) or clinic-based (12-17%; Manly et al., 2008). Nevertheless, Mitchell and Shiri-Feshki (2009) concluded that, "MCI is neither necessary nor sufficient for later dementia" (p. 261). In contrast, approximately 37-67% of all MCI cases remain stable MCI without progressing (Pandya et al., 2016). Moreover, due to individual differences in diagnoses and progression, a substantial number of individuals with MCI fail to either convert to dementia or even remain MCI at a

subsequent time point (Vandermorris et al., 2011); research frequently reveals high rates of *reversion* from MCI back to NC (Aerts et al., 2017; Malek-Ahmadi, 2016; Overton et al., 2019; Pandya et al., 2016; Roberts et al., 2014; Xue et al., 2019). Thus, while it is true that some individuals classified as MCI will develop dementia, many will remain consistently MCI or even revert back to NC (Vandermorris et al., 2011).

Variability in Reversion Rates

A wealth of recent longitudinal studies confirms the common occurrence of reversion from MCI to NC, however the estimated prevalence rates of reversion are highly variable. Just as progression rates differ based on the sample under study, higher reversion rates are documented in community-based compared to clinic-based cohorts (Manly et al., 2008). Those in clinic-based samples tend to have a greater likelihood of progressing due to greater cognitive impairment, generating lower reversion rates (Petersen et al., 2014). Previous meta-analyses report reversion rates of approximately 25-30% in community-based studies, 8-14% in clinic-based studies, and 18-24% when combining the two populations (Canevelli et al., 2016; Malek-Ahmadi, 2016). An additional meta-analysis including both community and clinic-based samples similarly suggested that approximately 28% of individuals with MCI will revert back to NC over time (Xue et al., 2019). However, such results are inconsistent in the wider literature. For example, within clinic-based studies, some researchers have reported reversion rates as low as 8% (e.g., Aretouli et al., 2013; Tokuchi et al., 2014) and as high as 23% (Diniz et al., 2009), while Ganguli et al. (2011) reported that improvement/reversion in community-based studies ranged anywhere from approximately 6-53% over the course of one year. More recently, two community-based studies that followed individuals for approximately six years reported that only 2% (Hu et al., 2020) and 7% (Welstead et al., 2021) of individuals with MCI reverted back to NC. In comparison, Overton et al. (2019) – also following individuals for six years – reported an exceedingly high reversion rate of 58% in their community-based sample.

Several other factors may impact reversion rates such that MCI instability may be due to a variety of subject-based factors (e.g., individual differences in demographics, depression, fatigue at time of testing), diagnostic criteria (e.g., number and type of tests used, cut-off score variations), or study-based factors (e.g., practice effects, measurement error) (Malek-Ahmadi, 2016; Moradi et al., 2021; Shimada et al., 2019). Reversion may thus be due to true recovery of illness or brain tissue, issues in testing, definition, or individual factors impacting cognitive function such as sleep or nutritional deficits, affect, social anxiety, and more (Canevelli et al., 2016; Moradi et al., 2021). Regardless, reversion to NC is consistently reported as a plausible long-term outcome following MCI

classification. Altogether, conventional classifications of MCI – with the intended purpose of predicting dementia progression – are highly susceptible to false positives (Shimada et al., 2019) and may not be indicative of progressive neuropathology. Due to these discrepancies, the prognostic and clinical value of cognitive impairment classifications have been questioned.

Predictors of Reversion

To better understand reversion from MCI to NC, a recent influx of studies investigated various predictors of reversion (e.g., age, depression, hypertension). However, this research is still in its infancy and findings are generally inconsistent. Furthermore, in comparison to the large number of studies that examine predictors of MCI progression to dementia, few have focused on predictors of MCI reversion to NC (Pandya et al., 2017).

Demographic Predictors

Researchers have found that being of a younger age is associated with a higher probability of reverting from MCI to NC (Gao et al., 2014; Malek-Ahmadi, 2016; Olazarán et al., 2011; Overton et al., 2019; Pandya et al., 2017; Sanz-Blasco et al., 2021; Xue et al., 2019). However, others found no significant age differences for MCI reversion (Hu et al., 2020; Sachdev et al., 2013). Additionally, some researchers report that males are more likely to revert back to NC compared to females who are more likely to remain stable (Baiyewu et al., 2002; Roberts & Knopman, 2013). Others found no significant differences in gender (Gao et al., 2014; Hu et al., 2020; Roberts et al., 2014). Marital status has been studied less frequently, yet findings are equally inconsistent. Pandya et al. (2017) reported that being unmarried was associated with MCI reversion, while Xue et al. (2019) found that family and marital status had no statistical significance between groups. Conversely, Roberts et al. (2014) reported that being married was indeed associated with increased likelihood of reversion.

Cognitive Reserve

Cognitive reserve theory – predominately indicated by premorbid IQ or years of educational attainment – posits that age-related functional declines as well as progressive neuropathology may be mitigated by pre-existing cognitive processing approaches (Osone et al., 2016; Richards & Deary, 2005; Roe et al., 2007; Stern, 2006). However, cognitive reserve has scarcely been investigated in the context of MCI stability. Select studies have reported that individuals with higher education levels have a higher probability of reverting from MCI to NC (Sachdev et al., 2013; Tokuchi et al., 2014; Xue et al., 2019), whereas Han et al. (2012) found that those with less educational attainment were actually more likely to revert compared to those with high attainment. A separate study found that, while years of education did not significantly differentiate those who reverted, converted, or remained MCI,

premorbid IQ was significantly higher in those who reverted (Osone et al., 2016). Conversely, Brodaty et al. (2013) and Lawson et al. (2017) found no significant differences in premorbid IQ.

Chronic Conditions

Various chronic conditions have also been studied in relation to MCI reversion. Makino et al. (2021) suggested that diabetes and prediabetes may inhibit MCI reversion. It has also been reported that the risk of MCI progression to dementia was three times higher in those with diabetes compared to those without diabetes (Hu et al., 2020). Cardiovascular history and hypertension (Welstead et al., 2021; Xue et al., 2019), as well as a history of stroke (Xue et al., 2019) were also each associated with an increased likelihood of remaining MCI at follow-up. In contrast, Sachdev et al. (2013) reported no differences in cardiovascular risk factors between reverters and non-reverters but found that arthritis was associated with an increased likelihood of remaining MCI at follow-up (i.e., stable MCI). However, presence of arthritis has rarely been studied in the context of MCI stability, and additional research is required to corroborate such findings.

Neuropsychiatric Predictors

Associations have also been found for select neuropsychiatric symptoms, although the findings are conflicting and sparse. Some researchers reported that fewer anxious-depressive symptoms were associated with reverting compared to those with higher anxiety, depression, or apathy (Pandya et al., 2017; Sugarman et al., 2018). A recent study demonstrated that treatment of depression increased the likelihood of reverting from MCI to NC (Sugarman et al., 2018). Likewise, Welstead and colleagues (2021) found that higher baseline depressive symptoms increased the likelihood of reverting from MCI to NC – likely implying that depression at baseline influenced initial MCI classifications. In contrast, Overton et al. (2019) did not find that depression significantly predicted reversion, and Sachdev et al. (2013) further reported that mental health status (depression, anxiety, and use of psychotropic drugs) was not discrepant between those who reverted and those who remained stable MCI.

MCI severity vs. subtype

Generally, research has been fairly consistent regarding reversion in single vs. multidomain MCI; individuals reverted more frequently if they were classified as MCI based on a single objective cognitive test (i.e., demonstrated less severe impairment) compared to more than one cognitive test (Aretouli et al., 2013; Diniz et al., 2009; Ganguli et al., 2011; Koepsell & Monsell, 2012; Loewenstein et al., 2009; Makino et al., 2021; Pandya et al., 2016; Ritchie & Tuokko, 2010; Roberts et al., 2014). Conversely, research investigating the stability of MCI subtypes – amnestic MCI (aMCI) versus non-amnestic MCI (naMCI) – is inconclusive and scarce. Some studies have reported that those with

naMCI were more likely to revert back to NC compared to those with aMCI, with a significant proportion of naMCI individuals not displaying cognitive impairment in subsequent assessments (Koepsell & Monsell, 2012; Pandya et al., 2016; Roberts et al., 2014; Thomas et al., 2019). However, other studies reported that aMCI was associated with higher likelihood of reversion (Diniz et al., 2009), or that there was no statistical difference between the two (Han et al., 2012; Xue et al., 2019).

Limitations in the Literature

Study Duration

Despite a persistent effort to examine the stability of cognitive impairment classifications, this concept is still poorly understood, and the research remains limited. In particular, multiple studies exploring reversion – and it's predictive factors – from MCI to NC follow individuals over the course of one (e.g., Diniz et al., 2009; Ganguli et al., 2011; Kang et al., 2014; Moradi et al., 2021; Thomas et al., 2019; Tokuchi et al., 2014) or two years (e.g., Baiyewu et al., 2002; Sachdev et al., 2013), which is likely not long enough to identify classification stability and whether individuals are truly experiencing persistent, pathological cognitive impairment. In the evolution of dementia, one to two years is a relatively short period, and short-term follow-up studies are fallible to misinterpreting both the risk of reversion and conversion. Shorter periods of observation may obscure the identification of slowly progressing conditions, compared to longer follow-ups that may permit the detection of those with more milder forms of impairment which may otherwise go undetected (Aretouli et al., 2013). Thus, a 1-year follow-up is likely not sufficient to determine cognitive impairment stability long-term (Moradi et al., 2021), and Pandya and colleagues (2017) recommend longitudinal studies with follow-up lengths greater than three years. Despite the long prodromal phase of dementia, pathological cognitive decline is often only accelerated and detectable around four to six years (Hall et al., 2000; Wilson et al., 2011); it is therefore important to follow MCI trajectories for a prolonged temporal period.

Repeated Assessments and Fluctuation

Although some studies have employed longer study durations, they remain limited by the number of follow-up assessments – generally examining individuals only once, or seldom twice, following their baseline assessment. A limited number of studies (e.g., Aertz et al., 2017; Bielak et al., 2010; Overton et al., 2019; Roberts et al., 2014; Sanz-Blasco et al., 2021; Welstead et al., 2021) have evaluated long-term trajectories of MCI using multiple repeated assessments. Multiple assessments are advantageous to detect the shape of change as well as better distinguish measurement error from true change (Aretouli et al., 2013; Singer & Willett, 2003). Moreover, results derived from two assessments (i.e., baseline and follow-up) provide a narrow window into the course of MCI and are unable to detect

fluctuations between classifications. For example, Overton and colleagues (2019) demonstrated that most individuals who reverted to NC actually reverted back to MCI at a later follow-up. Sugarman et al. (2018) found a similar pattern in 29% of subjects who reverted to NC, and results from our lab also demonstrated that over 25% of subjects fluctuated between NC and CIND over five years (Bielak et al., 2010). This is important, as individuals who fluctuate between classifications have been previously documented as more prone to dementia progression (Lopez et al., 2012; Roberts et al., 2014). Petersen (2011) suggests that unstable MCI may represent a pre-condition that will manifest into stable MCI with time; those who revert from MCI back to NC at one point may still be at risk of returning to MCI or progressing to dementia in the future (Koepsell & Monsell, 2012). Thus, research remains inconclusive regarding 1) whether individuals classified as stable MCI stay that way for a long time and 2) whether individuals who revert to NC remain NC if followed for long enough (Pandya et al., 2016). Ultimately, changes in MCI status may be missed if 1) stability is characterized based on a single follow-up, 2) too much time has passed without an evaluation, or 3) individuals are not followed for long enough to track long-term outcomes. Instability and fluidity between MCI classifications can jeopardize the utility and validity of the MCI framework, and additional research is required if MCI is to be deemed a sound concept that can identify individuals at risk of future dementia (Overton et al., 2019).

Examination of CIND and Subtype

Although an abundance of studies examine reversion in *MCI* classifications, reports seldom examine other definitions of cognitive impairment. The classification of CIND includes MCI (Tuokko et al., 2003), but has been studied much less frequently. That said, classification criteria for MCI and CIND are exceedingly similar. Additionally, in their study comparing reversion rates using different MCI definitions (including CIND), Matthews and colleagues (2008) reported that reversion and maintenance prevalence remained similar regardless of definition. The researchers observed that the dominant outcome is usually reversion to normality (as opposed to stability or progression) regardless of definition, and most definitions were found to be unstable. Nevertheless, given the heterogeneous reversion rates reported in the literature, it is important to study different definitions to help increase overall clinical utility.

Furthermore, only in recent years have researchers begun studying the stability of cognitive impairment *subtypes* such as amnestic CIND (aCIND) and non-amnestic CIND (naCIND), although this research remains limited (Oltra-Cucarella et al., 2018). Amnestic CIND suggests clinically significant memory impairment (that does not yet meet dementia diagnostic criteria), but other

cognitive capacities such as language, executive function, and visuospatial skills remain intact (Katayama et al., 2020). In contrast, naCIND reflects a decline in one or more of these cognitive capacities but memory remains relatively preserved. While CIND, like MCI, is thought to be reflective of a prodromal stage of dementia, its subtypes are thought to be reflective of the underlying pathology. This subcategorization is contingent on the assumption that distinct pathological processes underlie the cognitive changes and prognoses (Diniz et al., 2009). It is proposed that aMCI may be a precursor of AD while naMCI may be a precursor for other dementia subtypes (Han et al., 2012); however previous studies have been relatively unsuccessful in demonstrating an unequivocal prognostic importance of cognitive impairment subtypes (Diniz et al., 2009) and additional research is required.

Importance of Additional Research

Given the complex nature of cognitive function – and the intricacies and variations among the NC, CIND, and dementia continuum – CIND classifications currently represent poor predictors of future dementia (Ritchie & Tuokko, 2010). Further, despite a significant number of individuals demonstrating reversion from CIND to NC, this transition is not fully understood – largely due to limitations in study methodology and design. Instability in such classifications can impede the ability to correctly identify individuals experiencing true, persistent pathological impairment (Bielak et al., 2010; Tuokko & Hultch, 2006). This warrants continued investigation of CIND stability in order to improve CIND as a clinical entity for detecting at-risk individuals. Therefore, it is important to follow individuals for several years using multiple repeated assessments to better understand transitions between CIND and NC, and to accurately identify factors associated with true stability. Continued research on this topic can improve classification methodology and provide a framework for future identification and prevention.

The Current Study

There is a pressing need to enhance the understanding of CIND stability, its non-linear and long-term trajectories, and differences amongst stability predictors, in order to clarify and increase accuracy of this pre-clinical intermittent classification between NC and dementia. Using six-year longitudinal data, the current study sought to gain a better understanding of CIND classification stability across time in order to further its clinical utility as a classification tool. The objectives were to i) explore patterns of longitudinal stability in cognitive status across multiple assessments, and ii) investigate whether select baseline variables could predict 6-year cognitive status stability patterns.

It was anticipated that the overall reversion rates (from CIND to NC) would be higher compared to rates typically reported for clinical populations, but likely lower compared to other

community-based reversion studies (i.e., an estimated reversion rate of approximately 5-20%), as the current study extracted those who fluctuated from those who reverted. It was also expected that several patterns of stability (i.e., reversion, stability, progression, fluctuation) – with relatively equal cell sizes – would be revealed across the six years of study. Such patterns would demonstrate the high levels of instability in CIND classifications and provide preliminary information on the optimal follow-up duration required to identify true CIND stability.

Several baseline predictors were expected to significantly differentiate patterns of stability. Amongst the demographic predictors, it was hypothesized that age would significantly predict CIND stability subgroups, such that those who were younger would be more likely to fluctuate or revert in their cognitive status. It was also hypothesized that CIND severity would significantly predict subgroup membership. Specifically, those classified as CIND-S at baseline were predicted to have a higher likelihood of reversion and/or fluctuation, whereas those classified as CIND-M were predicted to have a higher likelihood of CIND stability. Such findings would corroborate previous research demonstrating the more labile, unstable nature of single-domain impairment compared to multi-domain (e.g., Diniz et al., 2009; Loewenstein et al., 2009; Ritchie & Tuokko, 2010; Sachdev et al., 2013). Further, it was hypothesized that CIND subtype would significantly predict subgroup membership; however, no specific hypothesis regarding stability pattern likelihood were made, as previous findings have been largely conflicting. It was also hypothesized that educational attainment and/or premorbid IQ would be negatively associated with CIND stability, providing support for cognitive reserve theory. Additionally, it was hypothesized that multiple chronic conditions would significantly predict subgroup membership. For example, in accordance with previous research (e.g., Hu et al., 2020; Welstead et al., 2021; Xue et al., 2019), a history of diabetes or heart disease were anticipated to result in an increased likelihood of CIND stability. Conversely, no hypotheses were made for history of arthritis, as limited studies have investigated the association between arthritis and CIND, and the relationship between arthritis and cognitive health has been inconsistent in the wider literature (see Appenzeller et al., 2004; Baker et al., 2017; Wallin et al., 2012). Finally, it was hypothesized that depression and negative affect would significantly predict CIND outcomes, whereas positive affect may be insignificant due to the negativity bias, which suggests that positive states are less strongly associated with physical health compared to negative states (see Dua, 1993). However, no directional hypotheses were made for depression or negative affect as depression has been associated with both stability (Pandya et al., 2017; Sugarman et al., 2018) and reversion (Welstead et al., 2021).

Methods

Participants

The current study examined archival data from Project Mental Inconsistency in Normals and Dementia (MIND), a longitudinal repeated measures study assessing cognitive change in community-dwelling older adults. Project MIND was approved by the University of Victoria Human Research Ethics Board and was conducted in accordance with institutional guidelines. Participants resided in Victoria, BC and were recruited through local media advertisements soliciting volunteers who were concerned about their cognitive functioning but had not been diagnosed with a neurological disorder. Initial exclusion criteria included physician-diagnosed dementia or a Mini-Mental State Examination (MMSE; Folstein et al., 1975) score less than 24, current psychiatric diagnosis, psychotropic drug use, drug or alcohol abuse, a history of significant head injury (e.g., loss of consciousness), other neurological or major medical illnesses (e.g., Parkinson's disease, cancer), severe sensory impairment (e.g., difficulty hearing a normal conversation, difficulty reading newspaper-size print), and a lack of English language fluency. The sample initially consisted of 304 participants, however, individuals missing three or more follow-up assessments were excluded from the present study (see Figure 1). Therefore, data for 259 participants (178 females, 81 males) aged 65 to 90 years (m= 73.65; SD= 5.71) were included for the present analyses. At baseline assessment, participants were generally well educated (m= 15.20; SD= 3.08; *range*= 7–24 years of education), performed well on the MMSE (m= 28.85; SD= 1.11; *range*= 25–30), and were in relatively good health (total number of chronic health conditions: m= 2.93; SD= 1.93; *range*= 0–10).

Procedure

Project MIND utilized an intensive repeated measures burst design (Sliwinski, 2008; Stawski et al., 2016) for the first four years (i.e., Years 1–4) of data collection, followed by a single follow-up assessment at Year 6 to evaluate change in cognitive status. Participants were initially screened for inclusion and exclusion criteria via a telephone interview. Baseline testing occurred across seven sessions (one group session and six individual) scheduled over approximately three months. The group testing session was held at the university and the individual testing sessions were conducted in the participant's home. The first two sessions (one group and one individual) were used to obtain demographic and health information and to administer cognitive measures. Participants then completed a burst evaluation, consisting of five individual biweekly testing sessions that varied across days of the week and times of the day. Within these sessions, participants completed various assessments to measure performance across several health domains (e.g., cognitive, psychosocial, physiological). The

entire testing battery was repeated annually four times. During each annual wave, the measures were identical, and the order of presentation did not vary. Although Project MIND employed this intensive sampling involving weekly assessments within a given year, cognitive status data was collected only once per annum; the current study therefore restricted analyses to annual data and examined change in cognitive status from Years 1, 2, 3, 4, and 6. Attrition rates for the entire sample (N=304) were 11.0%, 3.5%, 4.5%, and 9% between Years 1–2, 2–3, 3–4, and 4–6, respectively.

Measures

Cognitive Status

CIND status was derived psychometrically each year according to participant's performance on five cognitive tasks. The cognitive performance tasks consisted of indicators for perceptual speed (WAIS-R Digit Symbol Substitution; Wechsler, 1981), verbal fluency (Controlled Associations; Ekstrom et al., 1976), vocabulary (Extended Range Vocabulary; Ekstrom et al., 1976), episodic memory (Immediate Free Word Recall; Hultsch et al., 1990), and inductive reasoning (Letter Series; Thurstone, 1962). Participants were classified as NC or CIND based upon deficits spanning the five distinct cognitive domains; subjects were classified as CIND if they scored at or below 1.5 SDs relative to age- and education-matched peers on any of the cognitive tasks. Age- and education-based norms were derived from an external sample of 445 adults, aged 65 to 94 years, from the Victoria Longitudinal Study (Dixon & de Frias, 2004). The normative comparison sample was partitioned into four age and education groups (*age* = 65–74 years and 75+ years; *education*= 0–12 years and 13+ years) with means and standard deviations computed for each of the five reference cognitive measures. Given the demographic match, the use of local norms (i.e., Victoria, BC) is preferable for more accurate comparisons across tasks (Bielak et al., 2010). The cut-off criterion for deriving cognitive status classifications (i.e., scores at or below 1.5 SDs according to appropriate normative data) based on objective cognitive testing represents a stricter criterion and has been widely recommended and used in clinical and experimental research (e.g., Lowenstein et al., 2009; Peterson et al., 1999; Petersen & Negash, 2008; Vandermorris et al., 2011). Participants were re-classified each year following baseline assessment using an identical and blind classification procedure.

Baseline Predictors

Predictors of CIND stability outcomes included 15 variables assessed at baseline and grouped by the following domains: demographic (age, sex, marital status), CIND characteristics (severity, subtype), cognitive reserve (premorbid IQ, educational attainment), chronic conditions (heart disease,

diabetes, arthritis, stroke, total number of medications), and neuropsychiatric symptoms (depressive mood, positive affect, negative affect).

Demographics. Participants self-reported their age, sex (male or female) as well as marital status (0= *married*, 1= *single*, 2= *widowed*, 3= *divorced*, 4= *separated*). Due to cell size concerns and restrictions posed by the statistical analyses, individuals who indicated 'single', 'widowed', 'divorced' or 'separated' were collapsed into a single 'unmarried' category.

CIND Severity and Subtype. Participants classified as CIND at baseline were further subdivided based on CIND severity and subtype. Severity was determined according to deficits on a single (CIND-S) cognitive measure vs. multiple (CIND-M) measures (i.e., two or more). Subtype was separately classified as amnestic CIND (aCIND) if the memory domain was impaired (i.e., Immediate Free Word Recall; Hultsch et al., 1990) or non-amnestic CIND (naCIND) if the memory domain was intact, regardless of single or multiple domain impairment.

Cognitive Reserve. Cognitive reserve was indexed using premorbid IQ as well as years of educational attainment. Estimates of premorbid IQ were computed based on the National Adult Reading Test (NART; Nelson, 1982), as word-reading ability provides a valid indicator of premorbid intellectual functioning for a number of conditions (Bright et al., 2002; Nelson & O'Connell, 1978), and the NART demonstrates high correlation with Full-Scale Intelligence Quotient (FSIQ; Blair & Spreen, 1989). The NART has been standardized for North American populations, demonstrated to accurately predict IQ and brain dysfunction regardless of differences in demographic variables (Blair & Spreen, 1989; Bright et al., 2002), and previously utilized as a cognitive reserve predictor of MCI stability (see Osone et al., 2016). The NART is scored out of 61 representing the number of words pronounced incorrectly. These error scores were then transformed into estimated premorbid IQ using the prediction equation (127.8 - .78) produced by Blair and Spreen (1989).

Chronic Conditions. Participants self-reported having a history of heart disease, diabetes, arthritis and/or stroke. Chronic conditions were examined independently and coded as dichotomous variables (0= *no*, 1= *yes*). To assess number of medications, participants were asked to bring a 'brown paper bag' containing their regular medications being taken at the time of testing. Researchers recorded all current medications including vitamins, over the counter, and prescribed medications (sedatives, cognitive enhancers, mood altering, cardiovascular, blood glucose altering). Each medication was summed to provide a total number of substances.

Neuropsychiatric Symptoms. Neuropsychiatric symptoms were self-reported and included depressive mood as well as positive and negative affect. Endorsed symptoms consistent with depressive

mood were assessed using a seven-item questionnaire that asked participants to rate the number of times in the past week they: *could not shake off the blues, felt depressed, felt lonely, felt their life had been a failure, had crying spells, felt fearful, and felt sad*. Items were rated on a four-point scale (0= *rarely or none of the time (less than 1 day)*, 1= *some or a little of the time (1-2 days)*, 2= *occasionally or a moderate amount of time (3-4 days)*, 3= *most or all of the time (5-7 days)*). A sum score was derived with higher scores indicating greater depressive mood. Affect was measured using the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) which includes twenty items comprising of ten adjectives indexing positive affect (e.g., interested, excited) and ten items indexing negative affect (e.g., distressed, irritable). Participants indicated how they felt during the past week on a 5-point scale (0= *Not at all*, 1= *A little*, 2= *Moderately*, 3= *Quite a* bit, 4= *Extremely*). A sum score was calculated with higher scores indicating greater positive or negative affect.

Statistical Procedure

A latent transition analysis (LTA) approach was adapted in order to characterize transitions in CIND status across the five annual assessments. Despite latent class analysis typically preceding the use of LTA, the current study utilized the formerly derived CIND status subgroups (i.e., NC or CIND) as the categorical latent variables for each annual assessment. LTA tests the hypothesis of 'no change between time-points', which assumes that status membership at time 2 is the same as status membership at time 1 (Lanza et al., 2010). First, cognitive status membership probabilities were calculated at $t \geq 1$ to reflect the proportion of individuals that belong to either cognitive status group at each time point. Second, transition incidents were examined to identify the timescale in which the sample transitioned from a latent status at *time t* to a different latent status at *time t+1*. Finally, a matrix of transition probabilities was generated to reflect the percentage of individuals who changed in their cognitive status (NC or CIND) from *t1* to *t2*, *t3*, *t4*, and *t6*. Participants were then assigned to one of six outcomes based on their 6-year cognitive status stability pattern:

1) *Stable NC*: Remained NC at each assessment
2) *Progressers*: Progressed from NC and stayed CIND
3) *Stable CIND*: Remained CIND at each assessment
4) *Reverters*: Reverted from CIND and stayed NC
5) *NC Fluctuaters*: Progressed to CIND but returned back to NC at a later assessment
6) *CIND Fluctuaters*: Reverted to NC but returned back to CIND at a later assessment

The second research objective examined baseline predictors of these CIND stability patterns. For the purpose of the present study, in which the intent was to examine (in)stability in CIND, those

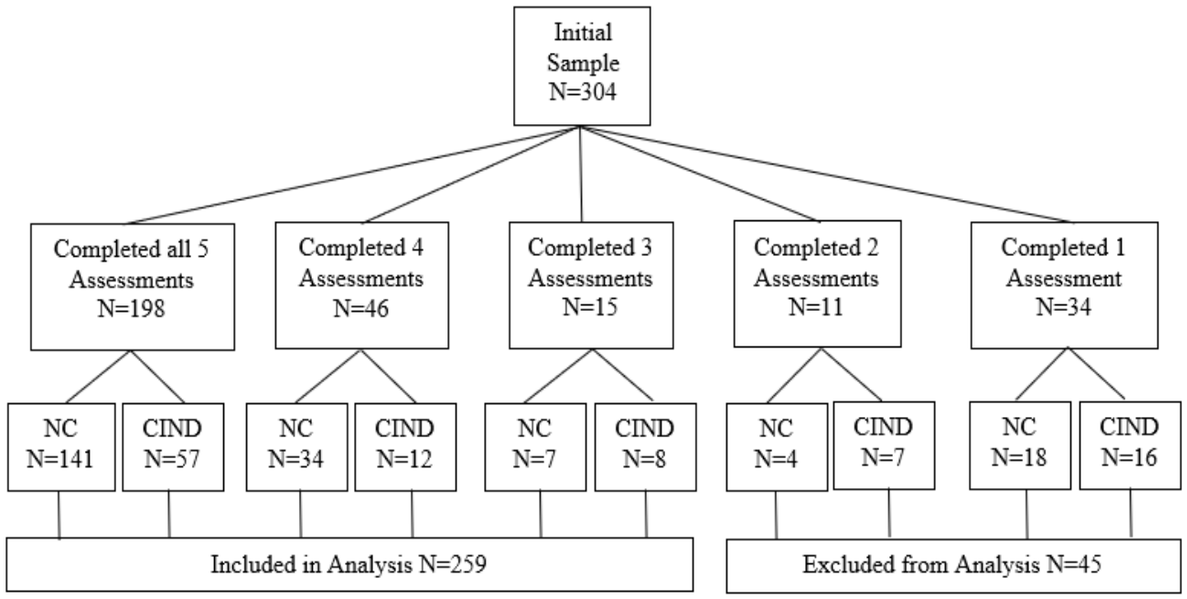
classified as Stable NC were excluded from further analyses. Additionally, NC and CIND Fluctuaters were collapsed into a single ‘Fluctuaters’ group for majority of the models; however, models that examined baseline CIND classifications (i.e., CIND severity and subtype) utilized the former CIND Fluctuaters subgroup. Multinomial logistic regression was employed to test whether baseline predictors were associated with increased likelihood of being classified as Reverters, Fluctuaters, or Progressers, relative to Stable CIND. Each predictor was investigated independently in univariate models, controlling for age (centered at 74 years) and sex, with two-sided significance tests set at $p<.05$ used for all analyses. Relative risk ratios were then derived for each significant predictor. Analyses were performed in R Version 4.1.1 (R Core Team, 2021) using various packages, including ‘nnet’ for logistic regressions (Venables & Ripley, 2002).

Results

Missing Data

The majority of the initial 304 participants completed all five assessments (Years 1, 2, 3, 4, and 6). However, 35% were missing at least one follow-up assessment. A non-significant (p>.05) Little's MCAR test suggested that cognitive status data were missing completely at random. Further investigation into the nature of missing values revealed that, 53% of the participants who did not return after baseline assessment (i.e., completed one assessment only) were NC, while 47% were CIND. Assuming data was missing completely at random, participants missing three or more assessments were excluded from analysis. Therefore, participants who completed at least three assessments – providing the ability to detect fluctuations in cognitive status – were included in the present analyses. See Figure 1 for a further depiction of missing cognitive status data.

Figure 1. *Missing data patterns across the five annual assessments*



Stability Patterns Across Years of Study

Participants (N=259) were classified into cognitive status subgroups at each wave of assessment based on their performance on five distinct cognitive domains. Table 1 displays the percentage of individuals classified as NC or CIND for each year of study. At baseline (Year 1), 182 participants were classified as NC and 77 were classified as CIND (see Table 2 for sample characteristics). A chi-square test of independence indicated that baseline cognitive status classifications did not differ by sex, $\chi^2(1)= 0.02$, $p= 0.90$. Additionally, distinct independent samples t-tests suggested that NC and CIND subgroups did not differ by age or total number of medications (p>.05); however, those classified as NC demonstrated significantly higher levels of education, $t(148)= 3.4$, $p< .001$ as well as scored higher on the MMSE, $t(123)= 2.2$, $p= .03$.

Table 1. *Proportions of cognitive status membership at each assessment*

	NC	**CIND**
YEAR 1	.70	.30
YEAR 2	.73	.27
YEAR 3	.74	.26
YEAR 4	.75	.25
YEAR 6	.76	.24

Table 2. *Sample characteristics as a function of baseline cognitive status*

	NC	**CIND**
Variable	*N=182*	*N=77*
Age (years)	73.3 (5.7)	74.5 (5.7)
Sex (% females)	69	68
Education (years)	15.6 (3.1)	14.2 (3.0)
MMSE score	29.0 (1.0)	28.6 (1.2)
[a]Medications	5.8 (3.5)	5.4 (3.3)

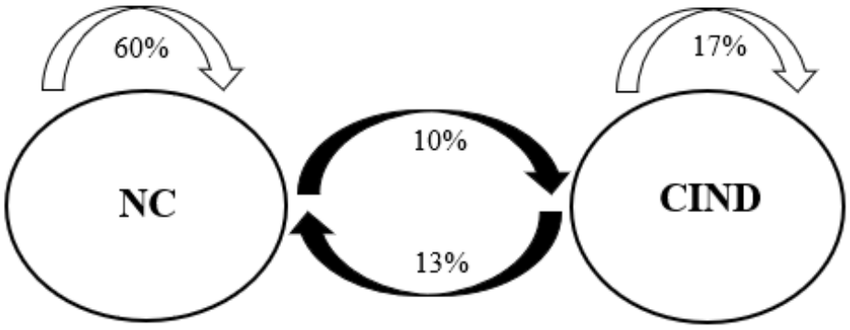
Note. NC = Normal Cognition; CIND = Cognitively Impaired, No Dementia.
MMSE = Mini Mental State Examination (Folstein et al., 1975).
[a]Self-reported number of total medications.

An LTA framework was then adapted to examine the stability in cognitive status membership across each wave of assessment. Table 3 represents a transition matrix, highlighting the instability in cognitive status. Year 4 demonstrated the greatest discrepancy between follow-up assessment and baseline classifications; the majority (51%) of those classified as CIND at baseline, as well as 16% of those classified as NC, changed cognitive status' by Year 4. A further investigation revealed that the majority (29%) of all transitions in the sample occurred at Year 2, followed by 28% at Year 3, 25% at Year 4, and 18% at Year 6. Figure 2 represents the sample's stability and transition patterns between Years 1 to 2.

Table 3. *Transition matrix displaying cognitive status parameters compared to baseline*

BASELINE		**FOLLOW-UP**	
		Status 1: NC	Status 2: CIND
STATUS 1: NC *(N=182)*	Year 2	**.85**	.15
	Year 3	**.86**	.14
	Year 4	**.84**	.16
	Year 6	**.88**	.12
STATUS 2: CIND *(N=77)*	Year 2	.43	**.57**
	Year 3	.43	**.57**
	Year 4	.51	**.49**
	Year 6	.44	**.56**

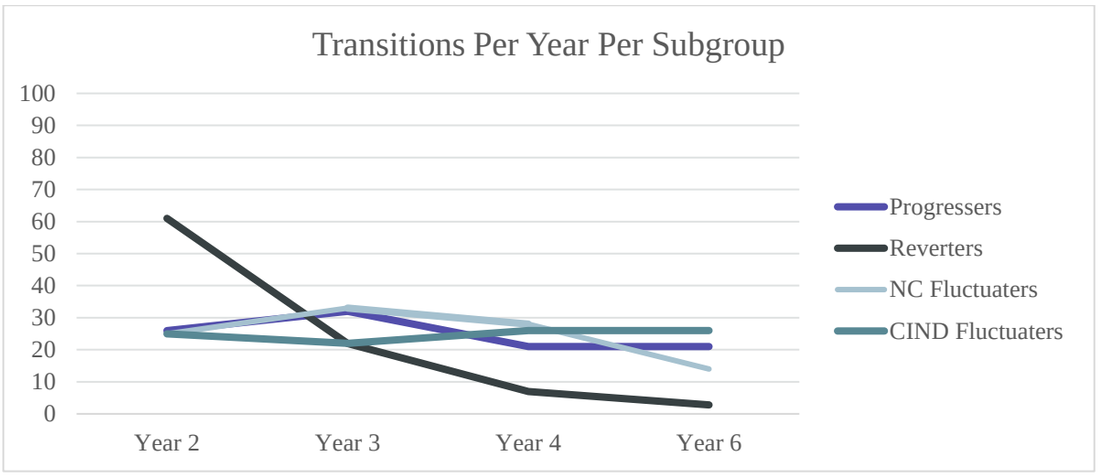
Figure 2. *Stability in cognitive status from Years 1 to 2*



Note. The white arrows reflect stable classification, the black arrows reflect transitions (i.e., progression or reversion) between cognitive statuses for the entire sample.

Of the initial 182 participants classified as NC at baseline, 126 (69%) remained NC even as long as six years following baseline assessment. However, 56 (31%) progressed to CIND and of these, 19 (34%) remained CIND while 37 (66%) reverted back to NC at a later assessment. Comparatively, of the 77 participants classified as CIND at baseline, 25 (32%) remained stable CIND across each annual assessment, whereas 52 (68%) reverted back to NC. However, more than half (56%) of these participants who reverted back to NC returned to CIND at a subsequent assessment. Participants were classified into one of six subgroups to reflect these cognitive status stability patterns: i) Stable NC (N=126), ii) Progressers (N=19), iii) Stable CIND (N=25), iv) Reverters (N=23), v) NC Fluctuaters (N=37; classified as NC at baseline) and vi) CIND Fluctuaters (N=29; classified as CIND at baseline). Figure 3 demonstrates the percentage of transitions that occurred each year per stability subgroup.

Figure 3. *Percentage of transitions at each year for each stability subgroup*



Baseline Predictors of 6-Year Stability Outcomes

The second research objective aimed to investigate whether select baseline variables could independently predict 6-year cognitive status stability. For the purpose of the present study, those classified as Stable NC were not included in these analyses. Additionally, NC and CIND Fluctuaters were collapsed into a single ‘Fluctuaters’ group (N=66) such that regression models compared

Progressers, Reverters, and Fluctuaters to Stable CIND. Of note, for CIND severity and subtype predictors, the sample was restricted to those classified as CIND at baseline (N=77). The variables included age, sex, marital status (N=68 married, N=65 unmarried), education, premorbid IQ, CIND severity (N=47 CIND-S; N=30 CIND-M), CIND subtype (N=60 non-amnestic; N=17 amnestic), heart disease (N=109 no; N=24 yes), diabetes (N=123 no; N=10 yes), arthritis (N=54 no, N=79 yes), stroke (N=123 no, N=10 yes), total number of medications, depressive symptoms, positive affect, and negative affect. Table 4 contains the parameter estimates for each univariate model. Of note, the model specifying stroke presence failed to converge due to cell size constraints (N=3 Reverters with a history of stroke); thus, parameter estimates for Reverters are excluded for this model. Baseline premorbid IQ, total medications, history of arthritis, and CIND severity significantly distinguished between select CIND stability subgroups. Those classified as Fluctuaters and Progressers were more likely to have a higher premorbid IQ at baseline compared to those classified as Stable CIND. Further, compared to Stable CIND, Fluctuaters were more likely to be taking fewer medications, and Progressers were less likely to have a history of arthritis. Additionally, of those classified as CIND at baseline, Fluctuaters and Reverters were more likely to be classified as CIND-S, whereas the Stable CIND subgroup was more likely to be classified as CIND-M. In fact, 72.4% and 73.9% of participants classified as CIND Fluctuaters and Reverters, respectively, were classified as CIND-S at baseline.

Subsequent relative risk ratios indicated that increases in premorbid IQ increased risk of fluctuating and progressing by 21% and 16%, respectively. For every one unit increase in medications at baseline, participants decreased their risk of fluctuating in their cognitive status by 3%, and those without arthritis were at a 15% increased risk of progressing relative to CIND stability. Finally, those classified at CIND-S were at a 22% and 19% increased risk of fluctuating and reverting, respectively, suggesting that those classified as CIND-M were at an increased risk of Stable CIND.

Further investigation into overall individual model fit revealed that only the premorbid IQ [$\chi^2(12)= 26.08$, $p<.01$; McFadden $R^2=.08$] and CIND severity [$\chi^2(8)= 15.60$, $p<.05$; McFadden $R^2=.09$] models (controlling for both age and sex) were predictive of overall stability classifications. The premorbid IQ model correctly classified 52.6% of participants, with 10.0% of Progressers, 0% of Reverters, 92.4% of Fluctuaters, and 28.0% of Stable CIND being correctly classified. Similarly, the CIND severity model correctly classified 52.0% of participants, with 34.8% of Reverters, 58.6% of Fluctuaters, and 60.0% of Stable CIND being correctly classified.

Table 4. *Univariate logistic regression models with stable CIND as referent group*

	Reverters (N=23)					Fluctuaters (N=66)					Progressers (N=19)				
	b	95% CI	SE	p	Exp(b)	b	95% CI	SE	p	Exp(b)	b	95% CI	SE	p	Exp(b)
Demographic															
Age	-0.10	-0.20, 0.00	0.05	0.06	0.90	-0.06	-0.14, 0.01	0.04	0.11	0.94	0.01	-0.08, 0.10	0.05	0.84	1.01
Sex	-0.46	-1.65, 0.74	0.61	0.45	0.63	0.03	-0.97, 1.03	0.51	0.95	1.03	-0.22	-1.47, 1.04	0.64	0.73	0.80
Marital Status	-0.82	-2.20, 0.56	0.70	0.24	0.44	-0.29	-1.38, 0.81	0.56	0.61	0.75	0.85	-0.64, 2.35	0.76	0.26	2.34
CIND characteristics															
CIND severity	-1.68	-3.01, -0.35	0.68	0.01*	0.19	-1.52	-2.72, -0.32	0.61	0.01*	0.22	--	--	--	--	--
CIND subtype	-1.09	-2.77, 0.60	0.86	0.21	0.34	0.36	-0.94, 1.65	0.66	0.59	1.43	--	--	--	--	--
Cognitive Reserve															
Premorbid IQ	0.06	-0.02, 0.13	0.04	0.12	1.06	0.09	0.03, 0.16	0.03	0.00**	1.09	0.19	0.08, 0.29	0.05	0.00**	1.21
Education	-0.05	-0.26, 0.15	0.10	0.60	0.95	0.07	-0.10, 0.24	0.09	0.41	1.07	0.21	-0.01, 0.44	0.12	0.07	1.23
Chronic Conditions															
Heart Disease	0.26	-1.29, 1.80	0.79	0.75	1.30	0.14	-1.08, 1.35	0.62	0.83	1.15	-0.35	-1.98, 1.27	0.83	0.67	0.70
Diabetes	-1.12	-3.54, 1.30	1.23	0.36	0.33	-0.40	-1.96, 1.16	0.80	0.61	0.67	-0.98	-3.35, 1.39	1.21	0.42	0.38
Arthritis	-0.17	-1.44, 1.11	0.65	0.80	0.84	-0.38	-1.43, 0.67	0.54	0.48	0.68	-1.62	-2.97, -0.27	0.69	0.02*	0.20
Stroke	--	--	--	--	--	-1.04	-2.55, 0.46	0.77	0.17	0.35	-1.45	-3.82, 0.93	1.21	0.23	0.23
Total Meds	-0.08	-0.25, 0.09	0.09	0.37	0.92	-0.14	-0.28, -0.00	0.07	0.04*	0.87	-0.03	-0.19, 0.13	0.08	0.73	0.97
Neuropsychiatric Symptoms															
Depression	-0.18	-0.40, 0.03	0.11	0.10	0.84	-0.07	-0.20, 0.05	0.06	0.26	0.93	-0.07	-0.25, 0.11	0.09	0.44	0.93
Pos Affect	0.01	-0.08, 0.10	0.05	0.86	1.01	0.03	-0.04, 0.10	0.04	0.39	1.03	-0.02	-0.10, 0.07	0.05	0.72	0.98
Neg Affect	-0.11	-0.28, 0.05	0.08	0.17	0.90	-0.08	-0.19, 0.03	0.06	0.16	0.92	-0.10	-0.28, 0.08	0.09	0.27	0.90

Note. The cell size for Reverters with a history of Stroke was too small (N=3) and the model failed to converge.
CIND=Cognitively Impaired, Not Demented; CI=Confidence Interval; Total Meds=Total Self-Reported Medications;
Depression=Endorsed Symptoms Consistent with Depressive Mood; Neg Affect=Negative Affect; Pos Affect=Positive Affect.
Stable CIND was coded as 0, Reverters coded as 1, Fluctuaters coded as 2, and Progressers coded as 3.
For CIND severity and subtype, Fluctuaters included only those classified as CIND at baseline (N=29).
All models controlled for both Age and Sex. ** p<.001; *p<.05.

Discussion

The present study was designed to address the existing limitations within the cognitive impairment literature by utilizing a 6-year study with multiple repeated assessments to gain a more thorough understanding of longitudinal CIND classification stability patterns, as well as to identify predictors of future stability. The primary findings show high rates of both reversion and fluctuation in CIND status. Additionally, logistic regression analyses identified a limited number of baseline predictors of CIND classification patterns. Premorbid IQ, total number of medications, presence of arthritis, and CIND severity at baseline were all significantly associated with select CIND stability outcomes.

Patterns of CIND Stability

In this community-based sample, 68% of those classified as CIND at Year 1 reverted from CIND back to NC at some point across the 6-year study. However, the majority of these individuals eventually transitioned back to CIND at a later assessment – highlighting the evident occurrence of CIND status fluctuation. In fact, the most common long-term stability pattern for those classified as CIND at baseline was indeed fluctuation, with 38% fluctuating between CIND and NC. Similar results were reported by Sugarman and colleagues (2018) in which 29% of individuals who reverted eventually transitioned back to MCI at a follow-up assessment. Such findings suggest that those who improve in their cognitive status remain at risk of re-transitioning to CIND if followed for long enough. Furthermore, fluctuation was apparent not only for those classified as CIND at baseline, but also for those classified as NC, generating a 26% fluctuation rate for the entire sample of older adults. This finding is important as few studies have followed individuals for long enough to account for such fluctuations, and instability/fluidity in the literature is likely underestimated.

Correspondingly, the current study's true reversion rate (i.e., reverted to NC and stayed NC) was 30%. This is consistent with previous meta-analyses that report reversion rates of approximately 25-30% in community-based studies. However, this was higher than predicted (i.e., 5-20%); it was expected that the rate of reversion would be lower given that the current study separately considered and extracted those who fluctuated from those who reverted. Further, Project MIND is composed of a relatively healthy sample, and it was anticipated that initial CIND classification would reflect stable pathological cognitive impairment rather than momentary poor cognitive performance due to external factors such as socioeconomic status. For instance, Welstead et al. (2021) followed a comparatively healthy sample for six years and reported a 7% reversion rate. Nonetheless, the current high reversion

rate suggests that CIND may not represent the prodromal stage of dementia, and provides further justification for continued research on factors associated with CIND reversion versus stability.

Previous studies have predominately examined cognitive impairment stability by employing a one-year study period and/or a single follow-up assessment which is likely to produce inaccurate stability patterns. The current study demonstrated that most transitions between cognitive statuses occur at Years 2 and 3 (i.e., one- and two- years following baseline assessment). Due to these transitions, cognitive status classifications by Year 4 were the least comparable to Year 1 classifications, suggesting that CIND status is likely to be unstable for at least four years following baseline assessment. In fact, 51% of those classified as CIND at baseline were no longer classified as CIND at Year 4. Likewise, 16% of those classified as NC at baseline were classified as CIND at Year 4. Such findings may explain the large range of reversion rates reported in the literature, as transitions from CIND to NC occur at various points in time. Consistent with previous recommendations (see Pandya et al., 2017), it is suggested that researchers assess individuals annually for at least four years in order to better determine and detect CIND stability.

Predictors of CIND Stability Outcomes

Demographic Predictors

Neither age, sex, nor marital status were significantly associated with increased likelihood of reverting, progressing, or fluctuating relative to CIND stability. This is in contrast to expectations in which age specifically was predicted to be associated with stability outcomes; previous studies have demonstrated that younger ages are more likely to recover from MCI back to NC (Gao et al., 2018; Xue et al., 2019), the prevalence of CIND classifications increase with age (Plassman et al., 2011), and older age is associated with increased incidence of progression from MCI to AD (Xue et al., 2019). However, the current findings are consistent with previous research reporting no significant differences between MCI stability and reversion for age (Hu et al., 2020; Sachdev et al., 2013), sex/gender (Gao et al., 2014; Hu et al., 2020; Roberts et al., 2014) or marital status (Xue et al., 2019).

Cognitive Reserve

Higher educational attainment has been previously associated with recovery from MCI to NC. It has been proposed that individuals with higher education levels may better understand and implement health knowledge and lead healthier lifestyles, thereby reducing MCI risk (Pandya et al., 2017; Xue et al., 2019). However, educational attainment within the current study – although significantly differentiating baseline cognitive status – was not associated with stability outcomes. In contrast, premorbid IQ was significantly associated with increased likelihood of being classified as Fluctuaters

and Progressers relative to Stable CIND. This is consistent with Osone and colleagues (2016) who similarly found that, while years of education did not significantly differentiate MCI subgroups, premorbid IQ was significantly higher in those who reverted. It was suggested that, compared to premorbid IQ – a more sensitive measure of cognitive reserve – educational attainment may have limited variance and is thus less sensitive to detecting an effect.

The results suggest that higher baseline premorbid IQ may delay or protect against recurrent CIND classification due to cognitive reserve. Individuals with greater reserve are posited to have a greater defense against the cognitive decline process prior to reaching a diagnosis threshold (Sachdev et al., 2013). For instance, in the current study, individuals were more likely to delay their CIND classification (i.e., be classified as NC at baseline) and progress at a later assessment compared to being classified as CIND at Year 1 (i.e., Stable CIND), independent of age or sex differences. Overall, higher baseline premorbid IQ, denoting greater cognitive reserve, may have exhibited protective effects against stable cognitive impairment. However, few studies have examined premorbid IQ and further research should explore this variable as an important predictor of long-term CIND stability.

Chronic Conditions

Arthritis was associated with decreased likelihood of progressing relative to CIND stability, whereas the total number of medications at baseline was associated with a decreased likelihood of fluctuating. Results suggest that individuals with arthritis or taking a higher number of medications were more likely to be classified as CIND at each of the 5 assessments including baseline.

Research has established a strong link between polypharmacy – the concomitant use of several drugs by a single individual (Morin et al., 2018) – and impaired cognition. Several studies (e.g., Hajjar et al., 2007; Maher et al., 2014; Rawle et al., 2018) have suggested that polypharmacy is strongly associated with poorer cognitive capacity and a diminished ability to perform instrumental activities of daily living. However, the association between arthritis and Stable CIND is more perplexing, as the relationship between arthritis and cognitive health has been inconsistent (see Appenzeller et al., 2004; Baker et al., 2017; Wallin et al., 2012). Previous studies have also suggested a potential relationship between arthritis, the long-term use of anti-inflammatory drugs, and cognitive health, in which anti-inflammatory agents are thought to protect against cognitive decline and AD (Grodstein et al., 2008; McGreer et al., 1990). However, Sachdev et al. (2013) similarly found that arthritis was associated with an increased likelihood of stable MCI and proposed that pain may be a potential mediator between arthritis and cognitive performance. This is corroborated by a separate study in which individuals with rheumatoid arthritis who reported higher pain also performed more poorly on cognitive tasks (Brown et

al., 2002). Future research should explore the role of pain (e.g., as a potential mediator) for CIND status stability and arthritis.

Given the significant medication findings, it is also surprising that arthritis was the only significant condition associated with stability outcomes. It would be expected that individuals taking more medications would likely have more chronic conditions (i.e., diabetes, heart disease, etc.) that may impact their cognitive health. However, these nonsignificant findings are likely the result of limited power and smaller cell sizes in both the outcome stability groups as well as in the predictors. For example, only 10 and 24 participants reported having a history of diabetes and heart disease, respectively. In contrast, several more participants reported having arthritis (N=79) compared to not (N=54). Due to these power limitations in the current study, future research should continue to investigate potential chronic conditions and comorbidities as predictors of CIND stability.

Neuropsychiatric Symptoms

No significant relationships were observed between CIND stability outcomes and depressive mood or affect. Researchers have suggested that MCI may be a misdiagnosis in those with depression, as treatment of depression increased the likelihood of reverting (Sugarman et al., 2018; Welstead et al., 2021). However, in general, associations between neuropsychiatric symptoms and CIND stability have been equivocal within the literature and further research is required.

CIND Severity and Subtype

Finally, baseline CIND severity was associated with a decreased likelihood of being classified as either Reverters or Fluctuaters, such that those with greater severity were more likely to be classified as CIND across the six years of evaluation. This corresponds with several previous studies indicating that it is more difficult to revert to NC with multi-domain cognitive impairment compared to single domain (Ganguli et al., 2011; Han et al., 2012; Loewenstein et al., 2009; Makino et al., 2021; Manly et al., 2008; Yaffe et al., 2006). However, the likelihood of CIND reversion or fluctuation was not significantly associated with CIND subtype.

Importantly, compared to subjects with less impairment, studies have shown that those with multi-domain cognitive impairment are also more likely to progress to dementia (Alexopoulos et al., 2006; Aretouli et al., 2013; Manly et al., 2008). Conversely, researchers have been generally unable to demonstrate the predictive validity of aMCI/naMCI in population-based samples. In their study, Ritchie and Tuokko (2010) reported that, with the exception of CIND-M, other classifications (e.g., aCIND) demonstrated poor sensitivity for dementia conversion. Indeed, in comparing predictive ability of different CIND models, the researchers found that CIND-M was the only diagnostic criteria to

significantly predict dementia five years later. The current study provides additional evidence that future stability in CIND status may be better predicted when the initial diagnosis is derived from multiple neuropsychological tests rather than memory tests (Han et al., 2012; Ritchie & Tuokko, 2010).

Severity for Improving the Clinical Utility of CIND

It has been suggested that individuals who are more variable in their cognitive course may be at higher risk of dementia progression, such that CIND fluctuation may represent an underlying pathological precondition (Lopez et al., 2012; Pandya et al., 2016; Petersen, 2011; Roberts et al., 2014). However, a final investigation revealed that the majority (72.4%) of those classified as CIND Fluctuaters were classified as CIND-S at baseline. Likewise, 73.9% of those classified as Reverters were also CIND-S at baseline. Therefore, it is likely that this fluctuation group was not a result of an underlying mechanism that will lead to eventual pathological cognitive decline, but rather a result of the transient, labile nature of CIND-S classifications (e.g., due to factors such as lifelong low performance). Classifying cognitive impairment based on poor performance on a single cognitive task may misclassify low-performing but otherwise cognitively intact participants (Brodaty et al., 2013). While CIND-S is subject to fluctuations and reversions, producing diagnostic (and prognostic) ambiguity, CIND-M classifications may be indicative of ‘at-risk’ individuals experiencing true pathological decline. In effect, CIND classifications could be maximized by considering CIND severity at initial assessment such that multi-domain impairment should be warranted in the initial classification criteria.

Implications

This research is timely given the aging population and the increasing prevalence of cognitive impairment and dementia. There is a pressing need for ongoing dementia prevention studies and methods for predicting those at risk of pathological decline. While dementia detection may be facilitated by the identification and quantification of select biomarkers (e.g., B-amyloid, tau-proteins) and neuroimaging techniques, these can be costly and invasive. Alternatively, routine screening for CIND status may represent a non-invasive and inexpensive tool for dementia detection. However, more research is needed to help differentiate false positives from those who remain stable CIND for a number of years and are at risk of true cognitive pathology. As CIND can be unstable or transitional, this necessitates that cognitive impairment classifications be sensitive yet accurate.

Individual Implications

The current study has implications for research and clinical settings as well as for individuals themselves. At this individual level, a false positive CIND classification can cause considerable

anxiety, uncertainty, and frustration given the general lack of treatment for CIND and dementia (Gomersall et al., 2017). Misclassifications may also lead to additional unintended negative consequences including stigmatization, discrimination, and over-medicalization (Canevelli et al., 2017), and can alter people's self-perceptions as well as life decisions (e.g., moving, retiring, looking into care facilities; Thomas et al., 2018). Moreover, if CIND is viewed as an imminent, unavoidable dementia indicator, then it may trigger the start of targeted yet unnecessary and potentially harmful treatment – particularly if pharmaceuticals are involved (Sugarman et al., 2018). However, rather than viewing CIND as an irreversible state leading to dementia, the current study provides support for recognizing CIND as a reversible, labile state. Illuminating the inherent instability in CIND classifications – even as long as six years following baseline assessment – demonstrates the heterogeneity in long-term outcomes and may help reduce over-diagnosis, stigma, anxiety, and unnecessary treatment. Further, identifying factors associated with future CIND stability may allow clinicians to better predict those at risk of dementia, as well as better inform their patients by providing a realistic prognosis and treatment recommendations.

Research Implications

The current study may also improve research and clinical standards for evaluating cognitive impairment. The present findings corroborate previous research demonstrating that CIND trajectories are highly variable; a substantial portion of individuals diagnosed with CIND (and synonymous classifications) will fluctuate in their cognitive status, reverting back to NC at subsequent assessments. Such unreliability in CIND classifications may disrupt the development of effective interventions for individuals with dementia, as inclusion of those who are on a reverting trajectory in research and clinical trials can bias findings (de Jager & Budge, 2005; Sugarman et al., 2018). Predicting stable CIND – representing an at-risk subgroup – across time may improve clinical trial research and the interpretation of results. Given the findings of the current study, dementia prevention research may be improved if individuals are classified by multi-domain impairment. Further, an increased understanding of the timescale in which CIND is most unstable (i.e., one- and two-years following baseline assessment) can help inform researchers on the minimal study period required to detect stability.

Clinical Implications

The identification of an at-risk group may contribute to early detection strategies for slowing cognitive decline. When the dementia cascade becomes realized, attenuating the process is challenging; early intervention of dementia – before prominent neuronal damage and notable symptomatology occurs – is generally viewed as most effective (Pike et al., 2021). Cognitive impairment in multiple

domains may improve classification methodology and represent an early and reliable marker for pathological impairment. A deepened understanding of predictors associated with CIND stability may also illuminate important risk (e.g., polypharmacy, arthritis) and protective (e.g., cognitive reserve) factors of cognitive impairment. A timely and accurate classification of CIND stability may aid healthcare professionals in supporting healthy aging and prolonging both independence and quality of life in older adulthood (Domínguez-Chávez et al., 2019).

The identification of individuals more likely to show positive outcomes (i.e., reversion or fluctuation) can also benefit the healthcare system by better allocating health resources. CIND stability information could be utilized in clinical practice to inform decisions about the frequency of future contact (e.g., decrease CIND-related visits) and the necessary monitoring required. Focused attention may thus be given to those who exhibit adverse trajectories (i.e., CIND stability) which may decrease disease burden for individuals, care-partners, and the larger healthcare system (Plassman et al., 2011).

Strengths and Limitations

The current study has several notable strengths including the study duration and number of repeated assessments; the four follow-up assessments (following initial baseline assessment) in addition to the extensive six-year study duration affords a more comprehensive investigation and understanding of CIND stability. Second, the current sample is composed of a relatively homogenous population of healthy individuals residing in the same geographical area. Thus, participants likely have similar life experiences such as education and socioeconomic status; using an alternatively heterogeneous sample to investigate CIND status stability would likely impact the accuracy of results and make predictions less precise (Pandya et al., 2017). Therefore, the sample homogeneity is ideal for modeling aging characteristics, as a broader and more diverse sample may complicate analyses due to cohort effects (Welstead et al. 2021). Third, the use of a community-based sample is advantageous to avoid the inherent cognitively impaired selection bias of clinic-based samples and is more representative of the general public (Ganguli et al., 2011; Ritchie & Tuokko, 2010). It has also been suggested that validating research criteria at the community level may be beneficial prior to incorporating into clinical practice (Ganguli et al., 2011). Fourth, the majority of studies within this literature have examined the recovery *rate* of MCI to NC but not recovery *factors* (Xue et al., 2019), while the present study looked at predictive factors for reversion as well as progression and fluctuation, relative to stability. Additionally, the current study is amongst the few that has examined the protective role of cognitive reserve in the context of MCI/CIND stability. Finally, the current study utilized a selective listwise deletion procedure in which only individuals with at least three of five assessments

were included in the analyses; this circumvented the need for multiple imputation – which may produce unreliable cognitive status classifications – while still permitting the examination of fluctuation between cognitive statuses.

However, the current study is not without limitations. First, despite the strengths of the healthy and homogenous sample, this may also restrict generalizability to the larger population. Nevertheless, although the sample was Caucasian, a previous CIND study (Plassman et al., 2011) reported no significant association between race and the incidence of CIND or dementia. A second limitation is the small cell sizes of CIND outcomes as well as some predictors (specifically chronic conditions and those with aCIND). Despite the reasonably large initial sample size, restricting analyses to those with three or more assessments and subsequently dividing the sample into different CIND outcomes resulted in small cell sizes that likely limited power to detect effects. Third, the current study was not able to determine which individuals eventually transitioned from CIND to dementia. Thus, although it is speculated that those who remained stable CIND represent an 'at risk' group, it was ultimately not possible to confirm this. Finally, the CIND outcomes were not fully validated as participants were not formally evaluated by a clinician. However, subjects were recruited based on an expressed subjective concern about their cognitive functioning (a common criteria used in clinical assessments of CIND), and the use of objective cognitive tests has shown to be relatively accurate and robust (Malek-Ahmadi, 2016).

Future Research

It is recommended that future research include information regarding dementia progression to confirm whether those classified as Stable CIND are indeed at risk of eventual dementia. Future researchers can also i) increase CIND sample size by utilizing a less conservative cut-off criterion (i.e., 1.0 SDs at or below age- and education-matched norms), ii) examine additional predictors of stability outcomes, and iii) investigate whether predictors can differentiate between CIND Fluctuaters and Reverters in order to identify whether these outcomes represent heterogeneous subgroups. Additionally, future analyses should examine the potential interaction between CIND severity and premorbid IQ as it may be likely that CIND-S represents a cognitively normal yet 'low-performance' group. Finally, future research should examine whether baseline predictors can predict Year 6 CIND status specifically, rather than predicting patterns across all years of measurement.

Conclusion

Cognitive impairment classifications such as CIND are characterized by prognostic and clinical heterogeneity. The current study exemplifies the considerable variability that exists across long-term outcomes, with several individuals reverting or fluctuating in their cognitive status across time. However, the relatively small number of individuals who remained stable CIND over the course of the study may provide important evidence for the identification of risk and protective factors, as well as implications for future research and targeted clinical management. The primary findings suggest that most individuals are unstable in their cognitive status for several years following baseline assessment, and factors such as cognitive reserve may delay or protect against detectable cognitive impairment. Moreover, considering cognitive impairment severity (i.e., single versus multidomain impairment) at the time of initial classification may improve CIND classifications. Due to the large number of individuals living with CIND or dementia, and the projected increase in these numbers, even small improvements in early detection or prevention procedures can have long and lasting impacts on the healthcare system and quality of life.

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