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Initial cognitive changes in Parkinson's disease

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Abstract

The focus on cognitive impairment in neurodegenerative diseases, including Parkinson's disease (PD), is shifting from the dementia stage to earlier stages of impairment, including mild cognitive impairment (MCI). This shift is driven primarily by the desire to improve long-term outcomes by delivering therapeutic interventions earlier in the clinical course, even pre-symptomatically in those at highest risk, and at the initial stage in the pathophysiological cascade that underpins common dementia syndromes. This manuscript focuses on key findings and challenges in studying earliest stages of cognitive decline in PD, including a detailed examination of neuropsychological testing, cognitive performance in early and prodromal PD, epidemiological research for PD-MCI to date, and expert recommendations for assessment.

Introduction

Similar to the focus and new diagnostic criteria for mild cognitive impairment due to Alzheimer's disease and preclinical Alzheimer's disease, the study of cognition in Parkinson's disease (PD) has shifted to increasingly early or initial cognitive decline, to better understand the unfolding process and potentially intervene before significant cognitive impairment takes hold. Crucial to this study is the administration of adequate neuropsychological testing and the application of sound epidemiological principles to provide valid prevalence and incidence rates.

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Neuropsychological Assessment of PD-MCI

The state of the art in how to assess neuropsychological status in PD has recently been reviewed[1] and the MDS criteria for MCI[2] address issues including cultural, linguistic and premorbid function issues in the determination of whether scores disclose relevant cognitive impairments or declines. For this reason we focus here on rarely addressed issues, specifically the numerous statistical and psychometric considerations that are not only common to all neuropsychological evaluation endeavors but are particularly salient to the assessment and diagnosis of PD-MCI.

Composite vs. Individual (Sub)Test Scores

One issue in determining the presence of MCI is which and how many neuropsychological test scores should be used, particularly because many tests yield multiple scores. The number of scores (and tests) selected should not be based on the expediency with which they permit one to “check the box,” but instead on the likelihood that the test is a reliable, valid and efficient measure of the construct.

A composite score is made up of several (sub)test scores combined in some way (e.g., by averaging). Composites (e.g., a working memory index score) often reflect factor scores derived from a measurement model. Generally, composite scores provide a more reliable and valid measure of a construct than item or subtest scores. This increase in reliability (a precondition for validity) stems in part from the fact that composites represent multiple samples of the cognitive or behavioral construct in question. Composites probably also better reveal changes in the construct that have meaningful implications (e.g., for functional capacity or clinically meaningful improvement/deterioration). Additionally, composites decrease the chance of Type I errors in diagnostic inference. Composites, however, also have potential liabilities. One concern is whether a composite has been constructed on the basis of a measurement model or simply on the basis of face validity; the selection of subtests or items contributing to the composite should be theoretically sound. Also, there needs to be clear understanding of the weighting of contributory scores in order to interpret composites. For example, a heavily weighted subtest score from a subtest for which the score distribution is heavily skewed can distort the composite score distribution in the direction of the skew. The measurement scale (e.g., nominal, ordinal, or interval), score distributions, and measurement errors of subtests or components also should be similar, because dissimilar properties can distort the composite. It is important to bear in mind that even if a composite is based on a combination of standardized scores (e.g., scaled or T-scores) then the standardization does not alter the shape of the underlying score distributions. It is also important to consider whether normative scores have come from reference or standardization samples with similar demographic characteristics (or are drawn from the same population); if not, the meaning of the composite becomes less clear because it becomes difficult to explain in what respect a score is abnormal. Importantly, identical test scores are not necessarily comparable and combinable simply because they have the same metric.

Perhaps one of the most critical issues for PD-MCI measurement and subtyping is that composites can obscure strengths and weaknesses in different cognitive domains and involve higher Type II error rates. This issue is in part why brief/screening measures yielding a

single score (often not norm referenced) are preferably avoided in PD-MCI diagnosis and why these measures afford only Level I assessment without possibility of PD-MCI subtyping[2] and are less accurate. The practice of evaluating multiple cognitive domains via one or two items from a screening test to subtype PD-MCI is to be eschewed, because these items may provide an unreliable sample of the cognitive domain or more strongly represent another cognitive domain[3].

Meaningful Change in Cognitive Test Scores, the Meaning of Test Score Abnormalities, and Implications for Cognitive Phenotyping

In evaluating the utility of tests used to identify PD-MCI, it is important to determine whether test score changes (e.g., as a function of disease progression or treatment) are clinically meaningful. One would expect that progression from PD-MCI to dementia represents a clinically meaningful change, and that a treatment resulting in reversion to normal cognition is similarly meaningful. Although there is no agreed-upon definition or criterion of what constitutes a clinically meaningful change in a test score, several approaches have been taken.

One approach determines whether there is a relationship between test score changes and changes in quality of life (QoL) or satisfaction with health status related to cognition or communication[4]. Although severity of PD-MCI does impact QoL[5], the approach may be limited because cognition-related changes in QoL may be difficult to detect reliably. One of the most commonly used QoL measure in PD, persons reporting worsening in cognition over 6 months declined an average of only 1.8 points (maximum score=100) on the PDQ-39 Cognition score, and this minimally important difference (MID) is likely unreliable given that the standard deviation was 15.6[6]. Furthermore, it is unclear how many of those reporting change as opposed to no change showed this MID. An approach to identifying a neuropsychological test score change representing a MID has not been used in PD; while such a project is of importance, the difficulty that persons with PD-MCI have in identifying difficulties in *specific* cognitive domains[7] needs to be taken into account.

Other approaches to determining whether a test score change is meaningful take a statistical tack and may utilize a corrected or uncorrected reliable change index (RCI) or standardized regression based formulas[8]. Practice effect-corrected RCIs have been reported for several tests in PD without dementia using an average test-retest interval of 18 months[9]. Test score changes should exceed the RCI to be considered meaningful. Another approach is to determine the base rate with which a test score change occurs in a reference sample; the rarer a change, the more likely it is meaningful. The base rate of impaired scores increases as the number of tests given increases[10]; thus, score changes should be considered as a function of both the univariate base rate and the number of tests administered[11]. The issue of Type I error in detecting abnormalities among multiple test scores can be addressed by using multivariate analytic methods that reveal whether a neuropsychological *profile* differs from the normative one[12], and additional procedures have been outlined to identify reliable test-specific deviations from the norm with adequate sensitivity when large test batteries are administered to patients[13] and when considering premorbid ability estimates[14].

When using multiple tests to phenotype PD-MCI, it is important to apply techniques that help identify meaningful changes and deviations from the norm, and minimize familywise Type I error rate, while maintaining sensitivity in the detection of test abnormalities. This enhances the phenotyping validity by reducing the probability that an abnormal test result occurred by chance or due to measurement error.

Computerized Testing

Neuropsychology has been criticized for failing to capitalize on technological advances[15]. Testing patients using locally-installed programs or web-based programs rather than pencil-and-paper tests offers potential advantages in terms of efficiency and cost. Recommendations have been offered to enhance the ethics, validity, and reliability of computerized testing[16]. While it is not logical to conclude that computerized testing of PD patients should not be done because of limited evidence to do so, it is the case that there is insufficient evidence to support the practice at this time, with the exception of a few test batteries. While the Cambridge Neuropsychological Test Automated Battery (CANTAB) has been extensively used in PD[17], studies have shown other test batteries such as Neurotrax[18-20] and Automated Neuropsychological Assessment Metrics (ANAM)[21] to have suboptimal sensitivity to cognitive impairment in PD in comparison to traditional tests or to lack adequate utility in detecting drug treatment effects or selecting candidates for deep brain stimulation. There is currently a move toward computer-assisted testing, wherein certain parts of tests (such as those not requiring manipulation of objects) can be administered via two tablet computers (one for examiner, one for examinee). This method is thought to enhance efficiency, speed of testing, and speed and accuracy of test scoring. Studies will need to be done to show comparability of these and traditional test methods in PD.

Resources for choosing cognitive tests

The IPMDS-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS[22]) has become the most widely used measure of PD impairment and severity. Divided into four separate Parts, the first item of Part 1 assesses Cognitive Impairment using a 4-point Likert scale ranging from no cognitive impairment to severe cognitive impairment precluding normal activities or social interactions. The concurrent validity of this single item to other measures of cognitive function was suboptimal[23]. The original manuscript[22] also includes an Appendix of Additional Scales that directs users to 8 detailed neuropsychological tests and provides usage ratings of either Recommended, Suggested or Listed for each scale.

The two IPMDS Task Force reports on diagnostic criteria for PD dementia and for mild cognitive impairment provide definitions on the types of cognitive domain impairment found with those diagnoses[2, 24]. In addition to the diagnostic criteria, both Task Force reports provide examples of cognitive tests that can be used to assess the specific cognitive domains. The list of possible tests is neither exhaustive nor meant to be interpreted as recommendations for use. Members of the task force produced a listing of cognitive tests recommended for use in a brief and more extended diagnostic examination[25]. The Parkinson

Study Group Cognitive/Psychiatric Working Group provided a review of tests commonly used in clinical trials and made the final recommendation for the use of a brief screening measure, the MoCA[26]. Other reviews have listed the strengths and weaknesses of different cognitive assessment measures and made recommendations for their use[27, 28]. Finally, a recent review of cognitive screening measures was conducted by the IPMDS Rating Scales Review Committee and followed a standardized literature search methodology and used an established pro forma for scale evaluation[29].

Another available tool is a subset of tests from the National Institutes of Health Toolbox for the Assessment of Neurological and Behavioral Function (http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox). The NIH Toolbox-Cognition Battery[30] is a collection of seven primary tests (Flanker Inhibitory Control and Attention Test, Dimensional Change Card Sort Test, Picture Sequence Memory Test, Picture Vocabulary Test, Oral Reading Recognition Test, Pattern Comparison Speed Test, List Sorting Working Memory test) designed to assess five cognitive domains: Executive Function, Episodic Memory, Language, Processing Speed and Working Memory. Test administration is computerized, requires approximately 30 minutes, is available in English and Spanish versions, and the tests do have normative data with standard scores[31]. A major drawback of this resource is its Anglo-centric focus, with the majority of validation studies conducted on North American samples.

A similar problem of Anglo-centric focus is found for another tool: the National Institute for Neurological Diseases and Stroke Common Data Elements (CDE) (https://www.commondataelements.ninds.nih.gov/PD.aspx#tab=Data_Standards). The NINDS CDE was developed to provide a set of data standards for use in neurological clinical research. PD is one of the diseases included in the CDE, and one of the PD modules is cognitive tests. The PD CDE for cognition includes 12 cognitive assessments listed; none were rated as core assessments, but all were rated as supplemental assessments.

Although there are many tools available for assessment of cognition in PD and their utility in research and clinical settings, each source of information has its limitations. The most common limitation is that many reviews are focused on assessments developed in or normed with English-speaking samples, and the adequate norming of cognitive measures is essential to interpretation of performance and adequacy of diagnostic classification. If the scale does not have applicable normative information for a given sample, the utility of that scale is greatly diminished. Additionally, many of the reviews are limited to screening measures or brief assessments of cognitive abilities. To our knowledge, no review has attempted to present clinimetric information on the vast number of neuropsychological tests designed to assess single cognitive functions, or are very selective in which individual function tests are included in the review. Finally, many of the reviews do not take a standardized approach to the review process or the resultant recommendations, although several recent reviews[27,29,28] are exceptions in that they follow either a standard approach to the review process or a standardized recommendation method.

Epidemiology of PD-MCI

Prevalence of PD-MCI

The prevalence of PD-MCI among non-demented patients with PD (Table 1), mostly in tertiary clinics varies widely (9-54%)[32-43], likely related to variability in PD-MCI criteria used. However, even those studies using the IPMDS Task Force Level II criteria for PD-MCI (published in 2012) and enrolling newly diagnosed, untreated PD report PD-MCI prevalence with substantial variation, from 20-41%[32-35]. This variability may relate to differences in the studies' operationalization of the IPMDS criteria; the criteria leave the choice of tests and cutoff score to the discretion of the investigator. Studies not using the IPMDS criteria have used various criteria to define PD-MCI (Table 1) and reported a lower, but still broad range, of prevalence estimates among newly diagnosed individuals: 9-24%[36-39]. Cross-sectional cohorts of patients with PD, enrolling patients with no restriction on disease duration, report a higher prevalence of PD-MCI, up to 55%[40-42, 44]. A large study incorporating data on 1346 patients without dementia of highly variable disease duration from 8 different centers found a prevalence of PD-MCI of 26%[45]. In this study a classification of PD-MCI required an average z-score within any one cognitive domain <1.5.

Incidence of PD-MCI

There are fewer studies of the incidence of PD-MCI compared with prevalence (Table 2). Most of these longitudinal evaluations followed early, initially untreated patients. Among those with normal cognition at baseline, one-year PD-MCI incidence in this population has been estimated to be 10%[34], rising to 20-30% over subsequent years[32, 34, 35, 46]. These rates are not reflective, however, of the proportion developing cognitive impairment, as they exclude those participants transitioning to dementia. They are also likely underestimates due to substantial attrition in participants over time, which is likely non-random with respect to disease progression, including cognitive decline. Pigott et al[47] studied cognitive evolution in a cohort of PD patients with variable disease duration (averaging 5 years) and normal cognition at baseline and reported Kaplan-Meier estimates of PD-MCI risk rising to 43% total at 6 year follow-up.

Focusing on cognition in *de novo*/early PD specifically, in a population-representative cohort with newly diagnosed parkinsonism and PD the UK, 36% of patients had cognitive impairment based on the Mini-Mental State Examination (MMSE)[43]. Follow-up of patients confirmed to have had PD for 3-5 years found that 10% developed dementia on average 3.5 years after PD diagnosis, and 57% showed evidence of lesser cognitive impairment[48]. In another UK cohort of newly diagnosed PD patients and age-matched healthy controls (HC), and applying International Parkinson and Movement Disorders Society (IPMDS)-recommended PD-MCI criteria[2], the frequency of PD-MCI was 43% using Level II criteria applied at 1.5 SDs below normative cognitive test values. Memory impairment was the most common domain affected (15%) [49]. The evolution of PD-MCI over 3 years was also assessed: applying Level II criteria 41% cognitively declined, 15% improved, and 19% fluctuated [50]. A single-center cohort study in Germany found that while PD patients performed significantly worse than HC on multiple cognitive tests at baseline, there were no

significant between-group differences in cognitive changes over 24 months. MCI rates of 15-20% have been reported in other de novo PD cohorts [36, 38].

Parkinson's Progression Markers Initiative (PPMI) is a multi-site longitudinal study of early, untreated PD patients and HC. At baseline, 22% of the 423 PD patients met the recommended screening cut-off for cognitive impairment (CI) on the MoCA (<26), but only 9% met detailed neuropsychological testing criteria for PD-MCI Level I impairment). Estimated rates of CI might be higher when using a screening instrument versus a cognitive test battery, as recommended cut-off scores for screening instruments typically prioritize sensitivity over specificity[51]. Applying the recommended formal IPMDS MCI Task Force criteria for MCI[2] to the PPMI cohort at baseline, only 2% of PD patients met criteria for MCI, due to infrequent recording of cognitive decline by the site investigators[39]. The discrepancy between the reporting of cognitive decline and actual performance on cognitive tests may be due to lack of patient awareness of early, mild cognitive changes in PD[7], or that the chosen cut-off points on neuropsychological tests over-identify patients as having cognitive impairment. The low reporting rate of cognitive decline raises questions regarding the value of including this criterion when diagnosing PD-MCI, a concern which has been considered previously[36, 52]. It also raises the question about how best to document significant cognitive functional impairment - an essential distinction between dementia and MCI (discussed in greater detail in previous manuscript). Finally, the low agreement between a screening instrument (i.e., the MoCA) and a detailed cognitive battery results demonstrates that the two methods of assessing cognition are not interchangeable.

In longitudinal analyses of the PPMI cohort, cognitive impairment was diagnosed in 15-38%, depending on the criteria applied, of participants at year 3. This means that over the first several years of the disease cognitive impairment increases in frequency by 50-200%[53]. The results are consistent with the relatively high frequency[36, 49] and worsening over time[48] reported in other early PD cohorts.

Cognition in prodromal or at-risk PD

The Honolulu-Asia Aging Study identified cognitive dysfunction (i.e., executive impairment) as one of several potential risk factor for future development of PD[54]. The Parkinson Associated Risk Study (PARS) assessed cohorts of healthy adults with and without hyposmia to characterize individuals at risk for PD. Individuals with both hyposmia and reduced dopamine transporter (DAT) binding had lower mean scores for global cognition, executive function/working memory, and memory compared with all other participants[55]. Combining hyposmia with relative impairment on specific cognitive domains increased the odds of dopamine transporter binding reduction compared to hyposmia alone. This study provides evidence that changes in global cognitive abilities, and specifically executive function/working memory, are present in individuals at risk for PD. In longitudinal analyses of this prodromal cohort, including 8 converters to PD, baseline cognitive scores did not significantly predict conversion to PD, but converters performed numerically worse on 5 of the 6 cognitive domains assessed[56]. In addition, lower baseline DAT binding among hyposmics predicted greater future decline over several years in processing speed/attention, and hyposmia itself predicted greater future decline in language and memory abilities.

Several studies have demonstrated cognitive deficits or cognitive decline in idiopathic REM sleep behavior disorder (RBD)[57, 58]. The PPMI also has enrolled prodromal LBD disorder participants: RBD (n=39); hyposmia (n=26); and non-PD mutation carriers (LRRK2 G2019S, n=88 and glucocerebrosidase (GBA) gene mutations, n=38). At baseline the RBD group performed significantly worse than the hyposmic and mutation carrier groups on tests of attention and visuospatial functioning, and the RBD group also performed worse than the hyposmic group on a test of global cognition[59]. Hyposmics and non-PD mutation carriers did not differ from each other, although a previous study did find worse cognitive performance in unaffected G2019S LRRK2 carriers[60]. These results suggest that among individuals across a spectrum of risk for PD, cognitive function is worse among those with RBD, which is the disorder most strongly associated with future risk of PD or dementia with Lewy bodies (DLB).

A recent study examined trajectories of daily functioning, and motor and non-motor features, in the 23 years preceding a PD diagnosis (n=109) in a nested case-control study within the prospective Rotterdam study[61]. From 7 years before diagnosis onwards, prediagnostic PD cases more commonly had problems in instrumental activities of daily functioning and more frequently showed subtle cognitive deficits in conjunction with subtle motor deficits. Another analysis of the same cohort also demonstrated that impairment in multiple cognitive domains in non-demented individuals is predictive of incident parkinsonism over a period of more than 8 years[62].

A recent review on cognitive changes in prodromal PD concluded that cognitive decline may occur in a substantial number of individuals who have the potential for developing PD[63]. Executive function in particular and, less frequently, memory scores are reduced. Additional prospective, longitudinal studies could clarify whether cognitive, and specifically executive, decline might be added to the prodromal non-motor symptom complex.

Risk factors for PD-MCI

Longitudinal studies offer the opportunity to identify risk factors for future development of PD-MCI. Not surprisingly, poorer cognitive performance and older age are associated with a higher risk of developing PD-MCI[36, 42, 47]. In particular, poorer performance on language, short-term recall and working memory tasks predicted future development of PD-MCI[47]. Other clinical features that have been associated with a higher risk of developing cognitive impairment include poorer olfactory performance, RBD, depression and greater motor impairment[42, 46]. Biomarkers have been found to have added predictive value, in particular APOE genotype, low CSF Abeta:total tau ratio, and lower putaminal DAT asymmetry[46].

Although not strictly speaking risk factors, a number of clinical and demographic variables have been found to be associated with the state of PD-MCI. Older age and more advanced motor impairment[32, 38, 39, 45] have been identified as features of patients with PD-MCI, consistent with the longitudinal studies. Studies also suggest that the axial symptoms and bradykinesia (i.e., postural instability gait difficulty [PIGD] phenotype) is associated with mild cognitive impairment[64]. Interestingly from a pathophysiological point of view, comorbidities that represent vascular risk factors (diabetes, hypertension and hyperlipidemia) have been associated with PD-MCI in cross-sectional study, as has more

white matter hyperintensity on brain MRI[65]. These findings may reflect multiple pathologies contributing to PD-MCI, including vascular disease.

Prognosis

PD-MCI has been shown to be an entity with highly variable prognosis, which probably reflects in part the heterogeneity of its substrate. Over a period of several years none of the possible outcomes (reversion to normal cognition, stability in a state of mild cognitive impairment or conversion to dementia) is rare. PD-MCI is unequivocally a risk factor for the development of dementia; this has been shown in multiple studies and Pigott et al[47] found a universal conversion from incident PD-MCI to dementia over 5 years in a cohort with average age of 69 years and an average disease duration of 5 years at study entry. The prognostic importance of PD-MCI is clear even in those who revert to normal cognition after PD-MCI has been diagnosed – these individuals appear to be on the transition edge between PD-MCI and normal cognition, and the fluctuation between the two states could reflect performance variability related to a number of factors (for example sleep quality, mood, medication state, motivation). Reversion to normal cognition from PD-MCI has been found to be associated with better cognitive performance, particularly in visuospatial tasks, and higher levels of apathy at the baseline assessment[35]. Conversion to dementia is more common when PD-MCI has been persistent over more than one evaluation[34].

Conclusions

Significant progress has been made recently in our understanding of the frequency, features, course and risk factors for PD-MCI, with a shift to studying patients from the time of disease onset and even in the prodromal phase. Although estimates vary depending upon definition and ascertainment and recruitment methods, PD-MCI prevalence commonly ranges from 25%-30%. Executive dysfunction is not only common in PD-MCI but may be seen in persons having the potential to develop PD. The large number of available, well-studied neuropsychological tests is beneficial in some ways, but challenges interpretation and generalizability of the results. There are numerous complexities and unresolved issues in the assessment of cognitive abilities in the PD population that need to be addressed through additional research or consensus opinion for the study of PD-MCI to continue to move forward.

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Table 1

Studies reporting the prevalence of PD-MCI

Population	Author	Year	Criteria for PD-MCI	Mean Age	N	Prevalence
Newly diagnosed						
	Domellof[33]	2015	IPMDS Task Force Criteria level II Modified – only one language task	70	136	41%
	Santangelo[35]	2015	IPMDS Task Force Criteria level II	59	76	33%
	Pedersen[34]	2017	IPMDS Task Force Criteria level II	68	178	20%
	Broeders[32]	2013	IPMDS Task Force Criteria level II	66	123	35%
	Aarsland[36]	2009	Non-demented, One z-score <1.5 SD below expected	68	196	19%
	Foltynie[43]	2004	Impairment on at least one of three neuropsychological tests	71	159	(36%)*
	Muslimovic[37]	2005	Score >2SD below normal on at least 3 tests.	66	115	24%
	Poletti[38]	2012	Impairment on one or more tests	67	121	15%
	Weintraub[39]	2015	<1.5 SD below normal on at least 2 tests	62	415	9%
Cross-sectional						
Mean duration 11.7 years	Janvin[44]	2003	Score >2 SD below control group on any one test from a battery	71	76	55%
Mean duration 5.5 +/− 4.5 years	Wang[42]	2014	Impairment in any of 4 cognitive domains and not qualifying for dementia by IPMDS criteria.	65	901	22%
Duration not stated	Monastero[41]	2012	Score below normal on at least one test in a battery	69	290	54%
Mean duration 5.2 +/− 4.6 years	Marras[40]	2013	IPMDS Task Force Level II	71	139	33%

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Table 2

Studies reporting the incidence of PD-MCI

Population	Author	Year	Criteria for PD-MCI	Mean Age at baseline†	Normal cognition at baseline (N)	Cumulative Incidence (%)**					
						Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Newly diagnosed											
	Pedersen[34]	2017	IPMDS Task Force level II	72	142	10% (/139)		23% (/135)		29% (/128)	
	Santangelo[35]	2015	IPMDS Task Force level II	59	51		29% (/41)		33% (/42)		
	Schrag[46]	2017	≥1 test >1.5 SD below normal, no functional impairment	61 (MCI + no MCI)	314		16% (/314)				
	Broeders[32]	2013	IPMDS Task Force level II	65	80			37 (/63)		15 (NS)	
Cross-sectional											
Average 5 years duration	Pigott[47]	2015	IPMDS Task Force level I	69 (MCI + no MCI)	141	8*	19*	28*	36*		43*(/55)

*Kaplan-Meier estimates of PD-MCI risk

**Denominators are all individuals still followed at the given year, including cognitively normal, MCI or dementia.

†Among individuals without MCI at baseline unless otherwise indicated