Published Ahead of Print on December 1, 2021 as 10.1212/WNL.0000000000013017

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The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000013017

Predictors of Incident Mild Cognitive Impairment and Its Course in a Diverse Community-Based Population

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Number of characters in title: 105

Abstract Word count: 250

Word count of main text: 3881

References: 43

Figures: 2

Tables: 5

Supplemental: Strobe Checklist

Statistical Analysis performed by: Statistical analysis was performed by Milou J. Angevaare, MD (Amsterdam UMC) and Jet M.J. Vonk, PhD (Columbia University)

Search Terms: [39] MCI (mild cognitive impairment), [54] Cohort studies, [59] Risk factors in epidemiology, [205] Neuropsychological assessment

Acknowledgements: This manuscript has been reviewed by WHICAP investigators for scientific content and consistency of data interpretation with previous WHICAP Study publications. We acknowledge the WHICAP study participants and the WHICAP research and support staff for their contributions to this study.

Study Funding: Data collection and sharing for this project was supported by the Washington Heights-Inwood Columbia Aging Project (WHICAP, PO1AG07232, R01AG037212, RF1AG054023) funded by the National Institute on Aging (NIA). This publication was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number UL1TR001873. Mirjam I. Geerlings was funded by a grant of Alzheimer Nederland (grant number WE03-2017-07).

Disclosures: The authors report no disclosures relevant to the manuscript.

ABSTRACT

Objective: To investigate socio-demographic and medical predictors of incident mild cognitive impairment (MCI) and subsequent course of MCI at follow-up, including sustained MCI diagnosis, classification as cognitively normal, and progression to dementia.

Methods: Within a community-based cohort, diagnoses of MCI were made using a published algorithm. Diagnosis of dementia was based on clinical consensus. Cox regressions estimated hazard ratios of incident MCI associated with several predictors. Modified Poisson regressions estimated relative risks associated with predictors of diagnostic status at follow-up after incidence.

Results: Among 2903 cognitively normal participants at baseline, 752 developed MCI over an average of 6.3 (SD=4.5) years (incidence rate: 56/1,000 person-years). Presence of *APOE ε4* and higher medical burden increased risk of incident MCI, while more years of education,

more leisure activities, and higher income decreased this risk. Of the incident MCI cases, after an average of 2.4 years follow-up, 12.9% progressed to dementia, 9.6% declined in functioning and did not meet the algorithmic criteria for MCI but did not meet the clinical criteria for dementia either, 29.6% continued to meet MCI criteria, and 47.9% no longer met MCI criteria. Multi-domain MCI, presence of *APOE ε4*, depressive symptoms and antidepressant use increased the risk of progression to dementia.

Conclusions: This community-based study showed that almost half of the individuals with incident MCI diagnoses were classified as cognitively normal at follow-up. Predictors of incident MCI demonstrably differed from those of subsequent MCI course; these findings can refine expectations for cognitive and functional course of those presenting with MCI.

Introduction

Identifying risk factors of Mild Cognitive Impairment (MCI)—a prodromal phase of dementia—in cognitively normal older adults can aid characterization of a target group for prevention or intervention strategies of dementia.[1-7] However, not everyone who is diagnosed with MCI subsequently progresses to dementia; longitudinal studies have shown that 5-53% of people identified as having MCI at one visit no longer meet MCI criteria at the next visit.[4,8-13] Thus, identifying risk factors of progression to dementia in individuals diagnosed with incident MCI is equally important to refine the selection of individuals at high risk for dementia.[10,14]

Characterization of MCI is typically based on the Petersen criteria, using cut-off scores for cognitive impairment and daily functioning.[9,10,12] MCI diagnosis can be further characterized by the type (i.e., amnestic vs. non-amnestic) and number of cognitive domains affected (i.e., single-domain vs. multi-domain).[2] While MCI criteria require relatively preserved daily functioning, previous studies have shown that individuals with MCI have more difficulties in activities of daily functioning than cognitively normal individuals,[15] particularly in case of multi-domain MCI.[16] In turn, multi-domain MCI has been consistently identified as a predictor of progression to dementia.[9,10]

We previously reported predictors of progression in prevalent MCI in a multi-ethnic community-based cohort.[4] This study extends these findings by investigating modifiable and non-modifiable risk factors of incident MCI among non-Hispanic White, non-Hispanic Black and Hispanic cognitively normal individuals. We also determine which factors predict progression to dementia or classification as cognitively normal at follow-up in those who developed incident MCI.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Columbia University Institutional Review Board, and each participant provided informed consent.

Participants

The participants for this study were selected from the Washington Heights-Inwood Columbia Aging Project (WHICAP), a longitudinal study of aging and dementia in community including non-Hispanic White, non-Hispanic Black and Hispanic people. Participants were recruited by random sampling of persons 65 years or older and eligible for Medicare from three census tracts in Northern Manhattan, New York, NY across three waves in 1992, 1999 and 2009 (described in detail elsewhere[17]).

Follow-up visits were scheduled every 18 to 24 months. Each visit consisted of a medical evaluation including general and neurological evaluations and health questionnaires, a standard battery of neuropsychological tests, and questionnaires regarding socioeconomic factors and functional abilities. The study and sampling methods have been described in more detail previously.[18,19] At the time of the current study, 6541 participants had been recruited and seen at a total of 20,036 visits. The current study selected participants using three criteria: 1) participants should have all the necessary data for determining MCI status during at least one of their visits (the first visit with these data was defined as that participant's baseline visit); 2) participants should be free of MCI or dementia at this baseline visit; 3) participants should have at least one follow-up.

Mild Cognitive Impairment and dementia

The MCI diagnosis was retrospectively applied for each visit independently using a published algorithm, blind to previous diagnoses, based on four criteria expanded from the Petersen criteria and developed for this ethnically and linguistically diverse cohort.[4,18] The first criterion is a subjective memory complaint, assessed by a questionnaire. The second criterion is objective cognitive impairment in at least one cognitive domain, defined as scoring 1.5 standard deviations below robust age, years of education, ethnicity, and sex/gender adjusted norms[18] for a composite score of neuropsychological measures within that domain. The third criterion was preserved daily functioning, quantified as impairment in fewer than three instrumental activities of daily functioning (e.g., using the phone, shopping and handling own medication) based on self or observer report.[20] The fourth criterion was no consensus diagnosis of dementia at that visit. Dementia diagnosis was considered at a consensus conference with neurologists and neuropsychologists present, based on clinical and neuropsychological data using the Diagnostic and Statistical Manual of Mental Disorders criteria (revised Third Edition)[21] (diagnostic procedures described in detail elsewhere[4,18]).

Four subtypes of MCI were defined based on domain(s) of objective cognitive impairment: single domain amnestic MCI, single domain non-amnestic (executive, language, or visuospatial) MCI, multi-domain amnestic MCI, and multi-domain non-amnestic MCI.

Demographic factors

Demographic factors (age, sex/gender, years of education, race/ethnicity) were collected at baseline. Race and Hispanic ethnicity were determined via self-report using the format of the 1990 & 2000 US census, in which participants were asked 1. to classify themselves racially (choose any that apply: White, Black, Asian, American Indian, Pacific Islander, or other) 2. if they were of "Hispanic" origin[4,18]. Subsequently, the WHICAP study

categorized race/ethnicity into three groups: non-Hispanic White, non-Hispanic Black, and Hispanic (of any race).We use the term sex/gender as participants were asked if they are male or female. This assessment did not allow us to determine if biological sex or gender was reported[23].

Socioeconomic factors

Primary lifetime occupation was assessed by self-report at baseline. For the current analyses, occupation was grouped into three training/skill levels: low (housewives and unskilled workers), medium (skilled and office workers), or high (managers, professionals and technical occupations). Household income was categorized into low (<$9,000/ year), medium ($9,000-36,000/ year), or high (>$36,000/year). Participants were asked about marital status at each visit; a dichotomous variable was created to indicate whether the participant was married or not. Participation in 13 separate leisure activities was assessed by self-report at each visit and analyzed as a sum score.[24]

Medical and genetic factors

Self-reported medical conditions were collected by a trained medical interviewer; an index of illness burden was calculated as the sum score of the presence of 15 chronic somatic conditions.[25] *APOE* genotyping in WHICAP participants has been described in detail previously;[26] participants were classified as either carrier (homozygous or heterozygous) or non-carrier of the *APOE ε4* allele.

Depressive symptoms and antidepressant use

Depressive symptoms were assessed at each visit using the 10-item version of the Center for Epidemiologic Studies-depression (CES-D) scale.[27] For the analyses, a

dichotomous variable indicating significant depressive symptoms using the conventional cut-off score of 4 was created. Participants were asked to provide a current list of medications or their medicine bottles at each visit, allowing current use of any class of antidepressants to be recorded.

Statistical analysis

Incident MCI

Participants were classified into three groups depending on their diagnostic status throughout the follow-up period: 1) those who remained cognitively normal throughout follow-up, 2) those with incident MCI, and 3) those who progressed to dementia directly from cognitively normal, without an intermediate diagnosis of MCI (Figure 1). Incidence rates of MCI and the four MCI subtypes (i.e., single-domain amnestic MCI, single-domain non-amnestic MCI, multi-domain amnestic MCI, and multi-domain non-amnestic MCI) were calculated per 1,000 person years by dividing the incidence rate by the length of follow-up; incidence rates and 95% confidence intervals were based on a Poisson distribution.

Cox proportional hazards models were used to identify predictors of incident MCI, including education, sex/gender, race/ethnicity, occupation, *APOE ε4* status, marital status, medical burden, leisure activity, income, antidepressant use, and depressive symptoms. First, we estimated a series of models that tested each predictor individually, adjusting for age at baseline and recruitment wave. Subsequently, we tested a full model that included all predictors. Due to interval censoring, the onset of MCI was set at the midpoint between the last visit being cognitively normal and the first visit with MCI or the first visit with a dementia diagnosis in those cases dementia diagnosis was not preceded by MCI. Participants that did not develop MCI or dementia were censored at the time of their last visit. Censoring includes loss of follow-up due to death or withdrawal; censoring was based on the last visit,

whether a participant was still taking part in further follow-ups or if there had been an end of follow-up due to death or other reasons.

We performed a sensitivity analysis of the full model to assess mortality as a competing risk, because of the likely association between development of MCI and death.[28] For this analysis, all those who were lost to follow-up due to death were hypothetically assumed to have died with MCI. Time to (hypothetical) MCI was calculated as the midpoint between date of the last visit and date of death. We compared the hazard ratios of this sensitivity analysis with those of the main analysis; similar hazard ratios would suggest non-informative censoring in case of death.

Data was missing for seven of the predictor variables for these analyses, ranging from <1%-24% per variable (Table 1B). The reason for missing data in most cases, was due to changes in the assessment protocol over time and the recruitment of new cohorts, which resulted in some variation in measures across visits and recruitment waves. For example, the CES-D was first implemented in 1999, so only 1992 cohort participants who were seen after 1999 were administered that measure. We employed multiple imputation to account for missing data, using pooled estimates from 10 imputations based on a fully conditional specification imputation method with 10 iterations.

Course of MCI

Only participants with at least one follow-up visit after diagnosis of incident MCI were included to analyze the course of MCI (i.e., status at the first follow-up visit after incident MCI) (Figure 2). Descriptive statistics were used to compare participants with and without a follow-up visit after incident MCI diagnosis.

We used modified Poisson regression (i.e., Poisson regression with a robust error variance) to estimate predictors' relative risks (RR) for each diagnostic category (i.e., sustained MCI diagnosis, progression to dementia, or "functional decline"—an additional outcome category that was identified during analysis) compared to those who did not meet cognitive criteria for MCI at follow-up. For prospective studies, odds ratios (obtained in a logistic model) overestimate relative risk if the outcome is frequent—as was the case in this study; therefore, we used modified Poisson regression to estimate relative risks.[29]

Predictor variables included education, sex/gender, race/ethnicity, occupation, *APOE ε4* status, marital status, medical burden, leisure activity, income, antidepressant use, depressive symptoms, and single vs. multi-domain incident MCI status. Due to a smaller number of participants available in this analysis compared to the analysis of incident MCI, the medium and high groups of income and occupation were combined. Models were adjusted for age at incident MCI and recruitment wave. Because the diagnostic status at follow-up after incident MCI may depend on time of follow-up, the natural log transformation of time to follow-up in months (i.e., months between incident and first follow-up after incidence) was used as an offset variable. First, we estimated a series of models that tested each predictor individually, adjusting for age and recruitment wave. Subsequently, we tested a full model that included all predictors. We employed multiple imputation to account for missing data, using pooled estimates from 10 imputations based on a fully conditional specification imputation method with 10 iterations. IBM SPSS Statistics version 25 was used for all analyses.[30]

Data availability

Data are available upon reasonable request to the WHICAP Publications Committee. Data requests should be submitted at cumc.co1.qualtrics.com/jfe/form/SV_6x5rRy14B6vpoqN.

Results

Incident MCI

The study sample consisted of 2903 participants with 11,208 visits (Figure 1) and an average of 3.7 (SD=1.8) visits over 6.3 (SD=4.5) years of follow-up. Table 1A shows the baseline characteristics for participants without incident MCI, those with incident MCI, and those who progressed to dementia without a diagnosis of MCI. Table 2 provides incidence rates of MCI in general, and per MCI subtype.

Table 3 shows the results of the Cox regression analysis of predictors of incident MCI. In a series of models that examined the individual relationships between each predictor and incident MCI, we observed higher risk of incident MCI with Hispanic ethnicity, being an *APOE ε4* carrier, having higher medical burden, and having more depressive symptoms, and a lower risk of incident MCI with more years of education, higher level of occupation, more leisure activities, and higher income. However, when all predictors were entered in the full model together, ethnic background, occupation, and depressive symptoms dropped out of the model; i.e., *APOE ε4* allele and higher medical burden were associated with a higher risk of incident MCI, while more years of education, more leisure activities, and higher income were associated with lower risk of incident MCI.

The hazard ratios obtained in the sensitivity analysis (i.e., a "worst-case" scenario in which all those who were lost to follow-up due to death were assumed to have died with MCI) were comparable to those in the main analysis (Table 3). These results suggest a limited effect of informative censoring on the hazard ratios.

Course of MCI

Of the 752 participants with incident MCI, 480 (64%) had at least one follow-up visit after on average 2.4 years. Compared to the participants that had no follow-up after their first MCI diagnosis, those with follow-up were slightly younger (79.9 vs. 81.4 years), were more likely to be part of the first two recruitment waves, had a lower medical burden (2.31 vs. 2.63), reported more leisure activities (6.83 vs 6.19), and were more likely to have low levels of occupation and income.

Of the 480 incident MCI cases with at least one follow-up visit, 62 (12.9%) progressed to dementia at follow-up, and 142 (29.6%) continued to meet MCI criteria (i.e., sustained MCI diagnosis), namely presence of subjective memory complaint and objective cognitive impairment with preserved daily functioning and no diagnosis of dementia. The remaining 276 (57.5%) participants did not meet full MCI criteria at their next follow-up visit. However, 66 of these 276 participants (24%) had developed functional impairment that ruled them out of consideration for MCI, and 46 of those 66 additionally continued to have objective cognitive impairment. Due to functional impairment these participants (9.6%) did not meet the algorithmic criteria for MCI, but they did not meet the clinical criteria for dementia either. These participants were categorized as having 'functional decline'. The remaining 230 participants (47.9%) consisted of non-demented participants who either had only subjective complaints, only objective cognitive impairment, or only no functional impairment, or a combination of two of those three criteria—but not all three. Figure 2 provides a breakdown of the number of participants that did or did not meet the different criteria.

Table 4A shows the characteristics across the four outcome groups of MCI course: sustained MCI diagnosis, follow-up classification as cognitively normal, functional decline,

and dementia. The functional decline group was more similar to the dementia group compared to the sustained MCI or cognitively normal groups.

Table 5 shows the relative risks of the associations of predictors with course of incident MCI across diagnostic groups compared with the group that was classified as cognitively normal at follow-up. In separate models per predictor adjusted for age and recruitment wave, having multi-domain MCI was the only factor that reliably distinguished those who had a sustained MCI course from those who were classified as cognitively normal at follow-up. Having multi-domain MCI, higher medical burden, reduced leisure activities, antidepressant use, and depressive symptoms were associated with higher risk of functional decline group relative to classification as cognitively normal at follow-up —apart from depressive symptoms, these associations remained in the full model. Higher risk of progression to dementia relative to classification as cognitively normal at follow-up was associated with having multi-domain MCI, , antidepressant use, and depressive symptoms in both separate models as well as in the full model. Additionally, higher risk of progression to dementia was associated with occupation and the presence of *APOE ε4* only in the full model. Years of education, sex/gender, race/ethnicity, marital status, and income were not associated with course of incident MCI.

Discussion

We examined predictors of incident MCI and predictors of diagnostic status at the next follow-up visit after incident MCI in a large racially and ethnically diverse community-based study. We found that having an *APOE ε4* allele and higher medical burden increased the risk of incident MCI, whereas more years of education, more leisure activities, and higher income decreased this risk. In the incident MCI group antidepressant use, depressive symptoms, and multi-domain MCI were associated with a worse follow-up diagnosis (i.e., functional decline or dementia) relative to the group that fell within cognitively normal limits

at follow-up. While higher medical burden and reduced leisure activities were additionally associated specifically with a higher risk of functional decline, the presence of *APOE ε4* was specifically associated with progression from MCI to dementia.

Years of schooling has consistently been shown to predict incident MCI in previous studies, but the relation of income or occupation to incident MCI is not well understood.[31] In separate models, we observed that all three factors, i.e., more years of education, higher income, and higher occupational level, were associated with lower risk of incident MCI. All three predictors are highly related to each other (e.g., household income is heavily determined by educational attainment and occupation), and in a full model occupation dropped out as a predictor of incident MCI, while household income and years of education remained. Income is more proximal in time to cognitive aging than education, and may be a relevant reflection of socioeconomic status among retirees. In this group, a higher income has been associated with better access to health care, increased social activities, fewer daily stressors, and slower cognitive decline[32].

Based on studies that show the incidence of dementia is higher among non-Hispanic Black and Hispanic older adults compared to Whites, we also expected higher MCI incidence in these groups.[33] We observed that in separate models, Hispanics were at higher risk of incident MCI, but this association did not survive the fully adjusted model. This change is likely due to collinearity of this group membership with other predictors, as for example, the Hispanic population sampled in the WHICAP cohort, representative of the Northern Manhattan community, is on average lower educated.[34] Future research is warranted to fully deconstruct differences across race and ethnicity with regard to risk and associated predictors of incident MCI, diagnostic status after incident MCI, and the longitudinal course between incident MCI and a diagnosis of dementia.

Our observation that a high proportion of people with incident MCI no longer met full MCI criteria at follow-up and fell within the cognitively normal classification again may be explained by several factors. First, the percentage of diagnostic reversion in community-based studies is higher than in clinic-based studies, which often report a lower percentage of reversion.[8,10,13] In most clinic-based studies, follow-up diagnosis is assigned without blinding the clinician to earlier diagnoses, while clinicians may be more likely to give a diagnosis of MCI if it has been given before.[9] Furthermore, clinic-based studies have a higher base rate of people who progress to dementia than population-based studies.[35] Michaud et al.[12] reported a lower, but still considerable, reversion rate of 25% in those with incident MCI in a clinic-based sample. While Michaud et al. reported 51% of their participants having multi-domain MCI, we reported only 26% of those with incident MCI to be characterized as multi-domain MCI. Additionally, the mean time to follow-up was shorter in our study compared to Michaud et al. (2.4 vs 4.3 years). A shorter follow-up time is likely related to less advanced disease at follow-up; slight fluctuations above and below the cognitive test cut-offs may be more likely earlier in the disease process. In our study, a large number of individuals with incident MCI did not meet full MCI criteria anymore because their performance on objective cognitive tests was above the 1.5 SD cutoffs at follow-up .

We found that participating in fewer leisure activities at the MCI incidence visit was associated with higher likelihood of being classified in the functional decline at follow-up compared to those whose cognitive test scores improved. This finding suggests that a decline in daily functioning is preceded by reduced participation in leisure activities. The functional decline group was comprised of participants who no longer fulfilled MCI criteria because their daily function declined, but their neuropsychological test scores remained mildly impaired, not yet meeting dementia criteria at consensus conference. In other words, these individuals fall in between the MCI and dementia classification. We found multiple similarities between the functional decline group and the group that progressed to dementia.

Although other population-based cohorts specify a maximum functional impairment allowed for the diagnosis of MCI,[8,9] these studies have not described this functional decline subgroup. The identification of this group is a result of diagnostic procedures in this study (and possibly other studies) and we do not posit this group as a new nosological entity. However, it is important to understand the trajectory of this group as being distinct from those that no longer meet MCI criteria for other reasons (e.g., improved cognitive function) in future population-based cohort studies, because of their similarity to those who progress to dementia.

The presence of depressive symptoms and antidepressant use were associated with higher incident MCI risk in the model only adjusted for age and recruitment cohort, but this association did not survive in the fully adjusted model. Our prior study reported no association between baseline depression and incident MCI,[36] while other studies did observe a relationship.[37] Nonetheless, depressive symptoms and antidepressant use were strongly associated with progression to the functional decline group or dementia at follow-up in our participants with incident MCI, and not with classification as cognitively normal. The observation that depressive symptoms at the time of neuropsychological assessment do not predict classification as cognitively normal at follow-up is of particular relevance as, for example, motivational symptoms of depression can temporarily affect attentional processes and performance on memory tests.[38,39] In addition, the association between depressive symptoms and antidepressant use and the pre-dementia and dementia groups strengthens the previously reported evidence for depressive symptoms as a predictor of progression to dementia.[40,41]

Strengths of this study include a large sample with a relatively high proportion of Black and Hispanic participants and extensive follow-up, which allowed for the study of outcomes following observation of incident MCI, which is likely to lead to less biased estimates than follow-up of prevalent MCI cases. Black and Hispanic older adults are less

likely to have a formal diagnosis of dementia, and when they are diagnosed, they are more severe in their disease.[42] This means that clinic-based cohorts are not appropriate for research on progression of cognitive impairment across different races/ethnicities.[43] The WHICAP cohort provides an opportunity to study the course of incident MCI in a representative cohort, and to do so among Black and Hispanic people without the kind of enrolment bias that affects clinic-based studies like NACC.

Although this extensive cohort allowed for study of follow-up after incident MCI , the proportion with follow-up after incident MCI is relatively small and the follow-up time after incident MCI is relatively short. Future research should investigate the course of MCI across multiple follow-up visits across a longer period of time to further dissect which factors are most informatively related to development of neurodegenerative disease. Another potential limitation is that we do not yet have plasma AD biomarker information on our participants, and thus this information could not take these disease markers into account.

In this community-based study including a relatively high proportion of Black and Hispanic participants showed that a large proportion of individuals with incident MCI may fall within cognitively normal limits at follow-up. Predictors of incident MCI demonstrably differed from those of subsequent MCI course; these findings can refine expectations for cognitive and functional course of those presenting with MCI.

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Figure 1: Flow-diagram participant selection

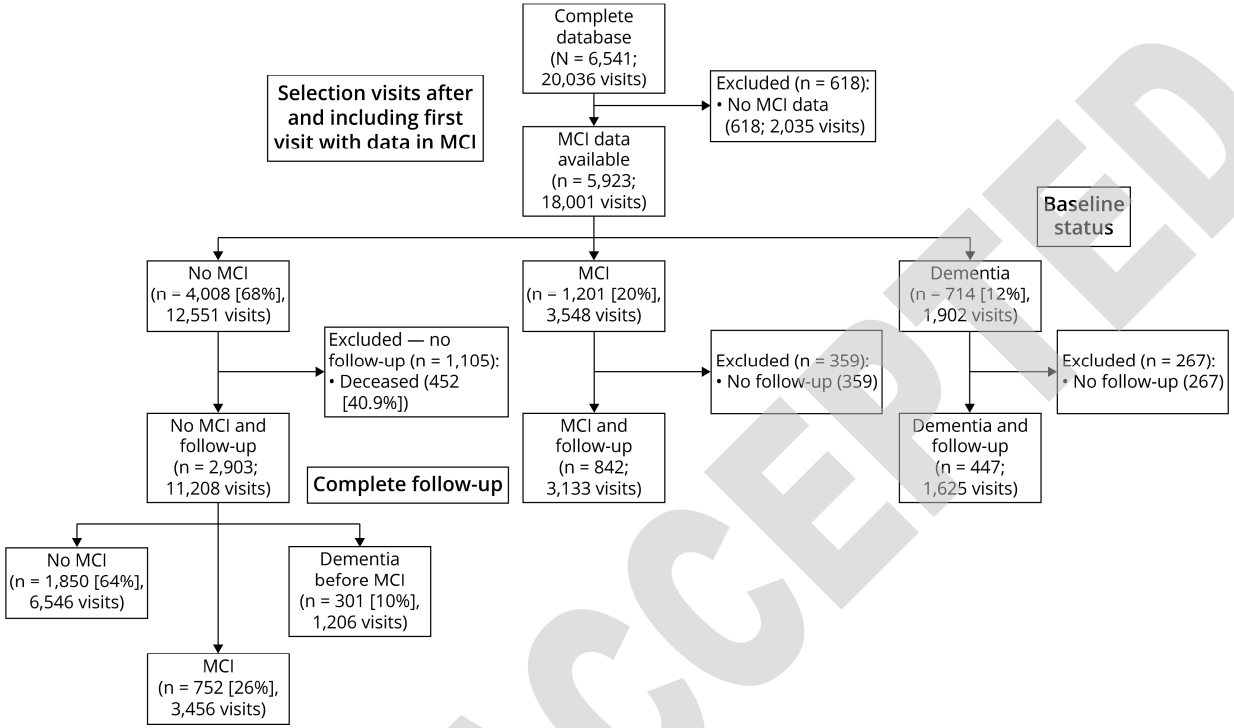

Figure 2: Flow diagram of course of MCI in those with follow-up after incident MCI

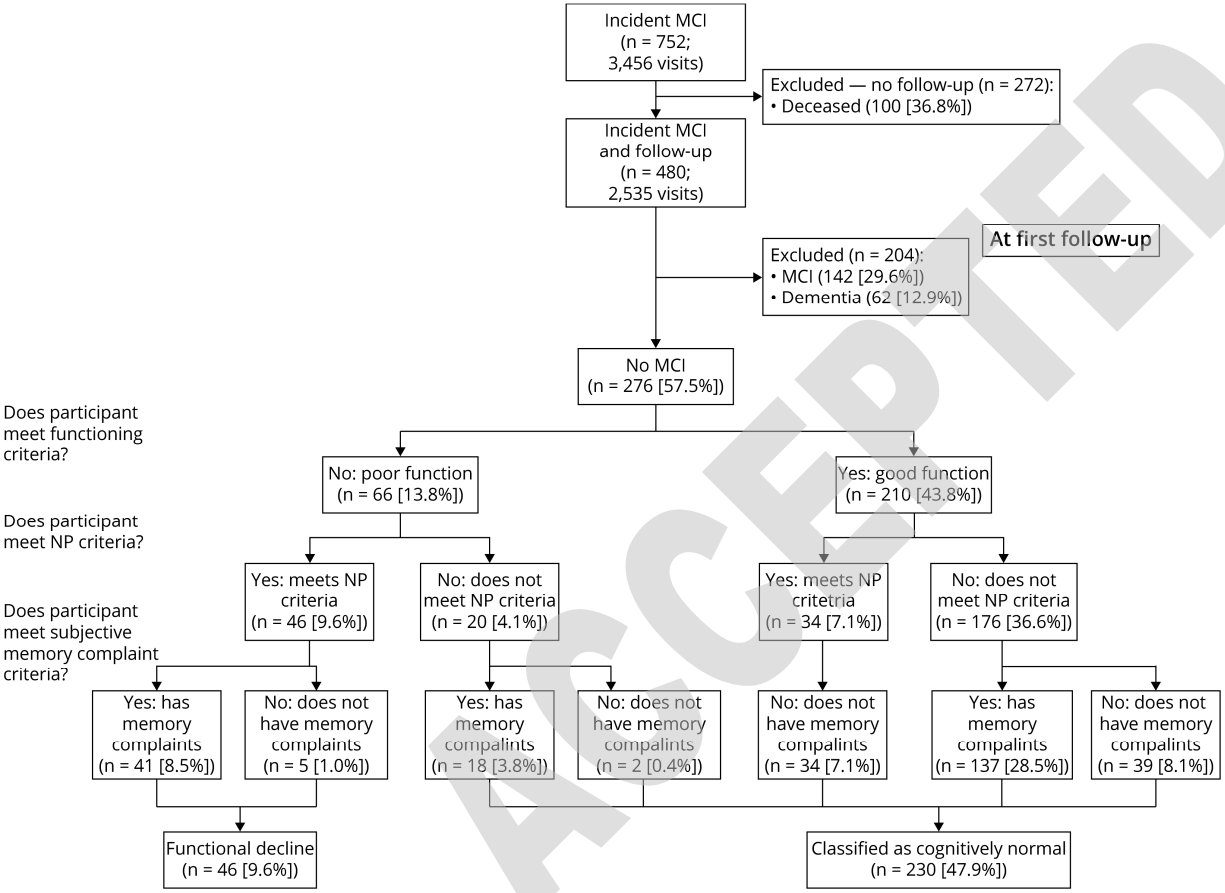

Table 1: A) Baseline participant characteristics among diagnostic groups (prior to multiple imputation), and B) distribution of variables among participants without and with missing values

		A			B	
Diagnostic group		**No incident MCI/dementia**	**Incident MCI**	**Incident dementia**	**Data complete**	**Data incomplete**
n (%)		1850 (63.7)	752 (25.9)	301 (10.4)	1627 (56%)	1276 (44%)
Age in years, mean (SD)		74.7 (6.0)	76.1(6.0)	79.5 (7.1)	74.9 (6.2)	76.3 (6.3)
Education years, mean (SD)		11.5 (4.8)	9.88 (4.8)	7.01 (4.5)	10.9 (5.0)	10.2 (4.9)
Years follow-up, mean (SD)		5.43 (4.1)	8.12 (4.8)	6.7 (4.6)	5.50 (3.78)	7.22 (5.17)
Cohort, n (%)	1992	340 (18.4)	242 (32.2)	112 (37.2)	1 (0.1)	693 (54.3)
	1999	674 (36.4)	345 (45.9)	118 (39.2)	724 (44.5)	413 (32.4)
	2009	836 (45.2)	165 (21.9)	71 (23.6)	902 (55.4)	170 (13.3)
Women, n (%)		1242 (67.1)	520 (69.1)	216 (71.8)	1089 (66.9)	889 (69.7)
Black, n (%)		582 (31.5)	228 (30.3)	79 (26.2)	477 (29.3)	412 (32.3)
Hispanic, n (%)		713 (38.5)	328 (43.6)	192 (63.8)	755 (46.4)	478 (37.5)
Occupation, n (%)	low	719 (41.1)	408 (56.8)	215 (75.2)	749 (46.0)	593 (52.7)
	medium	461 (26.4)	172 (24.0)	46 (16.1)	374 (23.0)	305 (27.1)
	high	569 (32.5)	138 (19.2)	25 (8.7)	504 (31.0)	228 (20.2)
APOE ε4 carrier, n (%)		459 (25.6)	195 (26.7)	86 (30.2)	428 (26.3)	312 (26.5)
Married, n (%)		614 (35.1)	207 (30.4)	76 (27.7)	557 (34.2)	340 (31.7)
Medical burden, mean (SD)		2.09 (1.6)	2.00 (1.5)	2.31 (1.6)	2.40 (1.6)	1.69 (1.5)
Leisure activities, mean (SD)		7.50 (2.5)	7.40 (2.4)	5.78 (2.5)	7.39 (2.5)	7.17 (2.6)
Income, n %	low	433 (27.4)	281 (44.1)	153 (61.7)	425 (26.1)	442 (52.9)
	medium	860 (54.5)	301 (47.3)	83 (33.5)	908 (55.8)	336 (40.2)
	high	285 (18.1)	55 (8.6)	12 (4.8)	294 (18.1)	58 (6.9)
Antidepressant use, n %		127 (7.3)	41 (6.0)	20 (7.1)	143 (8.8)	45 (4.1)
Depressive symptoms, n %		232 (15.4)	85 (16.6)	49 (26.1)	256 (15.7)	110 (18.9)

Event, n (%)	-	-	-	491 (30.2)	562 (44)
Time to event in years, mean (SD)	-	-	-	4.39 (3.5)	4.94 (4.5)

Note. MCI = mild cognitive impairment; participant characteristics based on data prior to imputation: 5.1% missing data occupation, 3.4% missing data *APOE ε4* carrier, 7.0% missing data married, 0.34% missing data leisure activities, 15% missing data income, 6.3% missing data antidepressant use, and 24% missing data depressive symptoms

Table 2: Incidence rates by MCI type (n=2,903; 13,449 person-years)

MCI type	Number of incident MCI cases (% All MCI)	Incidence rate per 1000 person years (95% CI)
Single domain MCI amnestic	224 (30%)	17 (15-19)
Single domain MCI non-amnestic	338 (45%)	25 (23-28)
Multi-domain MCI amnestic	117 (16%)	8.6 (7.3-10)
Multi-domain MCI non-amnestic	73 (9.7%)	5.4 (4.3-6.9)
All MCI	752	56 (52-60)
Dementia before MCI	301	23 (20-25)
All MCI & dementia before MCI	1053	78 (74-83)

Note. MCI = mild cognitive impairment

Table 3: Results of Cox regression analyses of the association of predictors with incident MCI

Characteristic	Separate models Hazard Ratio (95% CI) (n=2902, 1053 events)	Full model Hazard Ratio (95% CI) (n=2902, 1053 events)	Sensitivity analysis Hazard Ratio (95% CI) (n=2902, 1586 events)
Age at baseline (years)	-	1.06 (1.05-1.07), p<.001	1.06 (1.05-1.07), p<.001
Cohort, 1992	-	1 (reference)	1 (reference)
1999	-	0.93 (0.80-1.09), p=.372	0.86 (0.76-0.97), p=.017
2009	-	0.68 (0.56-0.84), p<.001	0.61 (0.52-0.73), p<.001
Education (years)	.93 (.92-.94), p<.001	0.95 (0.93-0.96), p<.001	0.96 (0.95-0.98), p<.001
Women	1.00 (.88-1.14), p=.988	0.88 (0.77-1.02), p=.097	0.80 (0.71-0.89), p<.001
Black	.94 (.82-1.07), p=.336	1.08 (0.90-1.30), p=.416	1.09 (0.94-1.25), p=.235
Hispanic	1.50 (1.33-1.70), p<.001	0.94 (0.77-1.16), p=.576	0.84 (0.72-0.99), p=.037
Occupation, low	1 (reference)	1 (reference)	1 (reference)
medium	.67 (.57-.77), p<.001	0.89 (0.75-1.06), p=.200	0.96 (0.83-1.10), p=.511
high	.50 (.43-.60), p<.001	0.85 (0.68-1.07), p=.164	0.93 (0.78-1.11), p=.394
APOE ε4 carrier	1.13 (.99-1.31), p=.078	1.18 (1.02-1.36), p=.025	1.11 (0.99-1.25), p=.082
Married	.92 (.80-1.06), p=.234	0.98 (0.84-1.14), p=.802	0.99 (0.87-1.12), p=.868
Medical burden	1.09 (1.04-1.14), p<.001	1.05 (1.00-1.09), p=.048	1.08 (1.04-1.12), p<.001
Leisure activities	.93 (.91-.95), p<.001	0.98 (0.95-1.00), p=.072	0.95 (0.93-0.98), p<.001
Income, low	1 (reference)	1 (reference)	1 (reference)
medium	.62 (.54-.72), p<.001	0.80 (0.68-0.95), p=.009	0.83 (0.72-0.96), p=.011
high	.43 (.34-.55), p<.001	0.73 (0.54-1.00), p=.053	0.79 (0.63-0.99), p=.044
Antidepressant use	1.21 (.93-1.58), p=.159	1.15 (0.87-1.51), p=.329	1.16 (0.92-1.46), p=.207
Depressive symptoms	1.19 (.99-1.43), p=.069	1.01 (0.83-1.24), p=.910	1.05 (0.89-1.24), p=.570

Note. Separate models include each predictor with adjustment for age and recruitment wave; full models include all predictors and covariates (i.e., age and recruitment wave); the sensitivity analysis was performed on the full model; one case was dropped due to censoring before earliest event in stratum

Table 4: A) Baseline participant characteristics among diagnostic groups based on MCI status at first follow-up after incident MCI (prior to multiple imputation), and B) distribution of variables among participants without and with missing values

		A				B	
Characteristic		**Cognitively normal**	**Sustained MCI**	**Dementia**	**Functional decline**	**Data complete**	**Data incomplete**
n (%)		230 (47.9)	142 (29.6)	62 (12.9)	46 (9.6)	263 (49%)	244 (51%)
Age in years, mean (SD)		78.5 (5.5)	79.5 (6.0)	83.6 (5.7)	83.1 (6.3)	79.8 (6.2)	80.0 (5.9)
Education years, mean (SD)		9.92 (4.8)	9.71 (4.8)	9.11 (5.2)	9.30 (4.7)	9.78 (4.8)	9.61 (4.9)
Months follow-up, mean (SD)		28.2 (10.5)	28.6 (10.6)	33.2 (10.1)	30.0 (11.5)	31.2 (11.4)	27.2 (9.6)
Cohort, n (%)	1992	86 (37.4)	59 (41.5)	25 (40.3)	19 (41.3)	31 (13.1)	158 (64.8)
	1999	108 (47.0)	68 (47.9)	28 (45.2)	22 (47.8)	154 (65.3)	72 (29.5)
	2009	36 (15.7)	15 (10.6)	9 (14.5)	5 (10.9)	51 (21.6)	14 (5.7)
Women, n (%)		163 (70.9)	102 (71.8)	42 (67.7)	36 (78.3)	164 (69.5)	179 (73.4)
Black, n (%)		67 (29.1)	51 (35.9)	22 (35.5)	12 (26.1)	68 (28.8)	84 (34.4)
Hispanic, n (%)		106 (46.1)	58 (40.8)	29 (46.8)	21 (45.7)	113 (47.9)	101 (41.4)
Occupation, n (%)	low	130 (58.3)	82 (61.2)	35 (59.3)	28 (63.6)	137 (58.1)	138 (61.6)
	medium	53 (23.8)	29 (21.6)	16 (27.1)	11 (25.0)	52 (22.0)	57 (25.4)
	high	40 (17.9)	23 (17.2)	8 (13.6)	5 (11.4)	47 (19.9)	29 (12.9)
APOE ε4 carrier, n (%)		60 (26.2)	36 (26.5)	25 (41.7)	13 (28.3)	65 (27.5)	69 (29.4)
Multi-domain MCI, n (%)		40 (17.4)	42 (29.6)	25 (40.3)	16 (34.8)	50 (21.2)	73 (29.9)
Married, n (%)		56 (32.4)	25 (25.0)	12 (26.1)	9 (26.5)	68 (28.8)	34 (29.1)
Medical burden, mean (SD)		2.33 (1.4)	2.25 (1.5)	2.13 (1.4)	2.67 (1.4)	2.67 (1.4)	1.97 (1.4)
Leisure activities, mean (SD)		6.95 (2.3)	7.25 (2.2)	6.16 (2.3)	5.83 (2.0)	6.79 (2.3)	6.86 (2.4)
Income, n (%)	low	82 (44.6)	54 (45.4)	25 (52.1)	15 (44.1)	83 (35.2)	93 (62.4)

medium	89 (48.4)	58 (48.7)	19 (39.6)	18 (52.9)	132 (55.9)	52 (34.9)
high	13 (7.1)	7 (5.9)	4 (8.3)	1 (2.9)	21 (8.9)	4 (2.7)
Antidepressant use, n (%)	12 (5.9)	8 (6.5)	10 (17.5)	8 (18.2)	23 (9.7)	15 (7.9)
Depressive symptoms, n (%)	17 (10.3)	12 (12.4)	9 (20.9)	10 (29.4)	34 (14.4)	14 (13.6)

Note. MCI = mild cognitive impairment; participant characteristics based on data prior to imputation: 4.1% missing data occupation, 1.8% missing data *APOE ε4* carrier, 26% missing data married, 20% missing data income, 11% missing data antidepressant use, 30% missing data depressive symptoms

Table 5: Relative risks of belonging to the sustained MCI, functional decline, and dementia groups compared to the group that was classified as cognitively normal at follow-up, computed using Poisson regressions corrected for age and time of follow-up

	Sustained MCI vs cognitively normal RR (95% CI)		**Functional decline vs cognitively normal RR (95% CI)**		**Dementia vs cognitively normal RR (95% CI)**	
n	372 (142, 230)		276 (46, 230)		292 (62, 230)	
	Separate models	**Full model**	**Separate models**	**Full model**	**Separate models**	**Full model**
Age at incidence (years)	-	1.02 (1.00-1.04), p=.073	-	1.10 (1.05-1.14), p<.001	-	1.10 (1.07-1.14), p<.001
Cohort,1992	-	1 (reference)	-	1 (reference)	-	1 (reference)
1999	-	0.80 (0.58-1.10), p=.170	-	0.74 (0.38-1.45), p=.3830	-	1.00 (0.59-1.67), p=.990
2009	-	0.86 (0.52-1.43), p=.560	-	.57 (0.21-1.54), p=.269	-	1.22 (0.66-2.26), p=.527
Education (years)	0.99 (0.96-1.02), p=.460	0.99 (0.95-1.03), p=.623	0.98 (0.93-1.03), p=.416	0.99 (0.91-1.07), p=.765	0.97 (0.92-1.01), p=.129	0.96 (0.90-1.02), p=.142
Women	1.05 (0.77-1.42), p=.767	0.94 (0.68-1.30), p=.697	1.29 (0.72-2.33), p=.390	1.19 (0.63-2.23), p=.597	0.80 (0.53-1.22), p=.309	0.71 (0.44-1.15), p=.169
Black	1.25 (0.95-1.65), p=.108	1.28 (0.88-1.86), p=.199	1.07 (0.59-1.95), p=.822	1.69 (0.77-3.72), p=.193	1.16 (0.77-1.77), p=.473	1.89 (0.99-3.61), p=.054
Hispanic	0.96 (0.73-	1.00 (0.62-	1.14 (0.68-	1.55 (0.66-	1.34 (0.86-	1.63 (0.80-

	1.27), p=.770	1.63), p=.987	1.90), p=.611	3.65), p=.311	2.08), p=.195	3.34), p=.178
Occupation, med-high	0.90 (0.68-1.19), p=.450	0.96 (0.68-1.37) p=.829	0.91 (0.53-1.56), p=.738	1.23 (0.61-2.47), p=.558	1.06 (0.68-1.64), p=.806	1.81 (1.07-3.06), p=.026
APOE ε4 carrier	1.08 (0.79-1.48), p=.641	1.04 (0.76-1.42), p=.791	1.21 (0.68-2.15), p=.522	1.13 (0.63-2.03), p=.691	1.47 (0.98-2.18), p=.061	1.65 (1.02-2.65), p=.040
Married	0.90 (0.63-1.29), p=.569	0.90 (0.61-1.32), p=.584	0.86 (0.45-1.65), p=.651	0.85 (0.43-1.72), p=.658	0.98 (0.60-1.61), p=.944	0.90 (0.53-1.56), p=.716
Medical burden	1.00 (0.91-1.11), p=.933	1.01 (0.91-1.12), p=.847	1.17 (0.98-1.39), p=.075	1.21 (0.99-1.48), p=.057	0.96 (0.83-1.11), p=.562	0.90 (0.77-1.07), p=.231
Leisure activity	1.01 (0.96-1.08), p=.651	1.02 (0.96-1.08), p=.460	0.86 (0.77-0.96), p=.010	0.89 (0.79-1.00), p=.042	0.94 (0.85-1.03), p=.183	0.99 (0.91-1.09), p=.892
Income, med-high	0.89 (0.65-1.22), p=.475	0.87 (0.60-1.26), p=.468	0.90 (0.5-1.65), p=.742	1.02 (0.51-2.03), p=.967	0.74 (0.46-1.19), p=.213	0.92 (0.55-1.55), p=.761
Antidepressant use	1.18 (0.68-2.04), p=.558	1.32 (0.74-2.36), p=.348	2.71 (1.44-5.12), p=.002	2.27 (1.11-4.61), p=.024	1.90 (1.24-2.91), p=.003	2.43 (1.47-4.02), p=.001
Depressive symptoms	1.02 (0.63-1.65), p=.929	1.04 (0.64-1.69) p=.883	2.10 (1.09-4.04), p=.027	1.67 (0.81-3.42), p=.160	1.84 (1.03-3.28), p=.038	1.80 (1.06-3.06), p=.030
Multi-domain MCI	1.52 (1.16-1.99), p=.003	1.53 (1.16-2.00) p=0.002	2.03 (1.20-3.43), p=.009	1.98 (1.17-3.35), p=.011	2.07 (1.34-3.19), p=.001	2.11 (1.31-3.39), p=.002

Note. Separate models include each predictor with adjustment for age and recruitment wave; full models include all predictors and covariates (i.e., age and recruitment wave); med = medium; MCI = mild cognitive

impairment. In the row “n” the total number of participants and the number of participants per category (in parentheses) are provided.

Appendix 1: Authors

Name	Location	Contribution
Milou J. Angevaare	Department of Neurology and Taub Institute for Research on Alzheimer's Disease and The Aging Brain, College of Physicians and Surgeons, Columbia University Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Medicine for Older People, Amsterdam Public Health Research Institute	design of the study, analysis and interpretation of the data, drafting and revising the manuscript
Jet M.J. Vonk	Department of Neurology and Taub Institute for Research on Alzheimer's Disease and The Aging Brain, College of Physicians and Surgeons, Columbia University Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands	analysis and interpretation of the data, revising the manuscript
Laiss Bertola	Department of Neurology and Taub Institute for Research on Alzheimer's Disease and The Aging Brain, College of Physicians and Surgeons, Columbia University National Institute of Science and Technology in Molecular Medicine (INCT-MM), Federal University of Minas Gerais, Belo Horizonte, Brazil	design of the study, analysis and interpretation of the data, revising the manuscript
Laura B.	Department of Neurology and Taub Institute for	analysis and interpretation

Zahodne	Research on Alzheimer's Disease and The Aging Brain, College of Physicians and Surgeons, Columbia University	of the data, revising the manuscript
Caitlin Watson	Department of Neurology and Taub Institute for Research on Alzheimer's Disease and The Aging Brain, College of Physicians and Surgeons, Columbia University	analysis and interpretation of the data, revising the manuscript
Amelia K. Boehme	Department of Neurology and Taub Institute for Research on Alzheimer's Disease and The Aging Brain, College of Physicians and Surgeons, Columbia University	analysis and interpretation of the data, revising the manuscript
Nicole S. Schupf	Department of Neurology and Taub Institute for Research on Alzheimer's Disease and The Aging Brain, College of Physicians and Surgeons, Columbia University	analysis and interpretation of the data, revising the manuscript
Richard Mayeux	Department of Neurology and Taub Institute for Research on Alzheimer's Disease and The Aging Brain, College of Physicians and Surgeons, Columbia University	revising the manuscript
Mirjam I. Geerlings	Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands	analysis and interpretation of the data, revising the manuscript
Jennifer J. Manly	Department of Neurology and Taub Institute for Research on Alzheimer's Disease and The Aging Brain, College of Physicians and Surgeons, Columbia University	design of the study, analysis and interpretation of the data, drafting and revising the manuscript

Predictors of Incident Mild Cognitive Impairment and Its Course in a Diverse Community-Based Population

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Neurology published online December 1, 2021
DOI 10.1212/WNL.0000000000013017