Abstract

Mild Cognitive Impairment (MCI) is a heterogeneous condition between normal aging and dementia. Upon neuropsychological testing, MCI can be divided into four groups: single-domain amnestic MCI (sd-aMCI), multiple-domain amnestic MCI (md-aMCI), single- and multiple-domain non-amnestic MCI (sd-naMCI, md-naMCI). Some controversy exists about whether the risk of progression to Alzheimer's disease (risk-AD) is increased in all MCI subtypes. We meta-analyzed the risk-AD for four MCI groups using random-effects meta-regression with the Hierarchical Robust Variance Estimator and sample size, criterion for objective cognitive impairment, length of follow-up and source of recruitment as covariates. From a pool of 134 available studies, 81 groups from 33 studies (N = 4,907) were meta-analyzed. All the studies were rated as having a high risk of bias. aMCI is overrepresented in studies from memory clinics. Multivariate analyses showed that md-aMCI had a similar risk-AD relative to sd-aMCI, whereas both sd-naMCI and md-naMCI showed a lower risk-AD compared to sd-aMCI. The risk-AD was significantly associated with differences in sample sizes across studies and between groups within studies. md-aMCI had a similar risk-AD relative to sd-aMCI in studies from memory clinics and in studies in the community. Several potential sources of bias such as blindness of AD diagnosis, the MCI diagnosis approach and the reporting of demographics were associated with the risk-AD. This work provides important data for use in both clinical and research scenarios.

Keywords: Alzheimer’s disease; Mild Cognitive Impairment; dementia; meta-analysis; robust variance estimator

Risk of progression to AD for different neuropsychological Mild Cognitive Impairment subtypes. A hierarchical meta-analysis of longitudinal studies

Mild Cognitive Impairment (MCI) is considered a transitional stage between normal aging and dementia, mainly Alzheimer's disease (AD) (Petersen, 2004; Petersen & Negash, 2008). Early definitions of MCI were biased towards memory impairments (Jack et al., 1999; Petersen et al., 1999), which was labeled as amnestic MCI (aMCI), with the focus being on abnormal verbal memory scores. With an increasing number of studies, it was found that other clinical and neuropsychological profiles were common in individuals with MCI (Ritchie & Touchon, 2000) and criteria were then expanded to include different subtypes according to the cognitive domain impaired: single-domain amnestic (sd-aMCI), single-domain non-amnestic (sd-naMCI), multiple-domain amnestic (md-aMCI) and multiple-domain non-amnestic MCI (md-naMCI) (Albert et al., 2011; Winblad et al., 2004).

In 2004, the International Working Group on MCI (Winblad et al., 2004) pointed at the controversies regarding the definition of MCI. Although one of the core criteria is the presence of objective cognitive impairment, no specific tests or cut-off scores (e.g., >1Standard Deviation -SD- or >1.5SD below the mean) have been recommended. Thus, the heterogeneity in defining MCI characteristics and how this impacts on prevalence rates and diagnosis accuracy have been consistently highlighted (Morris, 2012; Schinka et al., 2010; Ward, Arrighi, Michels, & Cedarbaum, 2012).

Studies on the progression from different MCI subtypes to dementia have reported inconsistent results. It is well known that variables such as older age, worse global cognitive functioning, lower educational level and the presence of at least one ε4 allele of the Apolipoprotein E (APOE) are related to an increased risk of developing dementia (Ding et al., 2015; McGuinness, Barrett, McIlvenna, Passmore, & Shorter, 2015; Ravaglia et al., 2008;

Serrano, Dillon, Leis, Taragano, & Allegri, 2013). However, the association between MCI subtypes and the risk of dementia is far from consistent. Whereas some studies have found an increased risk of dementia for md-aMCI compared to sd-aMCI (Bélanger & Belleville, 2009; Brodaty et al., 2013), others have reported the opposite pattern (Belleville, Gauthier, Lepage, Kergoat, & Gilbert, 2014; Ferman et al., 2013).

With regard to the type of dementia developed at follow up, some studies have reported an increased association between aMCI and AD (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003b; Ferman et al., 2013) and between naMCI and other types of dementia (Busse, Hensel, Gühne, Angermeyer, & Riedel-Heller, 2006; Ferman et al., 2013). Other studies have provided evidence of an increased risk of progression to AD (risk-AD) in all MCI subtypes (Espinosa et al., 2013; Han et al., 2012; Rountree et al., 2007). It has been suggested that individuals classified as md-MCI may be in a more severe stage of the disease due to a more widespread brain volume reduction, which in turn has been associated with an increased risk of AD (McEvoy et al., 2009; Whitwell et al., 2008). This model would hypothesize that individuals with mdMCI will progress to AD at a greater rate compared to individuals with sdMCI (Mitchell, Arnold, Dawson, Nestor, & Hodges, 2009). However, other studies have reported no specific association between MCI subgroups and AD or other dementias (Fischer et al., 2007; Jungwirth, Zehetmayer, Hinterberger, Tragl, & Fischer, 2012). Thus, it remains unclear whether subtyping MCI is useful in terms of prediction of progression from MCI to AD.

One variable that, to our knowledge, has never been investigated in previous studies is how differences in sample size among MCI subtypes affect the risk-AD. We consider this a highly relevant issue, because being labeled as aMCI may be more likely than being labeled as naMCI in samples recruited in memory clinics (Schinka et al., 2010), whereas the opposite pattern may be true for samples of community-dwelling individuals (Sachdev et al., 2015).

Also, differences in sample sizes may explain in part contradictory results with regard to the risk-AD for amnestic versus non-amnestic MCI groups. Both the source of recruitment and the sample size may bias studies on MCI towards samples of amnestic impairments, thus affecting estimates of the risk-AD. In support of this hypothesis, a higher rate of progression for larger groups has been reported in previous studies investigating the risk-AD (Ahmed, Mitchell, Arnold, Nestor, & Hodges, 2008; Bélanger & Belleville, 2009; Belleville et al., 2014; Ferman et al., 2013; Julayanont, Brousseau, Chertkow, Phillips, & Nasreddine, 2014; McGuinness et al., 2015; Rasquin, Lodder, Visser, Lousberg, & Verhey, 2005; Vos et al., 2013) or the risk of conversion to dementia in general (Lee et al., 2014; Rainville, Lepage, Gauthier, Kergoat, & Belleville, 2012; Villeneuve & Belleville, 2012). However, others have found no association between sample size and the risk of conversion to dementia or AD among aMCI (Aerts et al., 2017; Brodaty et al., 2013; Chang, Chiu, Chen, Cheng, & Hua, 2014; Ding et al., 2016; Manly et al., 2008; Palmer, Bäckman, Winblad, & Fratiglioni, 2008; Pozueta et al., 2011; Ravaglia et al., 2006) or naMCI groups (Brodaty et al., 2013; Chang et al., 2014; Ding et al., 2016; Ferman et al., 2013; Manly et al., 2008; McGuinness et al., 2015; Rasquin et al., 2005).

Other variables that could account for the heterogeneity in the risk-AD are related to methodological characteristics of studies. One of these is blindness of cognitive status at the time of AD diagnosis. It has been suggested that clinical diagnosis at any given time may differ when investigators are not blinded to previous clinical diagnoses, with individuals having MCI being less likely to be labeled as cognitively healthy at follow-up (Petersen et al., 2009). Similarly, investigators might be more prone to label participants as having dementia at follow-up if they are aware of previous objective memory impairments in their MCI sample, more even so if multiple domains are affected. Other variable is the approach used to diagnosing MCI. The algorithm-based approach identifies MCI when some predefined

criteria are met. Once an individual meets all of these criteria, commonly based on published reports (Albert et al., 2011; Petersen et al., 1999; Winblad et al., 2004), the diagnosis of MCI is straightforward. Conversely, in the consensus-based approach MCI is identified when two or more clinicians review each patient's medical history and cognitive data. This approach is difficult to replicate and introduces variability in MCI diagnosis (Duara et al., 2010), thus representing a possible source of bias in longitudinal studies.

Although several excellent reviews have analyzed MCI from different perspectives (Jekel et al., 2015; Langa & Levine, 2014; Petersen et al., 2001; Reijnders, van Heugten, & van Boxtel, 2013; Tampi, Tampi, Chandran, Ghori, & Durning, 2015), and previous meta-analyses on the risk-AD have been published (Bruscoli & Lovestone, 2004; Hu et al., 2017), to our knowledge differences in the risk-AD among MCI subtypes, controlling for other potential sources of bias, have not been analyzed. To fill that gap, this work aimed to meta-analyze the risk-AD according to different MCI subtypes with a robust methodology that takes account of both the variance between studies and the variance between groups within studies, also including as moderators of the effect estimates several variables known to be associated with the risk-AD.

Methods

This meta-analysis is reported according to the PRISMA (Preferred Reported Items for Systematic reviews and Meta-Analysis) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). This review was not registered prior to its onset, but the dataset can be accessed at doi:10.17632/pktk8vbfmp.1 for replication purposes. PubMed, Embase, PsycINFO and Web of Knowledge electronic databases were searched for relevant literature up to May 24, 2017, with a combination of the terms "*mild cognitive impairment* OR *MCI*" AND "*conversion* OR *progression*" in the title and abstract. Only peer-reviewed journal articles written in English from 1999 on were considered as per the date of publication of Petersen et al. (1999) MCI criteria (e.g., Embase search "'mild cognitive impairment':ab,ti or 'mci':ab,ti and ('convers*':ab,ti or 'progress*':ab,ti) and 'english':la and 'article':it and [1-1-1999]/sd" gave 2,858 results).

Inclusion criteria for this study were 1) original longitudinal studies, 2) focusing specifically on cognition and the risk-AD, 3) with pure MCI samples (that is, without diagnosis of any psychiatric or neurological diseases), 4) with a number of neuropsychological tests sufficient to divide MCI into one of sd-aMCI, md-aMCI, sd-naMCI or md-naMCI. This criterion required at least one memory and two nonmemory tests, so as to reduce selection bias whereby a) non-amnestic MCI groups could not be identified, or b) MCI groups could not be divided into single- and multiple-domains. Potential studies were excluded if no diagnostic criteria were specified. The first author conducted the literature research. Potential articles peer-reviewed by two authors following inclusion criteria. In case of discrepancy, this was resolved by consensus with the leading author. Efforts were made to contact authors of included articles, who were requested for missing data. We then searched through the reference section of included articles to identify any additional potential study.

Inter-rater agreement in article inclusion was assessed in a subsample of 300 articles by the first and last authors.

Assessment of bias

The quality of each primary study was assessed with the QUIPS (Quality on Prognosis Studies) tool (Hayden, van der Windt, Cartwright, Côté, & Bombardier, 2013). The QUIPS tool is a scale measuring 6 bias domains in longitudinal studies: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain is rated as having high, moderate or low risk of bias, and the overall risk is judged according to the risk of bias in the six domains assessed. We judged a study as having high risk of bias if at least one of the six domains was rated as having high risk; as having low risk of bias if all six domains were rated as having low risk of bias; and as having moderate risk of bias if none of the six domains was rated as having high risk of bias and at least one was rated as having a moderate risk of bias. Two authors rated independently each of the included studies.

One of the main issues in meta-analyses combining published studies is related to publication bias, which arises when some findings are more likely to be published according to the statistical significance or other reasons related to selective analysis reporting or selective outcome reporting (Sterne et al., 2011). To test for possible publication bias, we used the trim-and-fill funnel plot-derived method, which identifies possible publication bias by estimating the number of unpublished studies and adjusts results for this bias (Mavridis & Salanti, 2014). The trim-and-fill funnel plots are a visual manner to explore heterogeneity in effect sizes according to a specified measure of precision. Smaller studies, or groups, with larger error should scatter and spread at the bottom of the funnel plot, with larger and more precise studies narrowing at the top (Sterne et al., 2011). We plotted the log(odds) for each

MCI group against its variance using Meta-Essentials (Suurmond, van Rhee, & Hak, 2017), a friendly tool for conducting meta-analysis that is freely available at http://www.erim.eur.nl/research-facilities/meta-essentials/download/. Meta-Essentials tool was used to build funnel plots and to statistically test for funnel plot asymmetry with the Egger's test (Egger, Smith, Schneider, & Minder, 1997). The Egger's test measures the degree of funnel plot asymmetry by regressing the standardized effect size (i.e., log(odds) divided by its standard error) against the inverse of the standard error, with statistically significant p-values suggesting asymmetry. We calculated funnel plot and Egger's test for all the studies combined and for each MCI group separately, because asymmetry can arise from heterogeneity due to there being several distinct subgroups (Sterne et al., 2011).

Moderator variables

Due to the difficulties in gathering demographic variables for each MCI subtype in most of the included articles, we coded the presence of demographic information as a dummy variable to assess potential bias in the reporting of the results. Papers lacking information for one or more demographics were coded as 0, otherwise as 1. Regarding age, three dummy variables representing four mutually exclusive groups were coded, each representing around 25% of the distribution: participants aged up to 69.99 years (as the reference category), from 70 to 73.99, from 74 to 75.99 and ≥76. We imputed for each MCI subgroup with missing values the average age of the MCI participants reported in primary studies.

Most of the variables analyzed operate conceptually at the study level (e.g., MCI subgroup, length of follow-up in years) and vary only between studies. However, some variables such as age or sample size of each MCI subgroup may vary either between studies or between groups-within studies. For this reason, the variance of covariates that may operate both at the group and at the study level was decomposed into between- and within-studies

and included as covariates where possible. Due to the lack of available data on demographics, only the variance of sample size could be decomposed into between and within studies variance and included as covariate.

Variables considered as potential moderators of the risk-AD were:

- Sample size, decomposed into variance between studies and variance between groups within studies
- Demographics. We identified whether age, sex and level of education for each MCI subtype was reported in each study.
- The Standard Deviation (SD) used to define cognitive impairment (≤1SD vs. ≤1.5SD).
- The source of recruitment. For this variable, the category *community* included population-based studies and studies with community-dwelling adults, whereas *clinic* studies included participants referred to memory clinics (e.g., hospital or university clinics) seeking for specialized services. We acknowledge that this distinction is somewhat arbitrary, as individuals referred to memory clinics live in the community, and none of the population-based studies included in this review explicitly stated exclusion of participants that were attending memory clinics. However, the evidence available to date indicates that studies conducted in memory clinics report a higher risk-AD than studies conducted in the community (Mitchell & Shiri-Feshki, 2009).
- MCI diagnosis approach. Two different approaches were identified: MCI diagnosis based on algorithms and MCI diagnosis based on consensus. The algorithm-based approach included studies that reported using a set of criteria to define MCI (e.g., presence of subjective complaints, objective cognitive impairment, independence in activities of daily living). The consensus-based

approach included studies that explicitly reported diagnosing MCI by consensus among different specialists beyond the use of algorithms to diagnose MCI.

- Blindness of previous MCI at the time of AD diagnosis. We identified those studies that explicitly reported that AD diagnosis at follow-up was made by assessors blinded to participants' previous MCI status.
- Number of tests for neuropsychological assessment. We identified the number of tests used to define cognitive impairment

Each moderator variable was coded independently by two authors (J.O-C., M.S-S), and discrepancy was resolved by consensus with a third co-author (A.M-N). Some corresponding authors provided missing demographics upon request, so there is a mismatch between data reported in primary studies and the same data reported in this review for demographics, the SD used to define cognitive impairment and the number of cognitive measures in the neuropsychological assessment. For this reason, inter-rater reliability was calculated for source of recruitment, MCI diagnosis and blindness of AD diagnosis.

Meta-analysis

The odds of progressing to AD was calculated separately for each of the MCI subtypes, which were analyzed according to the definition used in primary studies. The risk-AD was analyzed with Odds Ratios (OR) because summary data from each MCI subtype were used in the analyses, and thus hazard ratios could not be calculated. The odds of progressing to AD for each subgroup was transformed to log(odds), and the variance of the log(odds) was calculated with the formula provided by Agresti (2002, p. 75). The "non-

progressors" category in each study included participants who remained MCI-stable and participants who reverted to normal cognition.

Because each study provided several MCI groups, the hierarchical Robust Variance Estimator (HRVE) was used to meta-analyze the risk-AD (Hedges, Tipton, & Johnson, 2010; Tanner-Smith & Tipton, 2014) as in previous research including several groups from the same study (Oltra-Cucarella et al., in press). With the HRVE, the risk of progression was analyzed using meta-regression with the method of moments after controlling for both variance between studies (τ^2) and the variance between-groups within studies (ω^2). Weights were calculated as the inverse of the sampling variance. The HRVE provides a coefficient β, its standard error, 95% confidence interval (CI) and a t-test with the number of studies minus the number of covariates minus one degrees of freedom. Univariate HRVE included only MCI groups, whereas multivariate HRVE included the following covariates: length of follow-up in years, SD used to define objective cognitive impairment, the source of recruitment, variance in sample size between studies, variance in sample size between groups within studies, the MCI diagnosis approach, blindness of AD diagnosis, and the reporting of demographics.

Heterogeneity

Statistical heterogeneity in meta-analysis refers to the differences in estimates of the true effects above what should be expected by chance. To estimate the extent of statistical heterogeneity, the Cochrane Q-test is usually calculated and compared against a χ^2 distribution with k -1 degrees of freedom (Higgins, Thompson, Deeks, & Altman, 2003). The HRVE does not allow testing hypothesis regarding heterogeneity (Tanner-Smith, Tipton, & Polanin, 2016), but provides a Qe statistic for each model along with degrees of freedom, the

variance between studies (τ^2) and the variance between-groups within studies (ω^2). Both τ^2 and ω^2 are reported for the reader to make a clearer picture of the variance within each model.

Models with no variance between-groups within studies would reasonably provide similar results as standard meta-analysis, because all the observed variance would be variance between studies but not between groups within studies. In such situation, the Q-statistic could be used to calculate heterogeneity. To test this assumption, we therefore calculated the Q-statistic for a random effect meta-regression with the method of moments using the macro for SPSS developed by Wilson (2005), and calculated the I^2 statistic for measuring heterogeneity (Higgins et al., 2003). The I^2 statistic gives a proportion of variance between effects that is not due to sampling variance, that is, the proportion of variability that would remain if sampling variance could be removed (Borenstein, Higgins, Hedges, & Rothstein, 2017). Values of 25%, 50% and 75% are considered as low, medium and high heterogeneity. In standard meta-regression the degrees of freedom are the number of groups minus one instead of the number of studies minus one. To test the power of each individual regression coefficient, we used the formula for random effects meta-regression provided by Hedges and Pigott (Hedges & Pigott, 2004)

Continuous and categorical descriptive statistics were analyzed with independent t-tests and χ^2-tests respectively. All analyses were run with $\alpha = .05$ because robust 95% confidence intervals are close to nominal when there are 20-40 studies with an average of more than one effect per study (Hedges et al., 2010), which is the case in this work.

Results

Articles search

Electronic searches yielded 13,647 results. After removing 9,224 duplicates, 4,443 primary studies were screened. One thousand two-hundred and seventeen eligible articles were identified after removing studies not meeting inclusion criteria. There were 100% agreement in inclusion and exclusion for the subsample of 300 articles.

After excluding 480 papers that did not specify diagnostic criteria, 766 papers were retrieved, of which 134 analyzed the risk of progression from MCI to AD (see flow chart in Figure 1). Six studies (Alegret et al., 2012; Brodaty et al., 2013; Busse, Angermeyer, & Riedel-Heller, 2006; Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003a; Busse et al., 2003a, 2003b) were not included because data reported were already reported in other included studies with the same sample, one was excluded because no specific criteria were used to diagnose AD (Sala et al., 2017), and two were excluded because no cognitive tests other than memory were used for diagnosing MCI (Dierckx et al., 2009; Larrieu et al., 2002). Thirty-eight studies did not state the standard deviation used to define cognitive impairment, and 54 studies reported progression to dementia in general without specifying the number of progressors to AD. We found 18 additional potential studies through the references section search and by asking experts on MCI. After approaching the corresponding authors of studies with missing data, we were able to include relevant data for 8 studies (Aerts et al., 2017; Alegret et al., 2014; Espinosa et al., 2013; Guaita et al., 2013; Han et al., 2012; Mistridis, Krumm, Monsch, Berres, & Taylor, 2015; Smith, 2014; Yates, Clare, Woods, & CFAS, 2017).

Eventually, 81 groups from 33 studies with a total sample size of 4,907 participants were analyzed: 30 sd-aMCI (n = 1,631), 23 md-aMCI (n = 2,069), 15 sd-naMCI (n = 807) and 12 md-naMCI (n = 400) groups (Aerts et al., 2017; Ahmed et al., 2008; Alegret et al.,

2014; Bélanger & Belleville, 2009; Belleville et al., 2014; Busse, Hensel, et al., 2006; Chang et al., 2014; Cloutier, Chertkow, Kergoat, Gauthier, & Belleville, 2015; Dewar, Pesallaccia, Cowan, Provinciali, & Della Sala, 2012; Didic et al., 2010; Espinosa et al., 2013; Estévez-González et al., 2004; Ferman et al., 2013; Forlenza et al., 2009; Genon et al., 2013; Guaita et al., 2013; Han et al., 2012; Huey et al., 2013; Julayanont et al., 2014; Lee et al., 2014; Manly et al., 2008; McGuinness et al., 2015; Mitchell et al., 2009; Nordlund et al., 2010; Palmer et al., 2008; Pozueta et al., 2011; Rasquin et al., 2005; Schmidtke & Hermeneit, 2008; Serrano et al., 2013; Smith, 2014; Summers & Saunders, 2012; Vos et al., 2013; Yates et al., 2017). Data for age in each MCI group were available in 41 groups (18 studies), for education in 35 groups (15 studies) and for sex in 35 groups (15 studies). Data for all three demographic variables were available for 29 groups from 13 studies, and thus could not be included as covariates because of the loss of degrees of freedom in the HRVE meta-regression. Studies meta-analyzed are reported in Supplemental material Table S1.

Criteria for MCI diagnosis

The most cited criteria were the ones set forth by Petersen (2004) and by Winblad et al. (2004). Other criteria included the ones reported by Manly et al. (2008) and the ones by Saunders and Summers (2010). A file containing all the relevant literature is available upon request.

Cohen's Kappa values were 0.86 ($p < .001$), 0.78 ($p < .001$) and 0.78 ($p < .001$) for source of recruitment, diagnosis approach and blindness for AD diagnosis respectively, indicating substantial inter-rater agreement (Landis & Koch, 1977).

Regarding the operationalization of cognitive impairment, 22 studies (66.7%) used 1.5SD below the mean as criterion for objective cognitive impairment. All but one study included subjective cognitive complaints or reported diagnostic criteria that include them as

mandatory for MCI diagnosis. Studies assessed on average 4.85 cognitive domains (SD = 1.08, range 3-8) with an average of 9.94 tests (SD = 4.10, range 4-21)

Risk of bias analysis

One of the studies' risk of bias could not be rated because data needed for rating bias are not available (Guaita et al., 2013). All the included studies were rated as having high risk of bias by the two raters, and thus this variable could not be included as a covariate. Thirty-two out of 33 studies were rated by the two raters as having a high risk of bias in the study participation domain (agreement = 96.9%). The other study was rated as having a high risk of bias in the study attrition domain.

Descriptive statistics

Ten (31.4%) studies included participants recruited from the community and 23 studies included participants from memory clinics. The 1.5 SD-cutoff was used in 5 of the community studies (50%) and in 17 (74%) of the clinic studies ($\chi^2(1, N = 33) = 1.79$, $p = .180$).

There were no differences between groups from community and clinic studies in sample size (Community: $M = 64.07$, $SD = 44.61$; Clinic: $M = 58.93$, $SD = 75.98$, $t(79) = 0.31$, $p = .754$), but follow-up was longer for groups of community-dwelling participants (Community: M = 3.50, SD = 1.64; Clinic: M = 2.65, SD = 1.38, $t(79) = 2.44$, $p = .017$).

Table 1 shows the risk-AD for each MCI subgroup in community and clinic studies. There was a higher percentage of individuals with aMCI in clinic (88%) than in community studies (51%) (χ^2 (1, $N = 4{,}907$) = 812.48, $p < .001$). Community studies reported a higher percentage of participants with sdMCI (66%) than clinic studies (41%) (χ^2 (1, $N = 4{,}907$) = 263.57, $p < .001$). Clinic studies reported a significantly higher risk-AD compared to

community studies (log(odds) for Community: M = -1.77, SD = 0.15; log(odds) for Clinic: M = -0.74, SD = 0.14, β = 1.11, 95%CI: 0.54, 1.69, $p < .001$, $\tau^2 = 0.44$, $\omega^2 = 0.04$).

Moderator analyses

There were no significant differences in the risk-AD between studies that reported demographics and those that did not (β = -0.57, 95%CI: -1.24, 0.09, $p = .087$, $\tau^2 = 0.64$, $\omega^2 = 0.03$) with the HRVE. Using standard multivariate meta-regression, differences were statistically significant (β = -0.57, 95%CI: -1.04, -0.10, $p = .017$, $\tau^2 = 0.63$), with studies reporting all the demographic variables showing a lower risk-AD.

With regards to the age grouping variable, there were no statistically significant differences in the risk-AD among groups compared to those aged less than 70 either with the HRVE (ps > .383, $\tau^2 = 0.74$, $\omega^2 = 0$) or with standard meta-regression (ps > .286, $\tau^2 = 0.67$). There were no differences in the risk-AD regarding the SD used to define objective cognitive impairment either with the HRVE (β = 0.28, 95%CI: -0.48, 1.04, $p = .463$, $\tau^2 = 0.73$, $\omega^2 = 0$) or with standard meta-regression (β = 0.28, 95%CI: -0.21, 0.77, $p = .270$, $\tau^2 = 0.68$). There were no statistically significant differences in the risk-AD between studies using an algorithm-based approach and studies using a consensus-based approach using the HRVE (β = 0.55, 95%CI: -0.03, 1.13, $p = .063$, $\tau^2 = 0.67$, $\omega^2 = 0.04$), although these differences became significant with standard meta-regression (β = 0.55, 95%CI: 0.04, 1.05, $p = .033$, $\tau^2 = 0.66$). Studies that reported blindness of previous cognitive status when diagnosing AD reported a lower risk-AD at follow-up both with the HRVE (β = -1.08, 95%CI: -1.77, -0.39, $p = .003$, $\tau^2 = 0.58$, $\omega^2 = 0.04$) and with standard meta-regression (β = -1.08, 95%CI: -1.78, -0.38, $p = .002$, $\tau^2 = 0.59$).

Funnel plots are reported as supplemental material. Asymmetry was statistically significant for the whole sample of MCI groups (Figure S1a). This would indicate that studies

with larger standard errors tend to be published when large effects are reported, suggesting possible publication bias. There was no statistically significant publication bias for any of the MCI groups when analyzed separately (Figure S1b-e).

MCI subtypes and risk of progression to AD

The mean sample size and the risk-AD for each MCI subgroup are shown in table 2. A total of 557 participants in the sd-aMCI (34.2%), 665 in the md-aMCI (32.1%), 81 in the sd-naMCI (10%) and 56 (14%) in the md-naMCI groups progressed to AD.

In all groups the risk-AD was lower than the probability of remaining as MCI or reverting to normal. The univariate model including the four MCI subtypes showed that md-aMCI had a similar risk-AD relative to sd-aMCI, whereas both sd-naMCI and md-naMCI had a significantly lower risk-AD relative to the sd-aMCI group (Table 3). Controlling the effects of the other covariates gave the same results, with both sd-naMCI and md-naMCI showing a lower risk-AD relative to sd-aMCI (Qe = 81.43, $\tau^2 = 0.10$, $\omega^2 = 0$). Clinic samples ($\beta = 0.68$, $p = .049$) and each additional participant across groups within studies ($\beta = 0.003$, $p = .024$) were associated with an increased risk-AD. Each additional participant across studies ($\beta = -0.006$, $p = .021$), studies with blinded AD diagnosis ($\beta = -1.17$, $p = .002$) and studies reporting demographics ($\beta = -0.52$, $p = .039$) were associated with a lower risk-AD.

Standard meta-regression gave similar results: both sd-naMCI and md-naMCI had a lower risk-AD than sd-aMCI. The risk-AD increased for clinic samples ($\beta = 0.52$, $p = .017$) compared to community samples, and decreased for studies with blinded AD diagnosis ($\beta = -0.88$, $p = .003$) and for studies reporting demographics ($\beta = -0.63$, $p < .001$). There was no evidence of heterogeneity ($I^2 = 0\%$, $Q(70) = 68.71$, $\tau^2 = 0.16$).

Due to the differences in the number of participants with different MCI subtypes according to the source of recruitment, we re-run multivariate HRVE analyses for MCI

subtypes from clinic studies only (Table 3). As for the whole pool of studies, both sd-naMCI and md-naMCI had a significantly lower risk-AD relative to sd-aMCI (Qe = 37.17, $\tau^2 = 0$, $\omega^2 = 0$). The risk-AD decreased for each additional participant across studies ($\beta = -0.009$, $p < .001$), for studies using a 1.5SD as cut-off for objective impairment ($\beta = -0.89$, $p = .038$), for studies reporting a blinded AD diagnosis ($\beta = -2.01$, $p < .001$) and for each additional test in the neuropsychological battery ($\beta = -0.08$, $p = .008$), and increased for longer follow-ups ($\beta = 0.28$, $p = .029$) and for algorithm-based MCI diagnosis ($\beta = 0.63$, $p = .025$). Using standard meta-regression both sd-naMCI and md-naMCI had a lower risk-AD compared to sd-aMCI; blinded AD diagnosis ($\beta = -1.41$, $p < .001$) and reporting demographics ($\beta = -0.83$, $p = .002$) were associated with a lower risk-AD, whereas algorithm-based MCI diagnosis ($\beta = 0.74$, $p = .006$) was associated with an increased risk-AD. Length of follow-up and the number of tests in the neuropsychological battery became non-significant. There was no evidence of heterogeneity ($I^2 = 0\%$, $Q(45) = 43.38$).

Due to the small number of studies from the community, differences in the risk-AD for MCI subgroups could not be analyzed with the HRVE. Standard meta-regression showed that none of the MCI groups had a significantly lower risk-AD compared to sd-aMCI (Table 3). The risk-AD was not associated with any of the moderators included in the model. There was also no evidence of heterogeneity ($I^2 = 0\%$, $Q(16) = 10.98$). The statistical power to detect as significant the differences in the risk-AD among MCI subgroups in community studies was very low.

Discussion

This work compared the risk-AD in four neuropsychological MCI subtypes by meta-analyzing longitudinal studies. To this end, we used the hierarchical Robust Variance Estimator meta-regression to control for the correlation between groups that are nested within studies, a statistical approach that controls for both the variance between studies and the variance between groups within studies. We meta-analyzed 81 groups from 33 studies (N = 4,907) and found that both sd-naMCI and md-naMCI groups showed a lower risk-AD relative to the sd-aMCI when variables other than MCI classification were taken into account. Our results cannot support that md-aMCI has an increased risk-AD compared to sd-aMCI, as the risk-AD was similar for both groups when the overall pool of studies were analyzed as well as independently for community and clinic studies. It is unlikely that the absence of differences in the risk-AD between sd-aMCI and md-aMCI reflects a diagnostic issue (i.e., sd-aMCI is diagnosed because of a lack of other cognitive tests in the battery), as all the studies meta-analyzed included several measures of amnestic and non-amnestic cognitive domains for MCI diagnosis and further MCI subtyping. Not surprisingly, our results are in line with those reported by Mitchell and Shiri-Feshki (2009), who found that amnestic MCI and mdMCI had a similar risk-AD (11.7% vs. 12.2%), both having a higher risk-AD compared to naMCI. One possible explanation is that severity of memory impairments, and not the number of tests, is related to the risk-AD, as has been suggested recently (Oltra-Cucarella et al., 2018).

These results are in line with previous research suggesting that naMCI is less likely than aMCI to progress to AD (Ferman et al., 2013). However, as we did not compare the risk-AD for naMCI against a normal control group, we cannot know whether the risk-AD is elevated in naMCI compared to healthy older adults. It has been suggested that naMCI may

be an atypical presentation of AD (Vos et al., 2013), so future studies should analyze whether the risk-AD is elevated in this MCI group irrespective of the risk of other dementias.

Studies with participants from the community reported more balanced rates of aMCI and naMCI, whereas studies with participants from memory clinics reported a higher number of participants with aMCI. In a study of prevalence of MCI in the community including harmonized data from 11 studies from USA, Europe, Asia and Australia, Sachdev et al. (2015) reported that the prevalence of naMCI was slightly higher (3.9%) than the prevalence of aMCI (2%), which suggests that naMCI may be more prevalent in community rather than in clinical settings. Our results suggest that the risk-AD in naMCI samples differ according to the source of recruitment, with a lower risk-AD in naMCI only in clinic samples. However, we acknowledge that statistical power to find such differences in the risk-AD (see table 3) makes us be cautious with regards to the difference in the risk-AD according to the source of recruitment. Future research will clarify this issue by providing more reliable data from larger samples.

We found that studies with small sample sizes reported higher estimates of the risk-AD. It is well known that risk estimates are biased upwards in studies with small sample sizes (Nemes, Jonasson, Genell, & Steineck, 2009), an issue that has been related to publication bias whereby small studies with significant results are more likely to be published (van Enst et al., 2015). More important, however, is the association found between the risk-AD and the variance in sample size between groups within studies, with studies with larger variance reporting a greater risk-AD. In fact, our results showed that naMCI groups had a lower risk-AD in clinic studies, which reported unbalanced sample sizes favoring amnestic impairments. How differences in sample size between MCI groups within studies affect the risk of progression to dementia or AD, and whether the same findings apply similarly to community and clinic studies, warrants further research.

The results reported here must be regarded with some limitations. In line with previous works using measures of progression such as risk ratios (Mitchell & Shiri-Feshki, 2009) or logistic regression (Chary et al., 2013), we used ORs instead of hazard ratios due to the impossibility to access raw data, which also prevented us from analyzing whether the risk-AD is linear during follow-up or rather accelerates or decelerates over years. If it was possible to obtain raw data from authors, an Individual Patient Data meta-analysis (Riley, Lambert, & Abo-Zaid, 2010) could be applied to analyze hazard ratios, to plot the risk-AD against years of follow-up, and also to analyze severity of memory and nonmemory domains using standardized measures. This approach could also allow analyzing whether any specific pattern of non-memory impairments (e.g., executive functioning, language, visuospatial abilities) is associated with an increased risk-AD in aMCI.

All the studies were rated as having a high risk of bias by two raters, with almost a perfect agreement regarding study participation. Two main issues related to the risk of bias deserve discussion. On the one hand, we used a tool for assessing the risk of bias in longitudinal studies that addresses 6 domains with several items within each domain (Hayden et al., 2013). As each domain is rated as having a high risk of bias when one item is rated as high risk of bias, including several items increases the probability of being rated as having a high risk of bias. However, this tool could only be measuring the quality of data reporting and not the risk of bias of the study itself.

On the other hand, there were some studies of which the primary aim was not analyzing progression from MCI to AD, and thus data on progression are reported as complementary to other main hypothesis. For example, Bélanger and Belleville (2009) analyzed semantic inhibition impairments, Dewar et al. (2012) analyzed how minimal interference could enhance memory across the AD spectrum including individuals with aMCI, Estévez-González et al. (2004) analyzed semantic knowledge of famous people, and

Smith (2014) analyzed anterograde and retrograde amnesia in persons with aMCI. Thus, rating those studies with a tool developed for epidemiological studies analyzing incidence or prevalence is problematic, as they are very likely to be rated as having a high risk of bias due to differences in the reporting of critical information.

One of the main findings is the number of variables that bias the risk-AD in previous research. Due to limitations associated with the reporting of results in primary studies, relevant variables potentially affecting outcome in MCI such as age, sex or education (Hu et al., 2017) could not be included as covariates in the analyses. We found significant differences in the risk-AD between studies that reported demographics and studies that did not, which might indicate that not reporting variables such as age, education or sex may be biasing upwards the true estimates of the risk-AD. Most of studies included in this meta-analysis reported the mean and standard deviation of each relevant variable either for the whole MCI group or separately for progressors and non-progressors. We strongly suggest that relevant variables be reported independently for each MCI group in longitudinal studies in order to facilitate their inclusion in future meta-analyses.

Our findings have implications for both clinical and research scenarios. We found that studies with blinded AD diagnosis reported lower risk-AD at follow-up. These findings support that being diagnosed with AD is more likely when clinicians are aware of previous cognitive impairments (Petersen et al., 2009), which could explain in part the differences in rates of progression to AD reported in the literature. These results highlight the importance of controlling for blindness of clinicians in future research. Similarly, we found that using an algorithm-based approach for diagnosing MCI might result in higher rates of progression to AD compared to consensus-based approaches. It has been reported that the consensus-based approach increases heterogeneity in MCI classifications and impedes replication, and an algorithm-based approach has been recommended (Duara et al., 2010). Although not without

limitations on its own (Binder, Iverson, & Brooks, 2009; Brooks, Iverson, & White, 2007), the use of algorithm-based approaches to diagnosing MCI is recommended according to our data, in agreement with previous reports (Duara et al., 2010).

Related to this point is the finding that the risk-AD decreased with increasing number of tests in the neuropsychological battery. A review by Binder et al. (2009) showed that the probability of obtaining one or more low scores increased as the number of measures increased, with a percentage of up to 59% of participants having at least one score 1.5 standard deviations below the mean. Recently, Oltra-Cucarella et al. (2018) reported that up to 90% of a sample of 280 individuals with normal cognition had up to two scores at least 1.5 standard deviations below the mean in a battery with 9 measures. These data suggest that increasing the number of tests in the neuropsychological battery increases the probability of false positive MCI cases, and also the probability of falsely being classified as having multiple-domain MCI if only two measures suffice for diagnosis in batteries with several measures. However, our findings apply only to individuals with cognitive complaints, as all the studies analyzed included subjective complaints as a requirement for diagnosis.

As pointed out by one of the reviewers, a meta-analysis can be very useful but is limited by the quality of the source data. As such, simply studying large sets of data does not obviate the problems with the underlying data sources. The large amount of missing information that could not be retrieved from the authors did not allow testing for some important moderators of the risk estimates. These findings, along with the statistically significant asymmetry in funnel plots when all MCI groups are analyzed points to a need for higher quality studies. However, it cannot be ruled out that asymmetry in estimates of progression to AD among MCI groups represents a true difference in the risk-AD for amnestic and non-amnestic MCI profiles. The high risk of bias of the studies analyzed and the lack of information moderating the risk-AD estimates affect the reliability of our results.

Thus, the lack of differences in the risk-AD for single-domain aMCI and multiple-domain aMCI must be taken cautiously until future research confirms this pattern of results.

There are several points in this meta-analysis that make us be relatively confident with our results. One of the main strengths of this meta-analysis is the use of the HRVE for meta-analyzing the risk-AD. As several studies provided data for different groups, analyzing groups as independent units of analysis without considering their correlation with each other may bias the results, which is true when ordinary meta-regression techniques are applied. Although neither power nor heterogeneity could be calculated, the HRVE allowed us decomposing variance into between studies and between groups-within studies components, which allows isolating the specific effects of covariates that may vary differently between or within studies, an improvement over other meta-analysis approaches that do not take account of correlated variables. Interestingly, our results were replicated using standard meta-regression when variance between groups within studies was zero or very close to zero, yielding the same results but providing the possibility to calculate measures of heterogeneity and statistical power. Of note is that some significant findings would become non-significant if criteria used to define statistical significance would turn to a more stringent level (i.e., α = .01). As previously stated, our results of a similar risk-AD for single-domain and multiple-domain aMCI replicate the findings reported by Mitchell and Shiri-Feshki (2009).

This is, to our knowledge, the first work analyzing the risk-AD for four MCI groups separately in a meta-analysis. Our main findings indicate that when sample size, length of follow-up, the source of recruitment, the criterion for objective impairment and other sources of bias are controlled, single- and multiple-domain aMCI groups have a similar risk-AD. These results highlight the importance of taking account of both the type and the number of cognitive impairments, as well as differences in sample size among MCI groups for the identification of early or very early AD. Future meta-analyses should improve the analysis of

the risk-AD by including additional clinical and demographical variables if the reporting of the results from primary studies is improved. According to the findings of a similar risk-AD for sd-aMCI and md-aMCI, it is necessary to more fully study which differences between these groups may be related to the risk-AD, and whether there is a genuine higher risk-AD for md-aMCI when other variables are controlled for. All the studies meta-analyzed included several cognitive tests to assess cognition, which could have implications for the MCI diagnosis. It has been reported that obtaining one or more scores below -1.5 standard deviations is common in older adults when several tests are administered (Binder et al., 2009; Brooks et al., 2007). Although individuals with md-aMCI could indeed have several cognitive domains affected, some proportion of individuals could have been diagnosed with md-aMCI only because of statistical chance, which could help to explain the lack of difference in the risk-AD relative to sd-aMCI.

Additionally, variables such as the number and type of tests used to define cognitive impairment, or variations in published diagnostic criteria should be included in future works analyzing the risk-AD. The MCI syndrome needs to be clearly defined and separated for samples of community-dwelling older adults and samples recruited in memory clinics, as both MCI subtypes and the risk-AD are strongly related to the source of recruitment. Our results need to be replicated in research on the risk of progression to dementia other than AD.

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Table 1. Prevalence of MCI subtypes and RCAD

	Community samples				Clinic samples			
	n	%n	Prog	%Prog	n	%n	Prog	%Prog
sd-aMCI	452	27.1	80	17.7	1,179	36.4	477	40.4
md-aMCI	397	23.8	82	20.6	1,672	51.6	583	34.9
sd-naMCI	645	38.7	67	10.4	162	4.9	14	8.6
md-naMCI	172	10.4	26	15.1	228	7.1	30	13.1
Total	1,666		255		3,241		1,104	

n: simple size. %n: percentage for each MCI group. Prog: number of progressors to AD. %Prog: percentage of progressors for each MCI subtype. MCI: Mild Cognitive Impairment. sd: single-domain. md: multiple domain. aMCI: amnestic MCI. naMCI: non-amnestic MCI.

Table 2. Risk of AD for MCI subgroups

MCI subgroup	n (SD)	n Progressors	n Non-Progressors	Odds	95% LCI	95% UCI	p
sd-aMCI	54.4 (55.6)	18.6 (27.3)	35.6 (35.3)	0.47	0.33	0.66	< .001
md-aMCI	86.2 (90.7)	27.7 (28.5)	58.5 (68)	0.52	0.36	0.75	< .001
sd-naMCI	53.8 (58)	5.4 (9.3)	48.4 (50.8)	0.11	0.07	0.16	< .001
md-naMCI	33.3 (44.2)	4.7 (6.5)	28.7 (38.5)	0.18	0.11	0.27	< .001

n: mean sample size (with Standard Deviation). Odds: the odds of progressing to AD. LCI: lower confidence interval. UCI upper confidence interval. MCI: Mild Cognitive Impairment. sd: single-domain. md: multiple-domain. aMCI: amnestic MCI. naMCI: non-amnestic MCI.
Uncorrected difference in the risk-AD between aMCI and naMCI: $\beta = 1.36$, $t(31) = 7.04$, $p < .001$
Uncorrected difference in the risk-AD between sdMCI and mdMCI: $\beta = -0.28$, $t(31) = -1.58$, $p = .124$

Table 3. Differences in the risk-AD among MCI subgroups, with sd-aMCI as the reference

	Log(odds)	OR	95% LCI	95% UCI	t*	p
md-aMCI[a]	0.11	1.12	0.78	1.61	0.59	.553
sd-naMCI	-1.54	0.21	0.13	0.36	-5.77	<.001
md-naMCI	-0.99	0.37	0.22	0.62	-3.87	<.001
Clinic studies[b]						
md-aMCI	0.12	1.13	0.76	1.66	0.62	.545
sd-naMCI	-1.73	0.18	0.09	0.33	-5.33	<.001
md-naMCI	-1.01	0.36	0.18	0.75	-2.74	.013
Community studies[c]					z	
md-aMCI	0.26	1.30	0.61	2.77	0.66	.508
sd-naMCI	-0.59	0.55	0.27	1.12	-1.65	.099
md-naMCI	-0.47	0.63	0.26	1.52	-1.03	.302

OR: odds ratio. LCI: lower confidence interval. UCI upper confidence interval. MCI: Mild Cognitive Impairment. sd: single-domain. md: multiple-domain. aMCI: amnestic MCI. naMCI: non-amnestic MCI. **t*-statistic derived from the hierarchical Robust Variance Estimator for differences in log(odds).

[a]Statistical power in standard multiple meta-regression: md-aMCI = 0.06, sd-naMCI = 0.99, md-naMCI = 0.84, follow-up = 0.05, SD = 0.11, source = 0.66, blindness = 0.85, diagnosis approach = 0.64, demographics = 0.79

[b]Statistical power in standard multiple meta-regression: md-aMCI = 0.06, sd-naMCI = 0.99, md-naMCI = 0.82, follow-up = 0.05, SD = 0.36, blindness = 0.94, diagnosis approach = 0.78, demographics = 0.88, number of tests = 0.17

[c]Statistical power in standard multiple meta-regression: md-aMCI = 0.10, sd-naMCI = 0.38, md-naMCI = 0.18, follow-up = 0.16, SD = 0.33, blindness = 0.22, diagnosis approach = 0.05, demographics = 0.19, number of tests = 0.13

Figure captions

Figure 1. Flow chart

Figure 2. Odds of progressing to AD for amnestic MCI

sd-aMCI: single-domain amnestic MCI

md-aMCI: multiple-domain amnestic MCI

Figure 3. Odds of progressing to AD for non-amnestic MCI

sd-naMCI: single-domain non-amnestic MCI

md-naMCI: multiple-domain non-amnestic MCI