**Title: Does the neuropsychiatric inventory predict progression from mild cognitive impairment to dementia? A systematic review and meta-analysis**

Sabela C. Mallo[a,1,*], Scott B. Patten[b,c,e,2], Zahinoor Ismail[b,c,d,e,3], Arturo X. Pereiro[a,4] , David Facal[a,5], Carlos Otero[a,6], Onésimo Juncos-Rabadán[a,7]

[a] Department of Developmental Psychology, University of Santiago de Compostela, Santiago de Compostela, Xosé María Suárez Núñez Street, Campus Sur, Santiago de Compostela, Galicia, ES–15782, Spain.

[b] Hotchkiss Brain Institute, University of Calgary, 3330 Hospital Dr. NW, Calgary, AB T2N 4N1, Canada.

[c] Department of Psychiatry, University of Calgary, 2500 University Dr. NW, Calgary, AB T2N 1N4, Canada.

[d] Department of Clinical Neurosciences, University of Calgary, 2500 University Dr. NW, Calgary, AB T2N 1N4, Canada.

[e] Mathison Centre for Mental Health Research and Education, 3280 Hospital Dr. NW, Calgary, AB T2N 4Z6, Canada.

[1]sabelacarme.mallo@usc.es

[2] patten@ucalgary.ca

[3] zahinoor@gmail.com

[4] arturoxose.pereiro@usc.es

[5]david.facal@usc.es

[6]coterortega@gmail.com

[7]onesimo.juncos@usc.es

*Corresponding author. Complete address: Developmental Psychology, University of Santiago de Compostela, Xosé María Suárez Núñez Street, Campus Sur, Santiago de Compostela, Galicia, ES–15782, Spain. Tel.: +34 881-813-949; Fax: +34 881-813-901 E-mail: sabelacarme.mallo@usc.es

**ABSTRACT:**

*Background:* Neuropsychiatric Symptoms (NPS) are common in Mild Cognitive Impairment (MCI). The Neuropsychiatric Inventory (NPI) and its shorter version, the Neuropsychiatric Inventory Questionnaire (NPI-Q), are the most common measures to asses NPS. Our objective was to determine if NPI/NPI-Q ratings predict conversion from MCI to dementia.

*Methods:* Empirical longitudinal studies published in English or Spanish, concerned about the role of NPS as a risk factor for conversion from MCI to dementia, with a diagnosis of MCI following clinical criteria, that reported NPI/NPI-Q total severity score in converters versus non-converters, were included. Random effects models were used and heterogeneity was explored with stratification and a random-effects meta-regression. The overall conversion rate and the standardized mean difference (SMD) for evolution, as a function of NPI/NPI-Q severity scores, were calculated.

*Results:* The overall conversion rate was 35%. Mean NPI/NPI-Q ratings were higher in converters versus in non-converters, with the overall SMD approached significance. Heterogeneity was observed in studies > 2 years of follow-up and in a study with a mean age of >80 years. This heterogeneity concerned the size, not the direction of the difference.

*Conclusions:* Our results suggest that NPI/NPI-Q ratings are associated with conversion from MCI to dementia.

*Keywords:* Neuropsychiatric Symptoms; Mild Cognitive Impairment; dementia; Neuropsychiatric Inventory; Neuropsychiatric Inventory Questionnaire; meta-analysis.

## 1. Background

In Mild cognitive impairment (MCI) individuals demonstrate objective cognitive impairment with minimal impairment of instrumental activities of daily living. MCI can be the first cognitive expression of Alzheimer disease (AD) or be secondary to other disease processes (Petersen et al., 2018). MCI is considered a cognitive stage of the cognitive continuum traditionally divided into three categories: cognitively unimpaired (CU), MCI and dementia(Jack et al., 2018). Although patients with MCI have an increased risk of progressing to dementia relative to age-matched controls, most remain stable or return to normality and, only a proportion convert to dementia(Cui et al., 2013; Facal et al., 2015; Michaud et al., 2017).

Neuropsychiatric symptoms of dementia (NPS), also known as Behavioral and Psychological Symptoms of Dementia (BPSD), are non-cognitive, behavioral or psychiatric symptoms that include disturbances of mood, perception, and behavior related to a neurocognitive disorder (Ballard et al., 2008; Lyketsos et al., 2011). Two previous systematic reviews (Apostolova and Cummings, 2008; Monastero et al., 2009) concluded that NPS are common in MCI. The NPS Professional Interest Area (PIA) of the International Society to Advance Alzheimer's Research and Treatment (ISTAART), described later life onset of sustained NPS as an at-risk state for incident cognitive decline and dementia with the development of the research diagnostic criteria for Mild Behavioral Impairment (MBI)(Ismail et al., 2017a, 2016). People with MCI and NPS have a greater impairment in global, cognitive and functional scores than those who have MCI without NPS (Feldman et al., 2004), and are more likely to be in clinical care(Ismail et al., 2017b).

The Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) is the most commonly used measure to asses NPS, both in clinical and research settings(Ismail and Mortby, 2017). The NPI is a structured informant interview with established reliability and validity(Cummings et al., 1994). Using the NPI, the researcher obtains a subjective assessment of the presence, frequency and severity of ten NPS (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior) and two neurovegetative domains (sleep and nightmare behavior change and appetite/eating change). Additionally, the informant provides an assessment of their level of distress in relation to specific symptoms domains. The items are behavior-based, observable and specific to dementia populations. The NPI utilizes a reference time of four weeks. Up to 30 minutes are needed to complete the test. The NPI-Q(Kaufer et al., 2000) is a brief (five minutes or less), reliable and informant-based screening version of the NPI. Despite the fact that both the NPI and NPI-Q are specific to dementia populations, several studies using these instruments concluded that NPS increase the risk of dementia in people with MCI at baseline(Donovan et al., 2014; Geda et al., 2014; Masters et al., 2015; Rosenberg et al., 2013). While some studies found that NPI or NPI-Q total score predicted progression from MCI to dementia(Banks et al., 2014; Mortby et al., 2017), others did not find this association(Brodaty et al., 2011).

It is important to determine whether the NPI and NPI-Q total scores constitute accurate and reliable measures to predict conversion from MCI to dementia. To our knowledge, no consensus has emerged yet, despite a growing literature of studies. This gap constitutes an impediment to research, policy and practice. It is important to determine whether these instruments allow us to identify patients at risk of dementia early on. Hence, the

instruments may help to increase the understanding of NPS and cognitive impairment, develop interventions and facilitate clinical treatment. It is possible that uncertainty continues to exist in this literature due to a lack of power in individual studies and differing study designs, issues that are best addressed through studies targeting knowledge synthesis. Thereby, we aimed to carry out a systematic review and a meta-analysis of the literature to determine (1) the rate of conversion of MCI to dementia and (2) whether severity of baseline NPS, measured by the NPI or NPI-Q, could predict conversion from MCI to dementia in people diagnosed with MCI at baseline according to diagnostic criteria in longitudinal studies comparing converters versus non-converters.

## 2. Methods

### 2.1. PICO Statement

P. Are elevated levels of neuropsychiatric symptoms, as assessed by the NPI or NPI-Q, associated with conversion of MCI to dementia?

I. People with MCI who convert to dementia.

C. People with MCI who do not convert to dementia.

O. An improved ability to anticipate this transition in a high-risk population (in both clinical and population-based settings).

### 2.2. Search Strategy

Our systematic review was conducted according to MOOSE(Stroup et al., 2012) standards and registered in PROSPERO("National Institute for Health Research. PROSPERO international prospective register of systematic reviews.," n.d.).

Articles published between January 1999 and September 2018 were selected from PsycINFO, PubMed, SCOPUS and Web of Science (WOS). These are the largest databases with comprehensive coverage and indexing of biomedical journals worldwide. We searched articles published after 1999 because diagnostic criteria for MCI was first established in 1999(Petersen et al., 1999). The keywords used were: ("Mild Cognitive Impairment" OR "cognitive impairment" OR "minor neurocognitive disorder") AND (progression OR evolution OR risk OR conversion) AND ("Neuropsychiatric Inventory") (eAppendix in the Supplement). Titles were screened first, followed by abstracts and full article texts. References were compiled using Mendeley Desktop 1.19.3, with duplicates removed using this software.

### 2.3.Study Selection

Two different reviewers (S.C.M and C.O) screened titles, abstracts and full text articles. Titles and abstracts were screened using Rayyan QCRI(Ouzzani et al., 2016). There was 81% consensus between the reviewers. Disagreements of eligibility were reconciled by the original reviewers and, if required, a third reviewer. Figure 1 shows the number of articles included at each selection stage.

Inclusion criteria were: 1) diagnosis of MCI at baseline following clinical criteria(Albert et al., 2011; Geda et al., 2008; Petersen et al., 2001, 1999; Petersen, 2004; Winblad et al., 2004); 2) report NPI or NPI-Q total severity score in converters versus non-converters; 3) longitudinal studies; 4) concerned about the role of NPS as a risk factor for progression from MCI to dementia; 5) empirical studies published in English or Spanish. Exclusion criteria were: 1) articles sampled or contained a majority of participants from a special

population (e.g.: people with cancer); 2) inability to contact the authors requiring important information related to an article; and 3) references consisting of abstracts alone.

### 2.4.Data Abstraction and Study Quality

A standardized excel form was developed, with the following variables: study information (i.e.: authors, year), substantive characteristics (i.e., country, mean age, education level), methodological characteristics (i.e., months of follow up, sample) and results, including the mean and standard deviation (SD) of the total severity score in the NPI/NPI-Q at baseline in stable vs. converters patients, necessary to calculate an estimate. Two different reviewers (S.C.M and C.O) abstracted data on each included study. Disagreements regarding data extraction were resolved by consensus or by an independent party (O.J.-R.).

Study quality was assessed using the quality assessment tool for observational cohort and cross-sectional studies from the National Heart, Lung and Blood Institute[31]. The tool contains 14 criteria on which quality is determined. The criteria were rated as either yes, no, or "other" (i.e., not reported), and an overall rating for the study as "good," "fair," or "poor" was provided.

### 2.5.Data Synthesis and Analysis

Funnel plots were used to visually assess possible publication bias. Begg's and Egger's tests were used as tests for publication bias, using "metafunnel" and "metabias" in Stata, version 14. A random effects model was used in addressing both of the study objectives because we anticipated heterogeneity between studies. Heterogeneity was assessed in the analysis visually using forest plots, the $Q$-test and $I^2$ index, and by reporting $\tau^2$ values from the random effects meta-analysis.

We calculated the proportion of MCI patients converting to dementia in each study. The "metaprop" command in Stata version 14.2 was used in the meta-analysis of these proportions. Given the asymmetry of sampling distributions for estimated proportions, the Freeman-Tukey double arcsine transformation was used for variance stabilization.

We calculated the standardized mean difference (SMD) for evolution from MCI to dementia as a function of NPI severity scores. As several different versions of the NPI were used in the studies included, Cohen's d was used to quantify effect size. Forest plots and meta-analytic estimates were stratified by a set of study characteristics in order to explore their impact on heterogeneity: study duration, mean age of the sample, methodological quality ratings, percent women in the sample, mean education level, and MCI definition, number of measurements.

## 3. Results

### 3.1. Identification and Description of Studies

We screened a total of 932 unique citations and excluded 845 (Figure 1). We reviewed the full text of 87 articles, and of these, 11 met all inclusion criteria.

INSERT FIGURE 1.

Studies characteristics are displayed in Table 1. Of the included studies, five were from Europe, one was from North America, three from Asia, one from South America and one from Australia. Dates of publication ranged from 2012 to 2017. The NPI was used in nine studies, while the NPI-Q was used in two. Five studies indicated that most of their participants had reached the educational level corresponding to secondary studies, four to primary studies, one to advanced studies and one did not report this information.

Seven studies (63.63%) had an overall rating of fair quality, while four (36,37%) studies were rated as good (eTable 1 in the supplement). The most frequently met quality criteria were items one, two, six, eight and nine, which were reported by all the studies. Item 12 was never reported and a number of items were rarely reported, specially item three and item. Importantly, item 13 refers to the loss to follow-up after baseline, and it is therefore one of the most important criteria considering the objective of our meta-analysis and key to differentiate good and fair quality studies.

### 3.2. Conversion rate

A forest plot showing the proportions converting from MCI to dementia is presented in Figure 2. This proportion ranged from 0.187(Osone et al., 2016) to 0.688(Mauri et al., 2012). The plot shows considerable heterogeneity ($I^2$ = 94.6%, $\chi^2$ = 183.93, d.f. = 10, p < 0.001, $\tau^2$= 0.119), but most estimates fell in the range of 10% to 30%. The $\tau$ value was 0.34, representing the standard deviation of estimates arising from these studies. When considered in relation to the overall estimated conversion rate of 0.35 (95% CI 0.25-0.45), see Figure 1, this is a large value, partially reflecting the Mauri et al.(Mauri et al., 2012) outlier. The funnel plot did not suggest publication bias and the Begg's (z=0.62, p = 0.53, continuity corrected) and Egger's tests were not significant (t=0.51, p = 0.624). Studies rated as having "good" methodological quality had a lower pooled conversion proportion (0.23, 95% CI 0.20-0.27) than those rated as fair (0.41, 95% CI 0.27-0.56). Studies with a duration of >two years had a higher conversion proportion (0.39, 95% CI 0.25-0.55) than those with less than two years or less of follow-up (0.26, 95% CI 0.20-0.32). The mean age of the sample, the proportion female, the number of assessments in the study, average

education level of study samples and the MCI criteria used in specific studies did not have a significant effect on the conversion proportion.

### 3.3. NPI ratings and conversion from MCI to dementia

The analysis of SMDs (Cohen's d) showed less heterogeneity, but the observed heterogeneity continued to be statistically significant ($I^2 = 70\%$, $\chi^2 = 33.33$, $p < 0.001$, $\tau^2 = 0.082$). The funnel plot did not suggest publication bias and the Egger ($t = -0.18$, $p = 0.865$) and Begg ($z=1.25$, $p = 0.213$, continuity corrected) tests were not significant. The pooled SMD was 0.21 indicating a small effect size, that approached statistical significance in the random effect model ($z=1.95$, $p = 0.052$), see Figure 3.

With restriction to the subset of seven studies having greater than two years of duration of follow-up ($I^2 = 74.6\%$, $\chi^2 =$ , 23.66, $p =0.001$, $\tau^2 = 0.14$) the SMD (0.34, 95% CI 0.01-0.67) did achieve statistical significance, $z=2.04$, $p=0.041$), see Figure 4. With removal of the Bidzan et al.(2017)(Bidzan et al., 2017) study there was no remaining heterogeneity ($I^2 = 0$ and $\tau^2 = 0$), such that the random effects model approximated a fixed effects model, the SMD was 0.198 (95% CI 0.034 – 0.361) remained significant ($z = 2.37$, $p = 0.018$). With stratification of the meta-analysis based on studies having above or below a mean age of 80 in their sample, the SMD was not significant in 10 studies with a mean age of less than 80 (SMD = 0.20, 95% CI -0.05-0.45, $z = 1.54$, $p = 0.124$) but was significant in the single study that had a mean age > 80(Forrester et al., 2016), SMD = 0.29 (95% CI 0.09-0.50, $z = 2.84$, $p = 0.005$). Stratification for additional variables did not explain observed heterogeneity.

## 4. Discussion

We conducted a systematic review and meta-analysis to clarify the extent of association of NPI ratings with subsequent conversion to dementia in people with MCI. Our motivation for conducting the systematic review was the inconsistent nature of the prior literature, which may in turn be due to imprecision of individual studies and methodological differences between them. Our meta-analysis was not entirely decisive in showing that mean NPI ratings are higher in respondents with MCI who convert to dementia, but an overall SMD approached significance ($p = 0.052$). However, there was considerable heterogeneity observed, and the effect was evident in studies having > two years of follow-up and in a single study with a mean age of > 80 years in its study sample. Furthermore, the estimated effect sizes within all subgroups were in the direction of higher NPI ratings in converters, such that the heterogeneity observed concerned the size, not the direction, of the difference. Taken together these results provide evidence that NPI ratings are associated with conversion to dementia in people with MCI.

In our meta-analysis, the overall conversion rate from MCI to all-cause dementia was 35%. Another meta-analysis(Mitchell and Shiri-Feshki, 2009) estimated that the cumulative proportion of conversion from MCI to dementia was 39.2% (including AD and vascular dementia). However, MCI has been considered as a highly complex diagnostic entity, with a heterogeneous transition between normal ageing and MCI subtypes, including progression of symptoms (worsening) or no change (persistent MCI) or even improvement of symptoms (recovery)(Facal et al., 2015). Research is needed to determine which variables are decisive to predict conversion to dementia, reversion to normal ageing or stability of the MCI diagnosis. Thus, it would be possible to improve the early identification of patients at risk of dementia and to develop prevention programs.

Some variables did not have a significant effect on the conversion proportion: age, percentage of women, education level, number of measurements and MCI criteria. However, the duration of the follow-up and the mean age of the sample did have a significant effect.

Seven of our studies were rated as having “good” quality, whereas four were rated as “fair”. Surprisingly, studies rated as having “good” quality had a lower conversion rate compared to those rated as “fair”. One reason for these results may be that quality studies had less percentage of attrition because the selection of participants was carried out in a more rigorous manner (items two, three, four and five). Besides, these participants are probably healthier versus those from studies rated as having “fair” quality. Therefore, they are more likely to continue in the study and less likely to convert to dementia. These results point to the need to a more rigorous selection of participants, by applying criteria such as clearly specify the study population, stablished the inclusion and exclusion criteria and provided a sample size justification.

Concerning the follow-up duration, our results indicated that studies with a duration of > two years had a higher conversion rate than those with less than two years of follow-up. In another meta-analysis(Mitchell and Shiri-Feshki, 2009) studies of less than three years were not included and they obtained a conversion rate of 39.2%, slightly higher than ours (35%). Previous researchers have pointed the potential role of follow-up duration in the progression of the symptoms(Facal et al., 2015). For example, a recent study(Cui et al., 2011) concluded that predictive values for MCI participants who converted after 12 months are generally higher than MCI participants that converted within 12 months. Thus, our

results are in accordance with previous findings that suggest that higher levels of conversion are found in longer follow-up studies.

We focused our meta-analysis on NPS, measured with the NPI and NPI-Q, and their role as risk factors from MCI to dementia. Our results showed that mean NPI and NPI-Q ratings were higher in MCI participants who converted to dementia versus those who did not, despite the overall SMD approached significance. A meta-analysis(Cooper et al., 2015) studying modifiable predictors of dementia in MCI determined that NPS predicted conversion from any type of MCI to all-cause dementia. The meta-analysis was performed with 5 studies and all of them used the NPI/NPI-Q. Our results are in accordance with this study, as in our research the estimated effect sizes within all subgroups were in the direction of higher NPI/NPI-Q scores in converters versus non-converters, the heterogeneity observed concerned the size, not the direction, of the difference.

However, it is important to note that the NPI and the NPI-Q, despite being the most commonly used instrument to asses NPS(Ismail and Mortby, 2017), are specific to dementia populations(de Medeiros et al., 2010). Therefore, our results may be related to the lack of sensitivity of the NPI-Q on the earliest NPS symptoms, based on the types of questions and the relatively short reference range of the NPI. The Mild Behavioral Impairment checklist(Ismail et al., 2017a) (MBI-C) is a case ascertainment instrument, specially developed to assess NPS in a community dwelling, functionally independent, older population, including MCI participants. It mandates NPS being sustained for six months and representing a change from the participant's longstanding pattern of behavior, to reduce the inclusion of transient symptoms and reactive states that might be captured as NPS-positive with a shorter reference range instrument. These requirements are not explicit

in many rating scales, such as the NPI and NPI-Q. The MBI-C was developed to operationalize the measurement of MBI and consists of 34 items organized according MBI domains: 1) drive/motivation (apathy); 2) affective/emotional dysregulation (mood/anxiety symptoms); 3) impulse control/agitation; 4) social inappropriateness (impaired social cognition) and 5) abnormal thoughts/perception (psychotic symptoms). The first cross-sectional validation analyses of the MBI-C have been published(S. C. Mallo et al., 2018; Sabela C Mallo et al., 2018), and longitudinal data are also emerging with this instrument demonstrating an association with cognitive decline(Creese et al., 2019). Studies with the MBI-C, which was specially developed for pre-dementia states, may provide valuable information about the role of NPS as predictors of cognitive decline, even from the preclinical phases.

In our meta-analysis, two variables explained the heterogeneity in results when analyzing NPS as predictors of conversion to dementia: study duration > two years and mean age > 80.

It is important to note that the seven studies that had more than two years of follow-up achieved a significance effect on heterogeneity. Hence, removing one outlier(Bidzan et al., 2017) (with very high NPS scores, probably because it is a Mental Health Clinic study), the random effects model approximated a fixed effect. Therefore, these results showed that the effect of NPS in conversion is higher in studies with more than two years of follow-up. These results suggest that time period is also an important variable not only in cognitive symptoms progression(Cui et al., 2011; Facal et al., 2015) but also in NPS progression. Further research with longer follow-up periods is recommended.

Additionally, a significant effect was found in one study with a mean age > 80 years. Thus, the effect of NPS in conversion seems to be higher in studies with very-old participants. Previous research has outlined that age is a risk variable when predicting the evolution from MCI to dementia(Matthews et al., 2008). Thus, age may be a risk factor not only for cognitive impairment but also for behavioral impairment, especially in very old participants. Future studies are needed to explore the effects of age on NPS symptoms.

To the best of our knowledge this is the first meta-analysis that estimates the predictive role of the NPS, measured with the NPI/NPI-Q, in conversion from MCI to dementia. Despite the fact that results were not entirely decisive, the overall SMD approached significance and the estimated effects sizes within all groups were in the direction of higher NPI/NPI-Q rating in converters versus non-converters. Hence, our results did not suggest publication bias. However, only 11 studies were included in our meta-analysis. Our inclusion and exclusion criteria may be related to these results. The NPI/NPI-Q scale is the most widely used in literature(Ismail and Mortby, 2017) and we wanted to analyze if the symptoms measured with this instrument increased the risk of dementia. On the other hand, we included only studies with people with MCI diagnosed on the basis of clinical criteria, following the recommendations from the National Institute on Aging-Alzheimer's Association(Albert et al., 2011). It is also worth mentioning that despite having contacted several authors to provide us with data on total NPI/NPI-Q scores in converters and non-converters, we did not get a response. Lastly, only one population-based study was included, therefore we could not study if the sample type was a significant source of heterogeneity. Previous studies have suggested that hospital-based samples report a higher prevalence of NPS probably reflecting differences in demographics, study settings, MCI

diagnosis and behavioral instruments used(Apostolova and Cummings, 2008; Monastero et al., 2009). Besides, four of our studies were rated as having "good" quality, whereas seven were rated as "fair". This result speaks to the need to further develop quality studies on this topic.

The evidence from this study suggest that NPI/NPI-Q ratings are associated with conversion from MCI to dementia. Our results indicated that the pooled SMD approached significance. Heterogeneity was observed in studies with > two years of follow-up and in a single study with a mean age of > 80 years. However, the heterogeneity concerned the size, not the direction of the difference, within all subgroups indicating higher NPI/NPI-Q scores in converters compared to non-converters. Further research on this topic is required.

**Disclosure statement**

The authors have no conflicts of interest to report.

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**Figure titles**

**Figure 1**. Flowchart of the article selection and inclusion in the meta-analysis.

**Figure 2**. Forest plot for the proportion converting from MCI to dementia, unstratified estimates from a random effects model.

**Figure 3.** Forest Plot: estimates of conversion of MCI to dementia. Standardized Mean Differences (SMD) based on Cohen's-d.

**Figure 4.** Forest Plot: estimates of conversion of MCI to dementia. Standardized Mean Differences (SMD) based on Cohen's-d, with restriction to studies with > 2 years duration of follow-up.

**Table 1.** Summary of included studies characteristics.

| Author, year | N MCI | Mean age | Education | % of women | Country, continent | NPI scale | MCI criteria | Dementia criteria | Sample type | Number of measurements | Follow-up (months) | NPI converters | NPI stables |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mauri et al., 2012**( Mauri et al., 2012) | 208 | 73.60 | School | 59.60 | Italy, Europe | NPI | Peterse n et al., 2001 | Hughes et al., 1982; AD: NINCDS-ADRDA; LB: McKeith et al. 2005; FT: Lund & Manchester Groups; vascular: Erkinjuntti et al., 2000 | Clinic al | 7 | 72 | 19.1 | 7.5 |
| **Somm e et al., 2013**( Somm e et al., 2013) | 132 | 69.8 | High school | 46.9 | Spain, Europe | NPI | Peterse n et al. 2004 | DSM-V and NINCDS-ADRADA (evolution to dementia measured as decline in the CDR) | Clinic al | 3 | 42 | 7.55 | 9.6 |
| **Kim et al., 2013**( Kim et al., 2013) | 236 | 71.51 | School | 62.71 | Korea, Asia | NPI | Peterse n et al. 1999 with modific ations | DSM-V and NINCDS-ADRADA | Clinic al | 2 | 17 | 4.93 | 6.84 |
| **Broda ty et al., 2014**( Brodat | 185 | 76 | - | 45.95 | Australi a, Asutrali a | NPI | Winbla d et al. 2004 | DSM-IV | Clinic al | 6 | 36 | 9.65 | 16.6 4 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| y et al., 2014) | | | | | | | | | | | | | |
| **Blanco et al., 2016**( Blanco Martín et al., 2016) | 81 | 71.24 | High School | 54.7 | Spain, Europe | | Winblad et al. 2004; Petersen et al. 2004 | DSM-V and NINCDS-ADRADA | Clinical | 4 | 36 | 6.64 | 7.46 |
| **Forrester et al., 2016**( Forrester et al., 2016) | 540 | 81.03 | University | 66 | USA, America | NPI-Q | Petersen et al., 2004 | AD:NINCDS-ADRDA; vascular: NINDS-AIREN; FT: Neary et al. 1998 | Clinical | 2 | 24 | 2.35 | 1.54 |
| **Osone et al., 2016**( Osone et al., 2016) | 113 | 77.4 | High school | 62.8 | Japan, Asia | NPI | Petersen et al., 2004 | Evolution to dementia measured as decline in the CDR | Clinical | 2 | 12 | 5 | 6.5 |
| **Acosta et al., 2017**( Acosta et al., 2018) | 42 | 73.2 | School | 64.3 | Mexico, America | NPI | Albert et al. 2011 | DSM | Population-based | 2 | - | 1.22 | 1.51 |
| **Bidzan et al., 2017**( | 75 | 77.1 | High School | - | Poland, Europe | NPI | Mayo Clinic criteria | DSM | Clinical | 3 | 84 | 41.62 | 16.49 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bidzan et al., 2017) | | | | | | | | | | | | | |
| **Galluc i et al., 2017**( Galluc ci et al., 2017) | 55 | 76.9 | School | 50.9 | Italy, Europe | NPI | Peterse n et al., 2004 | - | Clinic al | 2 | 26 | 21.88 | 20.8 1 |
| **Kim et al., 2017**( Kim et al., 2017) | 59 | 71.2 | High school | 72.88 | Korea, Asia | NPI | Winlab et al., 2004 | DSM-IV-TR and NINCDS-ADRADA | Clinic al | 2 | 24 | 4.6 | 6 |

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; AD: Alzheimer Disease; LB: Lewy Body dementia; FT: Frontotemporal dementia; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th edition NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN: National Institute of Neurological Disorders and Association Internationale pour la Recherche et l'Enseignement en Neurosciences Stroke.

**Figure 1**. Flowchart of the article selection and inclusion in the meta-analysis.

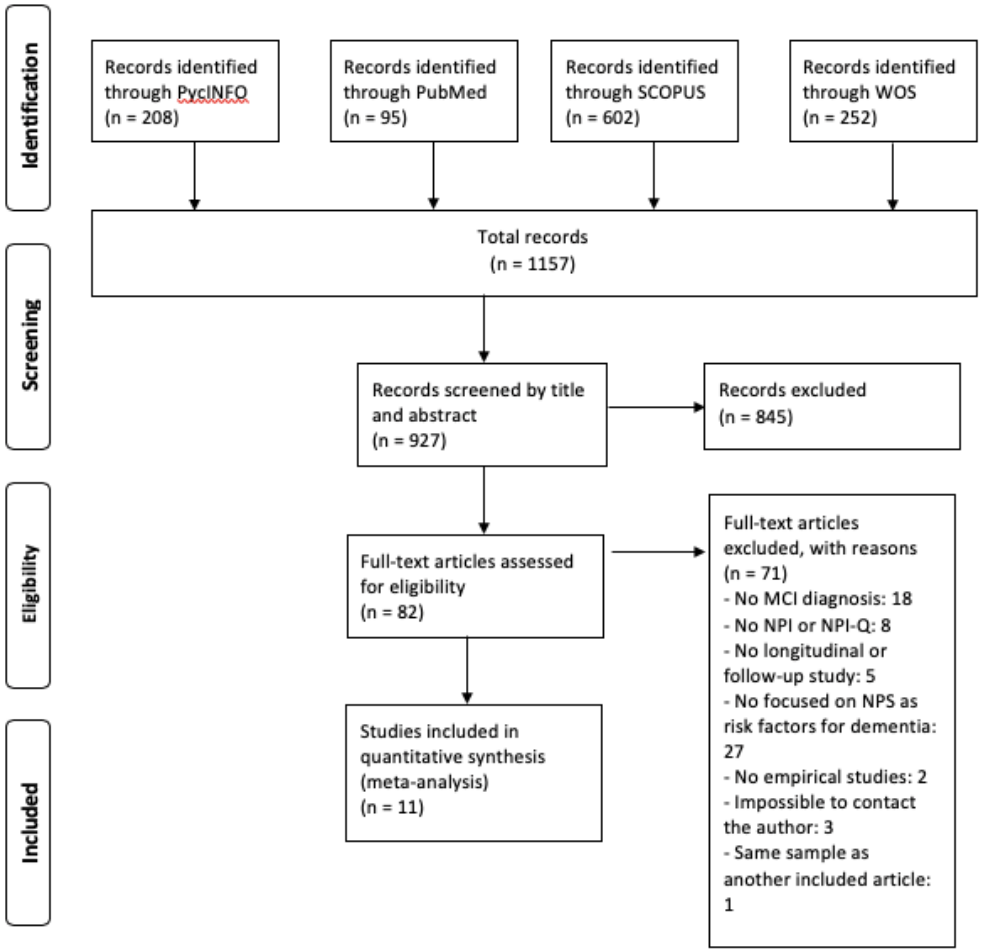
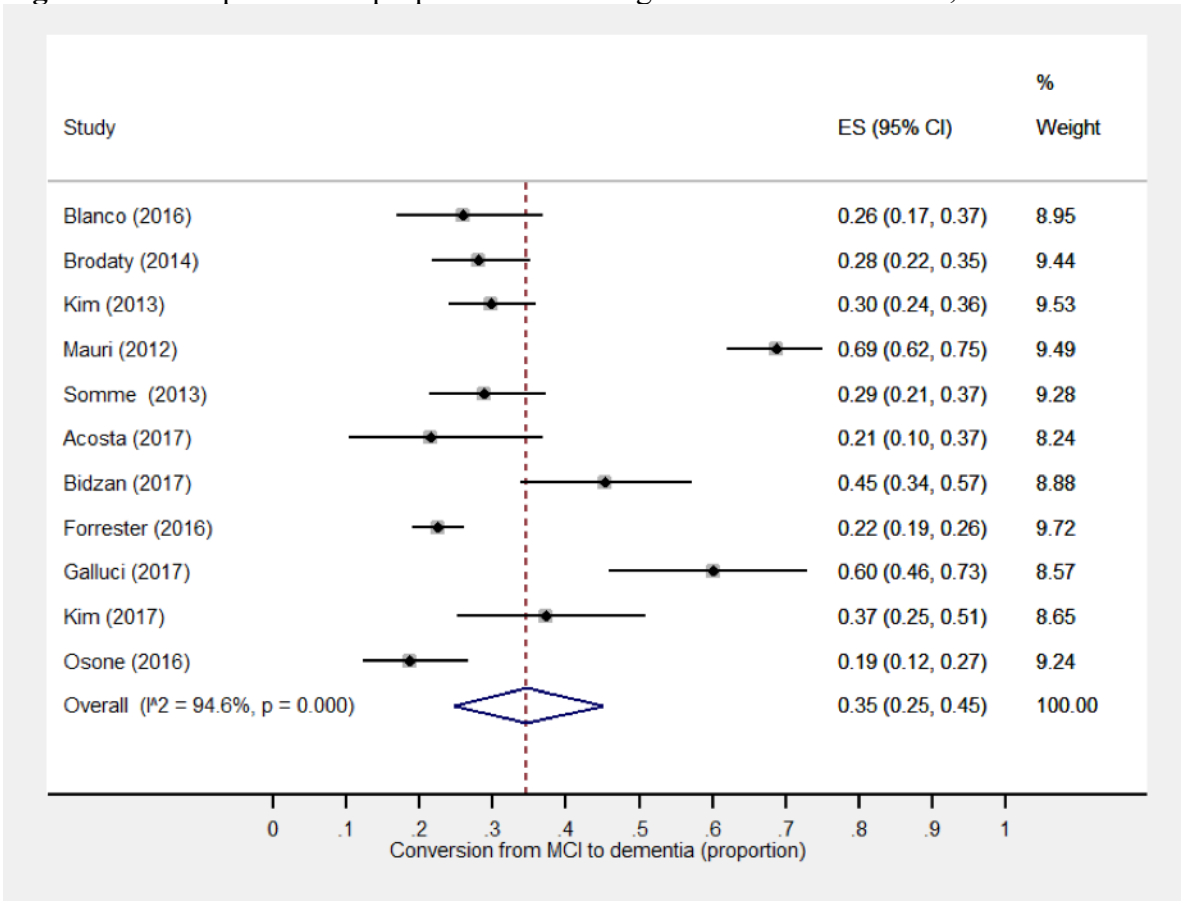


**Figure 2**. Forest plot for the proportion converting from MCI to dementia, unstratified estimates from a random effects model.



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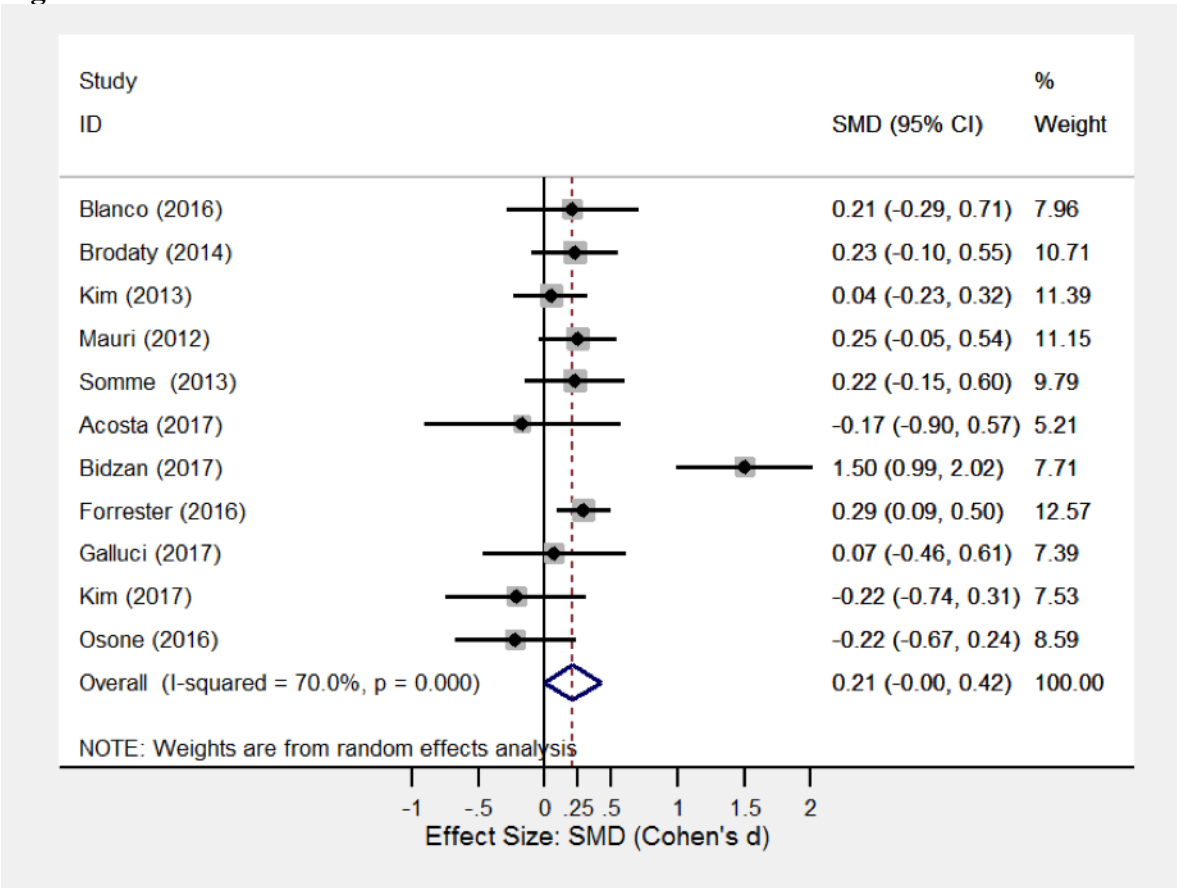

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