Risk of Dementia and Mild Cognitive Impairment in Older People with Subjective Memory Complaints: Meta-Analysis

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Abstract

Objective

To investigate if people with subjective memory complaints (SMC) but no objective deficits are at increased risk of developing mild cognitive impairment (MCI) and dementia.

Methods

Major electronic databases were searched till 03/2014 and a meta-analysis was conducted using inception cohort studies.

Results

Across 28 studies there were 29,723 unique individuals (14,714 with SMC and 15,009 without SMC) (mean 71.6 years) followed on average for 4.8 years through to dementia. The annual conversion rate (ACR) of SMC to dementia was 2.33% (95% CI = 1.93% - 2.78%) a relative risk (RR) of 2.07 (95% CI = 1.76 to 2.44) compared to those without SMC (n=15,009). From 11 studies the ACR of developing MCI was 6.67% (95% CI = 4.70 - 8.95%). In long-term studies over 5 years, 14.5% (9.67 -19.1%) of people with SMC developed dementia and 26.6% (95% CI =15.3-39.7) went on to develop MCI. The ACR from SMC to dementia and MCI were comparable in community and non-community settings.

Conclusion

Older people with SMC but no objective complaints are twice as likely to develop dementia as individuals without SMC. Approximately 2.3% and 6.6% of older people with SMC will progress to dementia and MCI per year.

Summations

- Among people with SMC but without objective complaints, the annual conversion rate (ACR) to MCI is 6.6%, whilst it is 2.3% to dementia, compared to 1% in those without SMC

- Over about 5 years, 24.4% of those with SMC will develop MCI, whilst 10.9% will convert to dementia, compared to 4.6% in those without SMC.

- Overall, the risk of developing dementia is double in those with SMC compared to those without SMC.

- **Considerations**

- It was not possible to stratify the results according to type of dementia or the diagnosis method.
- A wide range of definitions were used to capture SMC and it was not possible to conduct subgroup analysis to determine if this influenced the results.
- Most of the analysis had high heterogeneity and there was evidence of publication bias in some of the analyses.

Key words: dementia, mild cognitive impairment, subjective memory complaints

Introduction

Subjective memory complaints (SMC) are everyday memory and related cognitive concerns expressed by people who may or may not have deficits on objective testing. Although a definition of SMC has not been operationalized[1] numerous self-report measures have been developed.[2] In one large community survey about half of individuals reported minor memory problems.[3] In a UK survey, 31.7% reported forgetfulness in the last month, while 6.4% had forgotten something important in the last week.[4] A meta-analysis found that SMC were present in about 17% elderly people with no objective deficits.[5] The presence of SMC is associated with distress, reduced mental health, wellbeing and quality of life [6] and difficulties undertaking activities of daily living.[7] SMC also appears to be a risk factor for nursing home placement[8], future mortality[9] and is associated with increased healthcare costs.[10] However, perceived memory complaints may not always be a sinister finding since only a small proportion of memory complaints are severe enough to interfere with daily life and many with SMC do not deteriorate more rapidly than usual.[11] [12] [13] In addition, psychological factors such as depression influence expression of memory complaints[14] and some authors have suggested there is a distinct subgroup that has non-organic causes.[15] Indeed, considerable debate surrounds the relationship between subjective and objective memory complaints. SMC might not only to inform the current wellbeing of an individual, but also potentially predict future cognitive trajectory.[16] To date, some groups have found low correlation with objective tests whilst others have found a significant relationship. [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] To some extent this could be due to methodological issues for example with cross-sectional designs. There is also an issue of lack of power as several small studies have yielded ambiguous results.[27] [28] It is therefore still unclear whether SMC complaints are a risk factor for future cognitive decline, where baseline objective cognition is normal. In order to clarify this, a meta-analysis of prospective longitudinal studies is required that considers the influence of baseline objective cognitive testing, follow-up duration and recruitment setting (community v specialist settings e.g. memory clinics).

Aims

The primary aim of this study was to investigate the annual conversion rate (ACR) of people with SMC to a) MCI and b) dementia in prospective longitudinal studies. The secondary aim was to establish the cumulative proportion of those with SMC who progressed to a) MCI and b) dementia over the course of follow up. In addition, we sought to investigate if the conversion rates differed according to baseline objective cognitive testing, follow-up duration and recruitment setting. Finally, we calculated relative risks (RR) comparing the progression to dementia in people with and without SMC at baseline (where both subgroups were recruited from the same centre).

Methods

This systematic review is conducted in accordance with the MOOSE guidelines [29] following a predetermined protocol.

Inclusion and Exclusion

Studies were eligible that 1) included people with reported SMC at baseline, with or without a control group that did not have SMC. 2) Were prospective longitudinal studies with a follow up of at least 6 months 3) Measured objective cognitive performance including criteria for either MCI and/ or dementia (of any type) as an end point of the study using recognized diagnostic criteria (ICD10, or DSM IV). If we identified studies that appeared eligible but did not report the variables of interest, the protocol stipulated that we contacted the corresponding authors in order to ascertain these. We did not place any language restriction upon the eligibility of the searches. If we encountered multiple studies from the same data set we included the largest study and/ or the study with the longest follow up period. Studies were excluded that included participants at baseline that all had objective cognitive impairment. We excluded studies that did not report the proportion of subjects with cognitive decline (for example those that reported means alone).

Information sources and searches

Three independent authors (AJM, HB, BS) searched Medline, Pubmed, PsycINFO and Embase from inception till March 2014. This was supplemented by searches of Science Direct, Ingenta Select, Ovid Full text, Web of Knowledge and Wiley/Blackwell Interscience. The key words used were (subjective or personal or complaints or concerns) and (memory or cogniti*) and (Alzheimer* or dementia or MCI or mild cognitive impairment). In addition, the reference lists of all included articles were included and several leading experts in the field were contacted to ensure completeness of the data acquisition process.

Data extraction

Three authors (HB, BS, AJM) independently extracted data from all eligible studies using a predetermined form (Available upon request from the corresponding author). If any discrepancies were identified these resolved through discussion and with reference to the original manuscript and if necessary contact with the corresponding authors of the original articles. The data collected from each manuscript included details of the study (including year, setting, time of follow up) and participant demographics (number at baseline, mean age, % female), details of how SMC was measured/ defined, the method of cognitive assessment and diagnosis of MCI and dementia (including type). In addition, we extracted data on the number of people that progressed to MCI and dementia in each cohort and also those who were lost in follow up.

Meta-Analysis

We used the method previously described in a similar study from our group.[30] Our main analysis was the pooled annual conversion rate (ACR) which is calculated by dividing the number of cases who progresses by the person years of observation in each type of study. Each studies ACR was pooled in a meta-analysis which weighted for both study size and follow-up (person years). This statistic tells the reader/clinician: how many similar patients would typically progress each year. A secondary analysis was the cumulative progression which uncorrected for years of observation. This statistic tells the reader/clinician: how many similar patients would typically progress over time. We calculated rates of progression as a proportion of those recruited at baseline (inception cohort method) rather than those that survived to follow-up, since this most closely resembles clinical practice when attempting to give estimates of prognosis. In addition very few studies provided information on drop-outs. We also calculated person years of observation in each type of study. Weighted proportion meta-analysis was used to adjust for study size using the DerSimonian-Laird model and to account for the anticipated heterogeneity.[31]

In order to establish if people with SMC at baseline were more likely than those without SMC to develop dementia we calculated the relative risks (RR). We stratified the results and conducted subgroup analysis to

see if the results differed when we only included studies without abnormal cognitive function at baseline, those with long (4> years) and in those in community or specialist settings. The I^2 statistic was calculated for each analysis to determine heterogeneity.[32] In order assess the risk of bias we undertook a visual inspection of funnel plots and calculated the Harbord bias test.[33].

Results

Study selection, Study and participant characteristics

From a total of 111 valid hits, we considered the full texts of 79 articles. At the full text review stage 47 articles were excluded with reasons and 32 articles were included in the systematic review. The full search strategy including the reasons for exclusion at the full text review is represented in figure 1. Of 32 studies, 28 considered progression of SMC to dementia. .[34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61] 11 considered progression of SMC to MCI. [43 46 51 52 53 55 60 62 63 64 65]

Insert figure 1 about here

Across the 32 studies a sample of 29,723 unique individuals were represented including 14,714 individuals with SMC and 15,009 without SMC at baseline. The mean age of participants was 71.6 years and the percentage of females was 46.8%. Looking at studies of conversion to dementia, the majority of studies (21/28) recruited patients from the community or primary care (with community follow-up) but 7 were conducted in specialist settings (largely memory clinics). The method for diagnosing dementia and (21/28) used standard diagnostic criteria (DSM IV/ ICD 10). Non-standard criteria were used by 7 studies.[34 36 43 45 47 49 53] Where MCI was studied, all used Peterson criteria.[66] Objective cognitive performance was clearly documented at baseline in all but 4 studies. The most commonly used objective measurement of cognition was MMSE and the average score was 28.2. Fourteen of the included studies contained a group at baseline with and without SMC. The average duration for the follow up was 4.8 years for those progressing to dementia and 4.1 years for those potentially progressing to MCI. Further details of the included studies are presented in table 1.

Insert table 1 about here

Meta-analysis of the progression from SMC to mild cognitive impairment

1. Annual Conversion Rate

Data from 11 studies [43 46 51 52 53 55 60 62 63 64] were pooled and confirmed that the ACR of people with SMC developing MCI was 6.67% (95% CI = 4.70% to 8.95) (figure 2). This represented 14,287 person years of

observation. There was no publication bias (Harbord: bias = 3.24, P = 0.229) but there was high heterogeneity (I^2 = 94.1%, 95% CI = 91.9% to 95.5%).

Insert figure 2about here

2. Cumulative Conversion Proportion from SMC to MCI

Over a mean follow-up period of 4.1 years, data from 11 studies established that 24.47% (95% CI = 17.0 to 32.%7) of those with SMC went on to develop MCI.[43 46 51 52 53 55 60 62 63 64] There was high heterogeneity (I^2 = 94.5%; 95% CI = 92.5% to 95.8%) but there was not any evidence of publication bias (Harbord bias = 2.994, P = 0.17).

Subgroup analysis of progression of SMC to MCI

Over a mean of 5.3 years follow up, the pooled proportion of people with SMC that converted to MCI in the community studies was 34.2% (95% CI = 20.86 to 49.0; I^2 = 97.6%, Harbord bias=10.1 P = 0.01). The pooled cumulative proportion of people with SMC converting to MCI over a mean of 3.3 years in specialist non-community settings was 16.48% (95% CI = 10.53 to 23.44; I^2 = 66.7%, Harbord: bias = -0.76 P = 0.76). Next we calculated the ACR from SMC to MCI according to setting and this was 7.7% (95% CI 4.8% to 11.2%) in community settings and 5.6% (2.8 = 9.5%) for specialist non community settings. It was possible to pool the data from 7 studies that excluded participants with no clear cognitive test score at baseline and this established that 21.80% (95% CI = 14.76 to 29.79; I^2 = 93%, Harbord: bias = 2.118, P = 0.33) went on to develop MCI. Finally, we pooled the data from 5 long term studies that followed participants over 4 years (with a mean of 5.96 years) and this established that the proportion of those with SMC that developed MCI was 26.7% (95% CI = 15.39 to 39.74; I^2 = 93.4, Harbord: bias = 0.56 P = 0.91).[46 53 55 60 64]

Meta-analysis of the progression from individuals without SMC to dementia (healthy controls)

1. Annual Conversion Rate

From 14 studies involving healthy older adult controls without SMC and without objective cognitive complaints the pooled ACR was 1.00% (95% CI = 0.71% to 1.34%). There was high heterogeneity (I^2 = 93.1%, 95% CI = 90.5% to 94.6%) and no indication of publication bias (Harbord bias = 0.558, P = 0.741).

2. Cumulative Conversion Proportion

Across 14 studies involving 14,949 healthy older controls without SMC and without objective complaints that were conducted over four years established that 4.6% (95% CI = 2.8% to 6.9%) of participants developed dementia. The data was heterogeneous (I^2 = 96.3% (95% CI = 95.3% to 96.9%) but there was no evidence of publication bias (Harbord bias= -2.3, P = 0.39).

Meta-analysis of the progression from SMC to dementia

1. Annual Conversion Rate

28 studies examined progression of SMC to dementia representing 86,200 person years of observation.[34-61] The ACR of people with SMC developing dementia was 2.33% (95% CI = 1.93% to 2.78%) (figure 3). There was high heterogeneity (I^2 = 89.2%; 95% CI = 86% to 91.4%) and some evidence of publication bias (Harbord: bias = 2.55 P = 0.01) but the funnel plot was symmetrical (figure 2b).

Insert figure 3 about here

2. Cumulative Conversion Proportion from SMC to dementia

From 28 studies[34-61] 10.99% (95% CI = 8.20 to 14.12) of those with SMC developed dementia over the course of the follow up period of 4.8 years.[34-61] There was high heterogeneity (I^2 = 95.4%, 95% CI = 94.6% to 96.1%) but the funnel plot was symmetrical and the Harbord bias test did not indicate any evidence of publication bias (-0.7154, P = 0.64).

Subgroup analysis of progression of SMC to dementia

From 21 studies conducted in the community the cumulative conversion from SMC to dementia was 10.79% (95% CI 7.7 to 14.3, I^2 = 96.4%, Harbord: bias = -1.10 P = 0.6101) over a mean of 5.2 years. The cumulative proportion of people with SMC that developed dementia in specialist settings was 11.7% (95% CI = 5.0 to 20.7, I^2 = 83.8%, Harbord: bias = -2.20 P = 0.5378) over a mean of 3.2 years. After correcting for follow-up duration,

the ACR for community studies was 2.2% (95% CI = 1.8% to 2.6%) and 3.2% (95% CI = 1.1% to 6.3% in specialist non-community studies it was). Pooled data from 22 studies excluding participants with no clear cognitive test score at baseline established that 11.5% (95% CI = 8.18 to 15.36, I^2 = 95.4%, Harbord: bias = -1.189, P = 0.46) went on to develop dementia. The pooled cumulative progression proportion of those with SMC to dementia among 14 long term studies that followed participants over 4 years or more (a mean of 6.8 years) was 14.05 (95% CI = 9.67 to 19.08, I^2 = 95.6%, Harbord: bias = -1.1132 P = 0.59). [41 42 45 46 48 47 49 54 55 57 58 59 60]

Meta-analysis comparing the risk of developing dementia in people with and without SMC

It was possible to compare the risk for developing dementia in people with and without SMC using data from 14 studies, over a mean follow up of 4.94 years. The pooled RR was 2.07 (95% CI = 1.77 to 2.44) establishing that people with SMC (n=3,821) were twice more likely than those without SMC (n=15,009) to develop dementia (figure 4). The data was not heterogeneous (I^2 = 17.5% (95% CI = 0% to 56.2%) and there was no evidence of publication bias (Harbord = 0.93, P = 0.08).

Insert figure 4 here

Discussion

To our knowledge this is the first study to perform a quantitative data synthesis of studies reporting rates of progression of those with SMC to MCI and dementia. When considering dementia, we included 28 robust cohort studies and found that the overall ACR rate among 86,200 person years of observation was 2.33% in those with SMC at baseline compared to 1% in those without SMC. This represents a twofold increased risk of developing dementia in those with vs without SMC (RR 2.07, 95% CI= 1.77 to 2.44, p<0.001). The overall proportion that converted to dementia from 28 studies was 10.99% over the follow up period of about 5 years although it was 14% in long term studies that followed participants over a mean of 6.8 years. When we conducted subgroup analyses comparing studies in community or specialist non-community settings (mainly memory clinics) we found cumulative conversion rates from SMC to dementia at 10.7% over 5.2 years and 11.7% over 3.2 years respectively. Further to this, our results demonstrate that people with SMC are at increased risk of developing future MCI. The ACR for those with SMC to convert to MCI was 6.67% and the cumulative conversion proportion was 24.4%. When we conducted subgroup analysis we found that the cumulative conversion from SMC to MCI was 34.2% over 5.3 years in community settings and 16.5% over 3.3 years in specialist non community settings (mainly memory clinics). The sub group analysis based on setting determined that the ACR from SMC to dementia and MCI were broadly similar in community and specialist non community settings. Taken together, our results indicate that people with SMC are at increased risk of MCI and dementia.

There has been considerable debate about the significance of SMC in anticipating future cognitive decline. Several groups have reported that SMC are more a reflection of health anxiety than genuine cognitive symptoms, particularly in mid-life.[4] Against this, some studies have observed biological changes associated with SMC. Studies have shown that older people with SMC have increased rates of white matter lesions, temporal atrophy or hypometabolism and raised CSF biomarkers.[67 68 69 70 71 72 73 74] Such biological changes may occur in the absence of objective decline suggesting SMC may be a possible early marker of future

deterioration.[75 76 77 78] For example, several studies have found that SMC scores as well as a decrease of self-confidence about memory abilities in elderly subjects (or a subgroup of elderly who are ApoE4 carriers) may be related to the neuropathological hallmark of AD measured with PiB-positron emission tomography.[76 78 79] These results may be supported by longitudinal biological studies showing SMC at baseline is linked with subsequent change in hippocampal volume.[80]

Awareness of cognitive deficits has a u-shaped distribution being low with mild complaints, rising but then generally low with severe cognitive impairment.[81 82 83 84 85] Insight is usually preserved in mild dementia and in mild cognitive impairment (MCI).[86] Our findings in relation to SMC should be considered in the context of previously reported research in relation to MCI. In the case of MCI, Mitchell and Feshki found an ACR of 6.7% (95% CI = 4.6–9.1%) and a RR of 13.8 (95% CI = 8.44–22.6) in relation to progression of MCI to dementia.[30] Thus SMC are a much lower risk of progression than MCI (about 1/3 numerically) but still clearly important. SMC forms a core component of the criteria for MCI.[87 88] It may be therefore than SMC contributes part of the significance of MCI but MCI and SMC are not synonymous prognostically.[89] A key issue for MCI is that function must be unimpaired or minimally impaired in current guidelines. However impaired function can co-occur with SMC even in the absence of objective impairment. Data from the Spanish Neurological Diseases in Central Spain study (NEDICES) cohort involving 1,073 participants found that of 730 with pure SMC, 18.1% had significantly impaired function and 9.5% had severely impaired function measured by the Pfeffer scale.[90] It is likely that SMC and function are independent predictors of decline, but this requires further study.

Our results suggest that SMC should not merely be considered as a benign age related phenomenon since our meta-analysis demonstrates that those with SMC are at significantly increased risk of future cognitive decline, particularly of MCI. Yet there is considerable heterogeneity in samples with SMC. For example types of complaints may vary in mid-life vs late life.[91] Community dwelling participants with no functional limitation but isolated SMC are likely to be quite different from memory clinic attendees with SMC. We found that there

were comparable cumulative proportions with SMC that converted to dementia in community or specialist settings (10.7% and 11.7% respectively) although the mean follow up for community settings was two years less in on average (5.2 v 3.2 years) and is therefore of little surprise. When we investigated the ACR from SMC to dementia this was comparable for community settings (2.2%) and non-community settings (3.2%). Although we found that 34.2% of people with SMC converted to MCI in community settings compared to 16.5% in specialist settings after correcting for follow-up the ACR the results were similar (7.7% and 5.6% respectively). The similarities in ACR according to setting are likely to be because the subgroup analysis were underpowered. Clinically the approach to the management of SMC may have to be revised in light of these findings. SMC may be amenable to treatment in the absence of objective decline[92] and the next step is to study whether amelioration of SMC at early stage influences the rate of progression of cognitive decline.

We wish to acknowledge the following limitations. We had limited access to younger samples. As a result the prognosis of SMC in mid-life is uncertain. We were unable to stratify outcomes by types of dementia. This could be important as certain dementias may be more strongly liked with a long-prodromal period and high perceived subjective decline. In addition, due to limitations in the data it was not possible to establish if the method of diagnosing dementia (e.g. DSM-IV or ICD 10) influenced our results. Therefore, future research should investigate this. Another important limitation is that as expected, the studies included in our review adopted a wide range of methods to capture SMC, which is difficult to overcome since there is currently no gold standard to define SMC. Heterogeneity and lack of reporting of exact methods in primary studies prevented us from conducting subgroup analysis to see if the method of defining SMC affects the conversion rates to MCI and dementia. This is therefore another recommended topic for future research. We had modest duration of follow-up with a maximum of 8 years. It is therefore unknown whether the rate of progression accelerates, stays stable or declines with time. It is important to also note that almost all of the results within our review had substantial heterogeneity. Finally in some cases there was evidence of publication bias.

Conclusion

SMC may be a clinically meaningful indicator of future cognitive decline, with individuals experiencing SMC at increased risk of developing MCI and dementia. However the context and setting of the SMC report remains important.

Conflict of Interest

None to declare from any author.

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Table 1 – details of included studies

Study	Number with SMC at baseline	SMC participant characteristics	Settings	Method of assessing SMC	Follow up time (yrs)	Investigated MCI and/ or dementia	Method of diagnosing dementia/ MCI
Schofield 1997	23	75.5 years, 7.5% female	community	"Do you have problems with your memory?"	1	Dementia	AD(NINCDS)
Wang 2004	87	74.6 yrs, 14.2% female	community	5 specific questions	5.2	Dementia	DSMIV+AD(NINCDS)
Glodzik-Sobanska 2007	187	67 yrs, 15.9% females	volunteers	GDS 2	8.8	Dementia	MMSE
Geerlings 1999	250	74.5 yrs, 58.5% females	community	do you have complaints about your memory	3.2	Dementia	DSM IIIR or AGECAT + MMSE 25v26 +DSMIV
Diniz 2009	62	70.6 yrs, 9.8% females,	memory clinic	subjective cognitive complaint, preferably corroborated by an informant; in the course of diagnosis MCI	3.19	Dementia	The diagnosis of MCI was made according to the following criteria: (1) subjective cognitive complaint, preferably corroborated by an informant; (2) objective cognitive impairment in the neuropsychological assessment; (3) preserved global intellectual function
St John & Montgomery (2002)	293	75.3 yrs	community	"Please tell me if you had memory loss in the past year. You can just answer yes or no.	5	Dementia	DSM IIIR
Kim et al (2006)	135	71.3 yrs, 53.9% females	community	series of questions from the Geriatric Mental State Schedule	2.4	Dementia	DSMIV by expert panel, MMSE
van Oijen et al (2007)	1309	69.5 yrs, 60% females	community	Single Question : "Do you have memory complaints?"	9	Dementia	CAMDEX (three step_MMSE+GMS+CAMDEX) +DSMIIIR+AD(NINCDS)
Tobiansky et al (1995)	84	75.9 yrs, 66% females	community	Short-CARE	2	Dementia	GMS-A, HAS, CAMCOG
Mol et al (2006)	94	67.4 yrs, 46% females	community	'Do you consider yourself to be forgetful?'	6	Dementia	MMSE < 24
Nunes et al (2010)	15	68.8 yrs, 65.1%	memory clinic	SMC scale - 10 questions concerning difficulties in daily life memory tasks	3.5	Dementia and MCI	BLAD + DSMIVTR

Table 1 – details of included studies

		females					
Waldroff (2012)	177	74.8 yrs, 61.4% females	Community / GP	Self administered question 'How would you describe your memory?' 'less good', 'poor' or 'miserable'=SMC, 'excellent' or 'good'=no SMC	4	Dementia	ICD 10
Jessen et al (2014)	1061	79.7 yrs, 64.8% females	GP	Do you feel like your memory is becoming worse? Possible answers were no; yes, but this does not worry me; and yes, this worries me.	6	Dementia	DSM IV and ICD10 MMSE
Chary et al (2013)	45	74.7 yrs	Community	4 questions used: Coded as yes/ no 1. Do you frequently have forgetfulness in activities of daily living (ADLs; shopping list, in using household appliances, and so forth)? 2. Do you frequently have difficulties in retaining or remembering new simple inf	10	Dementia	DSM III R dementia and NINCDS-ADRDA
O'Brien 1992	68	67.2 yrs, 70.3 female	memory clinic	At follow-up, patients and spouses were questioned about any deterioration in memory, personality and social functioning since the initial assessment.	3.1	Dementia	ICD-10
Gironell 2005	116	68.8 yrs, 56.9% female	memory clinic	unclear	2.3	Dementia & MCI	Unclear
Prichep 2006	44	72 yrs, 15.2% female	community	GDS2	7	Dementia and MCI	NINCDS-ADRDA
Rountree 2007	17	69 yrs, 16% females,	memory clinic	Part of Petersen's clinical criteria for MCI	4.8	Dementia	Wechsler Memory Scale-Revised (WMS-R), Logical Memory II (LM II) impairment
Visser 2009	60	68.6 yrs, 47.6% females	memory clinic	NR	2	Dementia	DSMIV + NINCDS-ADRDA
Reisberg 1986	40	70.6 yrs, 53.8% females	community	GDS	3.6	Dementia	Unclear
Jorm et al (1997)	721	N/A	community	"Overall , do you feel you can remember things as well as you used to? That is is your memory the same as it was earlier in life?"	3.6	Dementia	MMSE, ICD-10, DSM-III-R
Schmand et al (1996)	357	58.3% females	community	10 questions on subjective memory complaints derived from CAMDEX	3	dementia	DSMIIIR + CAMCOG

Table 1 – details of included studies

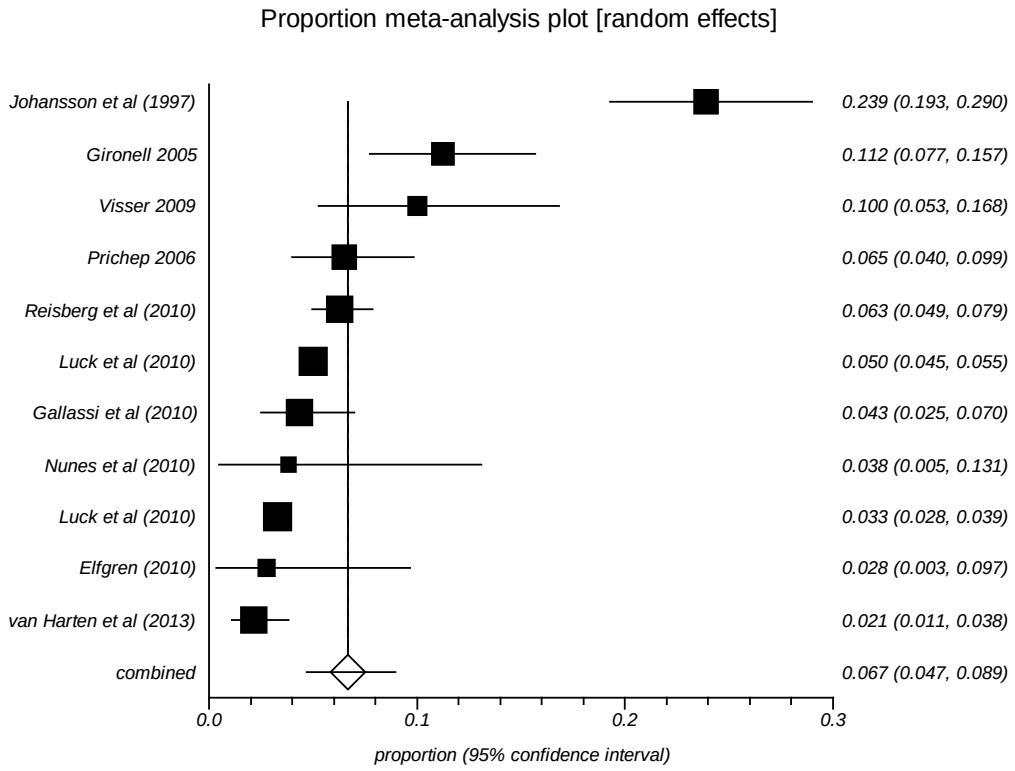
Reisberg et al (2010)	166	67.5 yrs, 63% females	Community	GDS	6.8	Dementia and MCI	MMSE, BCRS (Brief Cognitive Rating Scale)
Jessen et al (2010)	1388	79.7 yrs, 64.1% females	Community	Do you feel like your memory 's becoming worse?	3	Dementia	DSM-IC, ICD-10, MMSE
Jessen et al (2011)	1764	80.1 yrs, 65.5% females	Community	Do you feel like your memory 's becoming worse?	3.81	Dementia	DSM-IV, ICD-10, MMSE
Peres et al (2011)	2901	74.8 yrs, 58.8% females	Community	3 Questions: 1)forgetfulness in daily activities, 2) difficulties in retrieving and remembering new information, 3) difficulties in remembering or retrieving old memories.	15	Dementia	DSM-IIIR, MMSE
Gallassi et al (2010)	92	63.26 yrs	University Hospital of the Department of Neurological Sciences of Bologna	unclear	4	Dementia and MCI	DSM-IV
van Harten et al (2013)	128	60, yrs, 48% females	Outpatient clinic	presented with cognitive complaints, but cognitive and laboratory investigations were normal and criteria for MCI, dementia, or any other neurologic or psychiatric disorders known to cause cognitive complaints were not met	4	Dementia and MCI	NINCDS-ADRDA
Elfgren (2010)	24	59.6 yrs, 57.6% female	Outpatient clinic	Unclear	3	MCI only	DSM-IV, MMSE
Johansson et al (1997)	147	86.85 yrs, 64% females	Census data	4 questions: 1) on the whole, do you think your memory is good or poor? 2) Do you think you have a problem with your memory that makes your life more difficult? 3) Do you think that your memory has gotten worse over the past 2 years? 4) On the whole, do you think that	2	MCI only	MMSE, DSM-III-R
Luck et al (2010a)	519	81.3 yrs, 73.9% female	Community	Single item question: Do you have problems with your memory?	8	MCI only	DSM-III-R, DSM-IV, ICD-10
Luck et al (2010b)	2331	80.1 yrs, 65.5% female	GP	Single item question: Do you have problems with your memory?	3	MCI only	DSMIII, DSMIV, ICD-10

Key: AD= Alzheimer's disease, yrs = years, MCI= mild cognitive impairment, BCRS= brief cognitive rating scale, MMSE = mini mental state examination, NINCDS ADRDA=Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria, CAMCOG=

Table 1 – details of included studies

Cambridge Examination of Mental Disorders, CAMDEX= Cambridge Examination for Mental Disorders of the Elderly, GDS= global deterioration scale, AGECAT= Automated Geriatric Examination for Computer-Assisted Taxonomy, GMS= Geriatric Mental State, Short-CARE= Comprehensive Assessment and referral Evaluation,

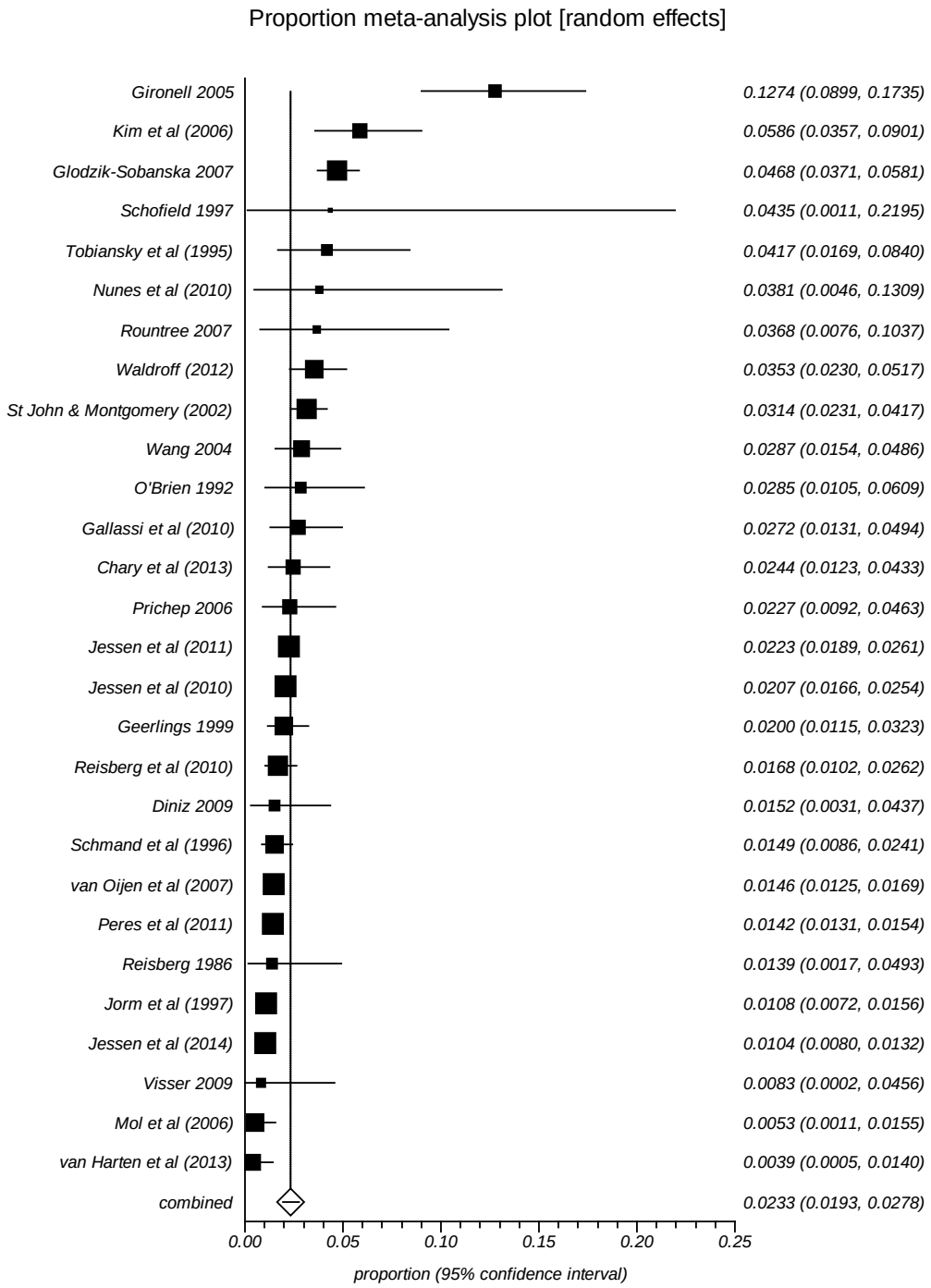
Figure2 random effects ACR of SMC to MCI among 11 studies



ACR = 6.7% (95% CI = 4.7% to 8.9%)

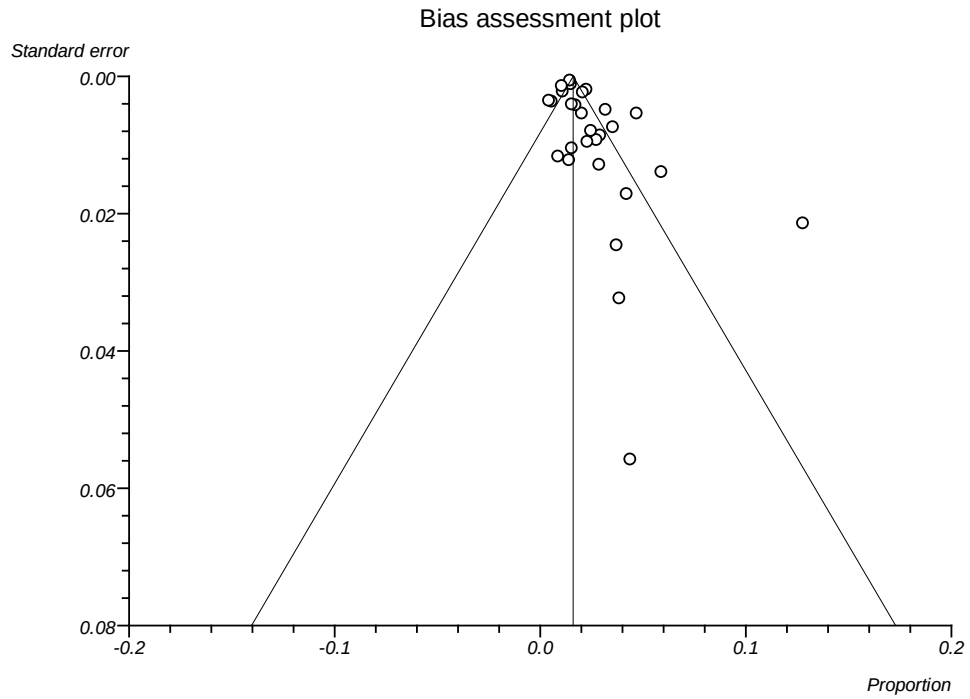
I^2= 94.1%

Figure 2 – Random effects ACR of SMC to dementia among 28 studies



ACR= 2.33% (95% CI = 1.92 to 2.77)

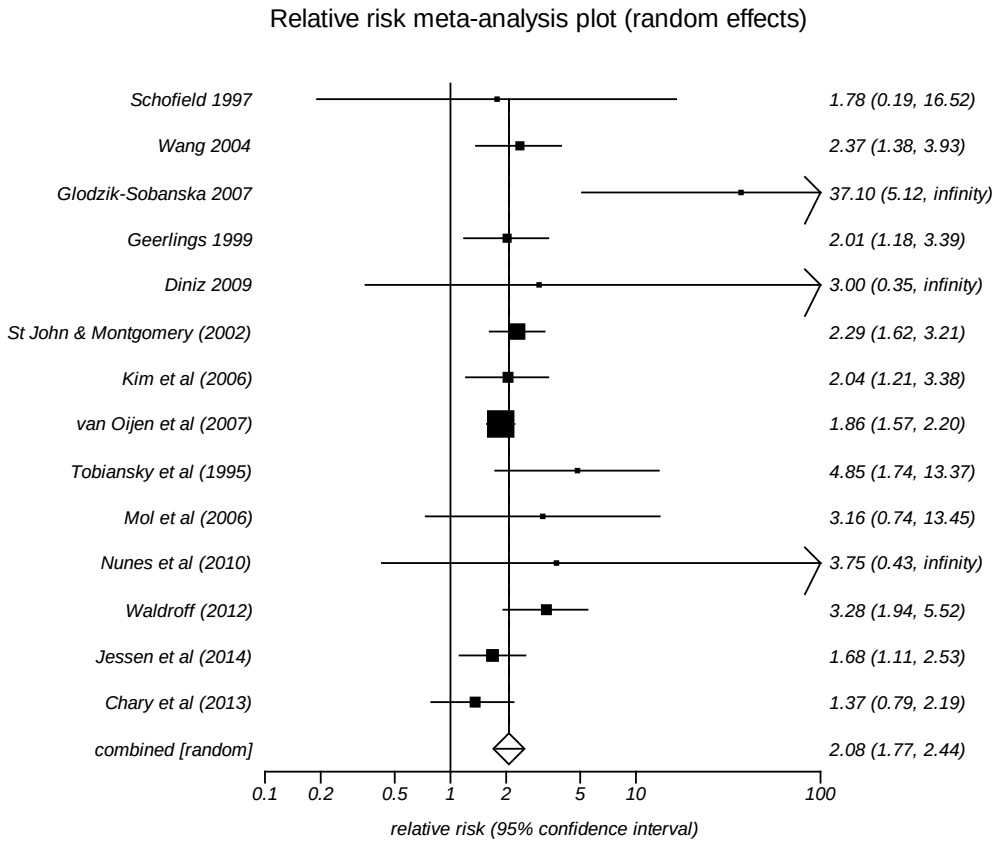
Figure 2b Funnel plot



Begg-Mazumdar: Kendall's tau = 0.190476, P = 0.1621

Harbord: bias = 2.552389, P = 0.0123

Figure 4: Relative risk comparing development of dementia among those with and without SMC



Pooled relative risk = 2.07 (95% CI = 1.76 to 2.44)