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Prevalence and Correlates of Severe Mental Illness Among Nursing Home Residents Without Dementia: Systematic Review and Meta-analysis

Running title: "MDD in nursing homes"

Michele Fornaro, MD, PhD

Marco Solmi, MD, PhD

Brendon Stubbs, PhD, MSc, BSc

Nicola Veronese, MD, PhD

Francesco Monaco, MD

Stefano Novello, MD

Andrea Fusco, MD

Annalisa Anastasia, MD

Domenico De Berardis, MD, PhD

André F. Carvalho, MD, PhD

Andrea de Bartolomeis, MD, PhD

Eduard Vieta, MD, PhD

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Abstract 249/250

Background: The elderly population and number of nursing homes residents are growing at a rapid pace globally. Uncertainty exists regarding the actual rates of corresponding severe mental illness (SMI) cases since previous evidence documenting high rates relies on sub-optimal methodology. **Aims**: To carry a systematic review and meta-analysis on the prevalence and correlates of SMI including major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia-spectrum diseases (SSDs) among nursing homes residents without dementia. **Method**: Major electronic databases were systematically searched from 1980 up until July 2017 for original studies reporting on the prevalence and correlates of MDD among nursing homes residents without dementia. The prevalence of MDD in this population was meta-analyzed through random-effects modeling, while potential sources of heterogeneity were examined through subgroup/meta-regression analyses. **Results**: Across 32 observational studies encompassing 13,394 nursing homes residents, 2110 cases were diagnosed as MDD, resulting in a pooled prevalence rate of 18.9% (95% C.I.=14.8%-23.8%). Heterogeneity was high (I^2=97%, p=<.001); no evidence of publication bias was observed. Sensitivity analysis indicated the highest rates of MDD among North American residents (25.4%, 95% C.I.=18%-34.5%, p=<.001). Prevalence of either BD or SSDs could not be reliably pooled due to the paucity of corresponding data. **Limitations**: The paucity of quantitative data precluded further stratification of MDD features. Methodological quality of the included studies varied, hampering the overall generalizability of the results. **Conclusions**: MDD is highly prevalent among nursing homes residents without dementia. Efforts toward the prevention, early recognition, and management of MDD in this population are warranted.

- PROSPERO protocol: CRD42018088312.

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The elderly population is increasing both in absolute numbers as well as in the percentage of the total population worldwide (1), with no exception for those with severe mental illness (SMI), including bipolar disorder (BD), major depressive disorder (MDD), schizoaffective disorder (SCZA) or schizophrenia (2). Whilst there is premature mortality among people with SMI, some individuals with SMI reach an advanced age and may experience considerable physical health burdens and multi-morbidity; therefore, they may be more likely to need admission to a nursing home environment (3, 4).

MDD is one of the most common mental disorders worldwide and is prevalent throughout the lifespan, with prevalence estimates of 1-5% in those 65 years of age and older (5).

Regrettably, little is known about the actual rates and clinical features associated with MDD among nursing home residents, essentially due to the almost invariable systematic exclusion of elderly patients from selection into studies and the subsequent publication bias.

In addition, nursing home residents with MDD may be either patients with disorder onset early in life (then lasting or recurring at an old age) or patients whose onset first occurs in late life, representing differential clinical and neurobiological phenotypes of depression (6-8).

MDD deserves further accurate clinical epidemiological assessment focusing on those cases not related to or overlapping with dementias, ideally providing clear-cut prevalence estimates of MDD among nursing homes, which are most likely populated with elderly people. Patient-tailored treatment and prevention of depression in the elderly population should promote cognitive health, enhancing the chances of independent living and overall quality of life.

To the best of our knowledge, the only systematic review on the prevalence of psychiatric disorders among nursing home residents dates back to the year 2010, failed to use any quantitative pooling whatsoever, and documented long-term point prevalence rates of an MDD diagnosis up to 10% for nursing home residents and 29% for depressive symptoms overall (9). However, it must be remarked that this report merged a variety of different clinical phenotypes of depression, including BD cases and those "confounded" by comorbid dementia(s), lifetime substance abuse and/or anxiety disorders, just to name few. The study also limitied the search strategy to only the EMBASE dataset (9) and failed to adopt any reliable (semi-)structured interview based on any major standard diagnostic coding.

Therefore, after stating the poor reliability of the previous reports on the matter, considerable uncertainty still surrounds the actual prevalence rates and clinical correlates associated with SMIs among nursing home residents.

We, therefore, aimed to conduct a systematic review and meta-analysis of the prevalence and clinical correlates of SMIs focusing on MDD among nursing home residents without dementia, to have the diagnoses assessed by structured interviews based on either the Diagnostic and Statistical Manual for Mental Disorders (DSM) or the International Classification of Diseases (ICD), and to strive to control or avoid as many confounding factors as possible (with a special emphasis on dementia-related processes).

Method

Search strategy and study selection

The present systematic review adhered to the PRISMA (10) and the MOOSE guidelines (11). The international prospective register of systematic reviews (PROSPERO) (https://www.crd.york.ac.uk/PROSPERO/) registration number is CRD42018088312.

Six authors divided into two teams (MF, AF, SN, AA and MS and FM) and independently searched PubMed, PsycINFO, and EMBASE databases for records indexed from the year 1980 onwards (last updated, June 2017). The string was searched in PubMed and was adapted across varying datasets: ((nursing home*[Title/Abstract] OR long-term care[Title/Abstract] OR homes for the aged[Title/Abstract])) AND (((((((("Psychotic Disorders"[Mesh] OR "Bipolar Disorder"[Mesh]) OR "Depressive Disorder, Major"[Mesh]) OR ("Mood Disorders"[Mesh] OR "Seasonal Affective Disorder"[Mesh] OR "Affective Disorders, Psychotic"[Mesh])) OR ("Depression"[Mesh] OR "Depressive Disorder"[Mesh])) OR "Schizophrenia"[Mesh]) OR "Schizophrenia Spectrum and Other Psychotic Disorders"[Mesh])) OR (psychosis)). Additional details for the search strategy across varying datasets have been provided in supplementary material n.1. Finally, the results were augmented by a manual search and cross-references as depicted in figure n.1 (study flow chart).

Studies were deemed eligible if they were original peer-reviewed articles (any language), but not case report/series (i.e., with a sample size<10), that reported the prevalence of either MDD, BD, or schizophrenia/schizoaffective disorder among nursing home residents, or contained data allowing us to compute the prevalence. Late-onset cases of BD were those patients aged 60 years or older (12), and this age threshold was likewise applied to MDD and schizophrenia cases as well. Either naturalistic studies or

interventional studies with baseline prevalence data were included. Diagnosis of MDD, BD, or schizophrenia had to be made according to any version of the DSM or ICD.

Data Extraction

Six authors divided into two teams (MF, AF, SN, AA and MS and FM) and independently extracted data using a predetermined extraction form, and including the following: MDD, BD, or schizophrenia prevalence (or variables needed to compute it), author, year of publication, year of data collection, country/continent of data collection, study design, demographic characteristics, underlying main condition, employed clinical rating scales and the diagnostic criteria were used in conjunction with a validated structured interview, and essential clinical and pharmacological moderators, including but not limited to, prescription of first (FGAs) or second-generation (SGAs) atypical antipsychotics as well as the percentage of major medical comorbidities. Any eventual within- and between-team disagreements were solved by the corresponding team principal investigator (MF for team n.1, and MS for team n.2), while between-team resolution was performed by a senior author (AFC) as necessary.

Quality assessment

We assessed the quality of the included studies using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort).

The quality of the interventional studies was assessed using the Cochrane Risk of Bias Assessment Tool (13).

For both rating tools, higher scores indicated poorer quality of the study.

Acceptable, good scores were computed based on percentile distribution.

Meta-analysis

Due to the anticipated heterogeneity, we utilized a random-effects meta-analysis and computed the pooled prevalence and 95% confidence intervals (C.I.s) with Comprehensive Meta-Analysis (CMA, version 2) (14). Heterogeneity was assessed with the Cochrane Q and I^2 statistics for each analysis (15). We conducted mixed-effect model meta-regression analyses with CMA, for outcomes with high heterogeneity (I^2>50% and/or p=≤.05) and reported by ≥4 studies, to investigate potential moderators of the observed prevalence of SMI in nursing homes. We conducted sensitivity analyses according to country, continent, criteria used to define a given SMI, period of data collection (in decades), specific psychiatric diagnosis (MD, BD, and schizophrenia), and the quality of the study (post hoc assessment of good, fair, or poor quality) based on either the NIH or the Cochrane tools mentioned earlier, and using quartiles, we then merged the studies into two main categories to allow sensitivity prevalence analysis across the two main categories (as depicted in table n.1 and its footnotes).

Depending on the available data, we aimed to investigate the following moderators: sample size, year of data collection, mean age, percentage of males, ethnicity, country, diagnostic criteria (DSM/ICD), major medical or psychiatric comorbidities whenever available, and quality of the study according to the NIH rating.

Publication bias was assessed via visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau (16) and Egger bias tests (17). In cases where publication bias was identified, we computed the trim and fill adjusted analysis (18) to remove the most extreme small studies from the positive side of the funnel plot, and re-computed the effect size at each iteration until the funnel plot was symmetric around the (new/adjusted) effect size.

Results

Out of the initial title and abstract assessment of 4776 hits after duplicate removal, we excluded 3882 papers, thus 894 full-text were further assessed (please refer to figure n.1 for details). A total of 36 studies (19-53) could be included in the qualitative synthesis corresponding to a grand total sample size of 13,754 of nursing home residents included for qualitative analysis. Among the 36 studies, three (42, 43, 53) were assessed using the Cochrane quality evaluation tool since they were interventional studies: two of which were randomized clinical trials (RCTs) (42, 53) and one was a non-controlled prospective trial (43). Finally, 32 studies reported on MDD cases (19, 21-40, 42, 44-53), 3 studies reported on schizophrenia (20, 43, 54) (one schizophrenia study also documented a subset of BD cases (54)), and one study provided stratified results both on MDD and BD samples (37). We could not locate any study reporting on SCZA cases.

Overall, 32 studies reporting on MDD samples (31 studies reporting just on MDD cases and 1 documenting BD cases as well) were included in the meta-analysis (19, 21-40, 42, 44-54).

Please refer to table n.1 for additional details, including the clinical features documented among nursing home residents with SMI.

Meta-analysis of major depressive disorder prevalence, publication bias, heterogeneity and categorical subgroup comparisons

The overall pooled MDD prevalence across 32 samples and 2110 MDD cases out of 13,394 nursing home residents pooled for quantitative analysis was 18.9% (95% C.I.=14.8%-23.8%); please refer to figure n.2 for details. Heterogeneity was high (I^2=97%, p=<0.001). Publication bias seemed unlikely (please refer to figure n.3 for

visual inspection of the funnel plot) (Egger test intercept=.726, (p=ns); Begg and Mazumdar's test, continuity-adjusted Tau=.00202, p=ns).

Subgroup analysis of major depressive disorder in nursing home residents

As detailed in table n.2, the prevalence rates of MDD among nursing home residents significantly varied across geographical regions, being highest (point-prevalence rates=25.4%, 95% C.I.=18%-34.5%, p=<.001) in North America and lowest in Oceania (5.7%, 95% C.I.=3.2%-10%, p=<.001), although publication bias for North American studies could not be excluded (p=.015). The total overall between-region difference (p=<.001) means that the estimated prevalence rates statistically significantly differed across varying sub-groups according to geographical region.

Similarly, the prevalence estimates of MDD varied according the design of the study, being the highest for prospective, non-controlled studies (44.1%, 95% C.I.=33.3%-94.7%, p=ns) and lowest for cross-sectional studies (17.2%, 95% C.I.=13.2%-22%, p=<.001). There was a total overall between-design difference (p=<.001).

In addition, the prevalence of MDD was higher among Caucasian nursing home residents (35.2%, 95% C.I.=16.7%-59.7%, p=ns) vs. Black/African American counterparts (17.5%, 95% C.I.=11.2%-26.4%, p=<.001) and was lowest among Hispanics or Latinos (5.7%, 95% C.I.=3.2%-10%, p=<.001). There was a total overall between-race/ethnicity difference (p=<.001).

A DSM-III diagnosis of MDD was documented among 12.4% of the residents (95% C.I.=8.2%-18.2%, p=<.001), and a DSM-IV diagnosis of MDD was documented among 21.3% of the residents (95% C.I.=15.2%-29.2%, p=<.001). A diagnosis of MDD made according to the ICD-9 or the ICD-10 criteria was documented among 30.9% (95%

C.I.=13.3%-56.6%, p=ns) of the nursing homes. There was a total overall difference based on diagnostic criteria (p=<.001).

Concerning major psychiatric or other medical comorbidities, diabetes was recorded among 18.3% of the residents (95% C.I.=5.8%-44.9%, p=.023), anxiety comorbidity was seen among 43.1% of the residents (95% C.I.=10.8%-82.7%, p=ns), and cognitive impairment (yet not leading to dementia) was recorded among 18.5% of the residents (95% C.I.=6%-44.5%, p=.021). There was a total overall difference in psychiatric or other medical comorbidities (p=<.001).

Finally, those observational studies appraised as moderate-to-poor quality according to the NIH tool mentioned earlier and the ad hoc created percentile recoding (please refer to the footnotes in table n.1) documented point-prevalence rates of MDD up to 17.1%, ranging between 12.1% to 23.4% (95% C.I., p=<.001). In contrast, those non-interventional studies appraised as average-to-good quality documented point-prevalence rates of MDD at 18.3% (95% C.I.=12.5%-26%, p=<.001). There was a total overall difference between studies with varying quality (p=<.001).

Mixed-effect meta-regression analysis of potential continuous variable moderators of major depressive disorder patients

Supplementary materials n.2-5 provide a graphic synthesis of mean age at onset and mean age predictors respectively. Mixed-effect meta-regression analysis demonstrated that the publication year predicted higher rates of MDD among nursing home residents (β=.007, 95% C.I.=.001-.013, p=.019, k (number of studies)=32) and that age inversely predicted MDD prevalence (β=-.031, 95% C.I. .008-.046, p=<.001, k=22). Additionally, the higher the proportion of males among nursing home residents was, the higher the

overall rate of MDD was (β=.017, 95% C.I.=.010-.024, p=≤.001, k=25). As largely expected, the higher the antidepressant drug utilization was, the higher the overall rate of MDD diagnosis was (β=.006, 95% C.I.=.002-.015, p=.014, k=8).

Variables unable to be included in the analyses

We were unable to extract sufficient data to allow reliable pooling of the following clinical moderators: mean age at onset of MDD, current use of lithium, anti-consultant mood stabilizers, benzodiazepines, FGA or SGA drugs, current psychotropic polypharmacy (namely, two or more psychiatric drugs at once), obsessive-compulsive disorder, post-traumatic distress disorder, impulse-control disorder, suicidal behaviour, substance use (including abuse of over-the-counter pain-killer medications), tobacco use, and cardio-/cerebrovascular diseases (including obesity). In addition, we could not even run an exploratory meta-analysis of schizophrenia prevalence among nursing home residents due to the paucity of corresponding original studies (n=3) and the fact that these studies did not follow a naturalist approach. Similarly, BD nursing home residents could be appraised only for qualitative synthesis since the corresponding original studies were too few in number (n=2).

Major biases found across the included studies reporting on major depressive disorder cases

The following issues were documented in at least three studies: a relatively small sample size, a lack of clear-cut definition of the time frame the MDD symptoms were assessed, and/or a lack of an accurate description of the severity of the underlying psychiatric or other medical condition(s).

Discussion

This systematic review included 36 studies encompassing 13,754 individuals. Of these, it was possible to pool data from 13,394 individuals identifying 2110 MDD cases (documented by 32 original studies). In addition, we identified 192 schizophrenia cases described by 3 corresponding reports, but it was not possible to reliably pool data from these cases for quantitative synthesis due to non-naturalistic designs (the qualitative synthesis is nonetheless summarized in table 1). The mean prevalence of MDD across varying geographical regions was 18.9%. Mixed-model meta-regression analysis of the MDD subset revealed that the more recent the publication year was, the higher the reported prevalence of MDD among the nursing home residents; the older the mean age of the residents was, the lower the reported prevalence of MDD among the nursing home residents; the higher the proportion of males among the nursing home residents was, the higher the rates of MDD overall; and, as expected, the higher the antidepressant drug utilization, the higher were the rates of MDD overall.

Finally, despite substantial heterogeneity, MDD prevalence was significantly affected by geographical region, study design, and ethnicity moderators. Nonetheless, concerning the study design, the only statistically significant rates of MDD were the ones related to cross-sectional reports due to the paucity of prospective studies.

Overall, the present report provides more accurate insights into the prevalence and clinical features associated with nursing home residents without dementia diagnosed with MDD than previous evidence (9). In fact, that published report provided only a qualitative synthesis of the evidence and failed to discriminate comorbid MDD cases with or without dementia, despite the intricate relationship that exists between depression and cognitive deficits, especially in the elderly (55). In addition, we retained only those studies relying on the structured interview(s) validated according to mainstream diagnostic codes rather

than merging overt MDD with depressive symptoms. Aiming at enhancing the quality of reporting, we purposely excluded those studies in which the diagnosis of MDD was not assessed by a structured interview. Nonetheless, we acknowledge that the use of structured interviews among nursing home residents may not be as popular as it is among the non-elderly adult population. Therefore, future primary studies should promote the use of standardized clinical ratings among the elderly SMI population.

Strengths and limitations

There are several limitations of the present study that should be acknowledged, allowing a critical interpretation of the results.

The limitations include the high heterogeneity of the studies and populations, the relatively narrow range of the queried databases, as well as the assessment and diagnostic strategies for SMIs. This is with special reference to the lack of original studies involving BD samples and schizophrenia cases, and the total lack of studies providing clear-cut stratification of SSDs.

Moreover, the studies assessing schizophrenia patients did not follow a naturalistic approach, in contrast to the ones documenting MDD (or BD) samples. This issue coupled with the paucity of corresponding primary studies following a naturalistic approach precluded meta-analytic assessment. In addition, due to the scarcity of corresponding data, we could not further stratify for earlier vs. later onset of MDD. Similarly, additional information is critically needed with respect to further potential confounding factors (namely, specific non-psychiatric medical comorbidities or accurate records of pharmacological resource utilization).

In this regard, it must be remarked that many elderly patients diagnosed with MDD are exposed to benzodiazepines, antipsychotics, and other tranquilizers, whereas antidepressant drugs could be under-utilized (56, 57).

Nonetheless, people with highly disabling SMIs (namely, schizophrenia as well as BD), the onsets of which usually occur earlier in life than MDD onset and require exposure to higher/prolonged doses of drugs with significant cardiometabolic side effects, may have reduced life expectancy compared to their counterparts diagnosed with major depressive disorder (58, 59). This issue concurs with limited evidence on the matter. While one may assume that most severe SMIs would be admitted either to long-term psychiatric asylums or even to correctional institutes (as BD may lead to anti-social behaviour associated with higher use of the illicit substance) (60) rather than general medicine or multi-disciplinary nursing home facilities, the actual current practice suggests that there was a reduction in long-term institutional care places, with more patients, especially those that are functional, receiving treatment in the community rather than in care homes, which possibly contain more severely disabled patients. This perspective may explain the higher rates of MDD (and possibly other SMIs as well) over time (in line with the publication year trend).

Clinical implications

Taken together, the results from the present systematic review and meta-analysis lay the groundwork for replication studies to specifically address the above-raised issues considering that the actual prevalence of MDD among nursing home residents without dementia is high, which may also be the case for BD and schizophrenia, and where systematic assessment is particularly urged. There are several areas of research and need for stratification of nursing home residents with SMI that need to be addressed by future clinical research. For example, little is known about the rates of suicidal behaviour in such

populations, although the finding of lower rates of MDD among the older residents could be explained by increased mortality among the individuals who already committed suicide and/or had lower life expectancy due to severe medical morbidity. Similarly, nursing home residents who experience prolonged bed rest are at increased risk both for depression and for cardiometabolic issues, urging for patient-tailored physical therapy interventions as well. In addition, future clinical research on nursing home residents without dementia needs to systematically assess the cognitive and the treatment adherence profile of those individuals admitted to long-term facilities for the aged.

Finally, given the high resource utilization, the socioeconomic burden and increasing life expectancy worldwide (despite the gap that still exists between people with SMI and the general elderly population), the present topic of research represents a crucial priority for practising clinicians, nursing personnel, and those involved in insurance plan making, as well as policymakers.

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Authors and date	Design of the Study	Year of data collection (note: may differ from the year of the publication of the study)	Country	Diagnosis	Diagnostic criteria	Population definition, as from the original paper (nursing home resident, veteran nursing home residents…)	Source of data (i.e. "nursing home, national databank, or else)	Total sample (in nursing home)	Mean age (SD) specify all sample or SMI only	Male % specify all sample or SMI only	Ethnicity specifies all sample or SMI only - (descriptive i.e. Afro-American %, Asian %....)	Main comorbidity-specify all sample or SMI only - (descriptive i.e. CVD %, OB%....)	Quality (NIH or Cochrane)
Hyer L.A. et al., 1984 (Hyer & Hyer, 1984)	Cross-sectional	1984	North America	MDD	DSM-III	"Better functioning" residents in seven intermediate nursing homes	Various nursing homes in the USA	133	-	-	-	Chronic brain syndrome (24,4%)	4 (NIH)
Kay D et al., 1987 (Kay, Holding, Jones & Littler, 1987)	Cross-sectional	1986	North America	MDD	ICD-9	Nursing Home	Various nursing homes in Hobart	196	-	39.80 %	-	-	4 (NIH)
Parmelee P.A. et al., 1989 (Parmelee, Katz & Lawton, 1989)	Cross-sectional	1989	North America	MDD	DSM-III	Nursing home resident	Jewish veteran residents	586	-	-	-	-	2 (NIH)
Parmelee P.A. et al., 1989 (Parmelee, Lawton & Katz, 1989)	Cross-sectional	1986	North America	MDD	DSM-III	Nursing home or congregate residents	Various nursing homes in USA	730	84	30%	Caucasian	-	5 (NIH)
Junginger J. et al., 1993 (Junginger, Phelan, Cherry & Levy, 1993)	Cross-sectional	1993	North America	MDD	DSM-III	Nursing home resident	Various nursing homes in Louisiana	100	-	24%	Caucasian: 96%; Other:4%	-	3 (NIH)
Gerety M.B. et al., 1994 (Gerety et al., 1994)	Cross-sectional	1992	North America	MDD	DSM-III	Nursing Home	Veterans Affairs, nursing homes	134	78.9	44%(all sample)	Caucasian: 74%; Latinos/Hispanic 26%	-	5 (NIH)
Burrows A.B. et al., 1995 (Burrows, Satlin, Salzman, Nobel & Lipsitz, 1995)	Cross-sectional	1994	North America	MDD	DSM-III	Nursing home resident	Hebrew rehabilitation center, Massachusetts	37	88.4	10.80 %	-	-	3 (NIH)
Class C.A. et al., 1996 (Class, Unverzagt, Gao, Hall, Baiyewa & Hendrie, 1996)	Cross-sectional	1994	North America	SCZ	DSM-III	Nursing home resident	Six nursing homes in Indiana	34	77.02 (9.3)	-	Black/African-American	-	4 (NIH)
Bartels S.J. et al., 1997 (Bartels, Mueser & Miles, 1997)	Cross-sectional	1997	North America	BD-I, BD-II, SCZ	DSM-III	Nursing home resident	State-wide study of older adults receiving state-funded mental health services in community mental health centers and in nursing homes.	94	76.1 (6.2)	38%	Caucasian, Black/African-American (percentages undisclosed)	-	5 (NIH)
Albrecht Junghans R.E. et al., 1998 (Albrecht Junghans & Espino, 1998)	Cross-sectional	1996	South America	MDD	DSM-III	Nursing home	Greater Mexico City area database	193	73.3	45%	Latinos/Hispanic: 98%; Other: 2%	-	7 (NIH)
Koenig H.G. et al., 1998 (Koenig & Kuchibhatla, 1998)	Cross-sectional	1996	North America	MDD	DSM-IV	Nursing Home/Hospital	Duke University Medical Center	542	70.2	48%(all sample)	Black/African-American: 100%	-	5 (NIH)

Laprise R. et al., 1998 (Laprise & Vezina, 1998)	Cross-sectional	1996	North America	MDD	DSM-III	Nursing Home	-	66	78.06	46%(all sample)	-	-	6 (NIH)
Butler R. et al., 1998 (Butler, Fonseka, Barclay, Sembhi & Wells, 1998)	Cross-sectional	1993-1996	Oceania	MDD	DSM-III	Rest Home	-	100	-	-	-	Anxiety:3%(all sample), Schizophrenia (all sample):2%	6 (NIH)
Falck R.P. et al., 1999 (Falck, Pot, Braam, Hanewald & Ribbe, 1999)	Prospective OPEN	1999	Europe	MDD	DSM-IV	Nursing home resident	Dutch urban nursing home resident	57	-	-	-	-	2 (NIH)
Goodwin P.E. et al., 1999 (Goodwin & Smyer, 1999)	Cross-sectional	1987	North America	MDD	DSM-III	Nursing home	NMES Institutional Population Component IPC data set	2923	81.7 (al sample)	31.2% (all sample)	Caucasian:93%; Other: 5%	-	6 (NIH)
Streim, J.E. et al., 2000 (Streim et al., 2000)	RCT	2000	North America	MDD	DSM-IV	Public Veteran Affairs Nursing Homes	Eight participating Nursing Homes	69	79.49 (4.2)	66.70 %	Caucasian: 78.3%; Other: 21.7%	-	7 (Cochrane)
Rabins P.V. et al., 2000 (Rabins et al., 2000)	RCT	1993-1996	North America	MDD	DSM-III	Nursing home resident	Psychogeriatric Assessment and Treatment in City Housing program	446	73.1	22.90 %	Caucasian: 10%, Black/African-American 90%	-	7 (Cochrane)
Erlandsen C et al., 2000 (Erlandsen, 2000)	Prospective, non-controlled interventional study	1973-1995	Europe	SCZ	ICD-10	Nursing home resident/psychiatric care centers	Local monitoring systems	112	-	-	-	-	4 (Cochrane)
Harralson T.L. et al., 2002 (Harralson et al., 2002a)	Cross-sectional	2000	North America	MDD	ICD-9	Nursing home resident	Four Nursing Home in Philadelphia	208	84.6 (8.1)	32%	Black/African-American: 42%; Caucasian: 58%	Diabetes among depressed: 22%; Diabetes among non-depressed: 18%	5 (NIH)
Anderson R.L. et al., 2003 (Anderson, Buckwalter, Buchanan, Maas & Imhof, 2003)	Cross-sectional	2001	North America	MDD	DSM-IV	Nursing home resident	Minimum Data Set	145	84	36%(all sample)	Caucasian 100%	-	7 (NIH)
Allgaier A.K. et al. 2004 (Allgaier, Kramer, Mergl, Fejtkova & Hegerl)	Cross-sectional	2004	Europe	MDD	DSM-IV	Nursing home resident	Various nursing homes in Munich	92	84.5 (8.6)	26.10 %	-	-	4 (NIH)
Damian J. et al., 2004 (Damian, Valderrama-Gama, Rodriguez-Artalejo & Martin-Moreno, 2004)	Cross-sectional	2002	Europe	MDD	DSM-IV	Nursing home resident	-	800	83.4	25%(all sample)	-	GAD:26.8%(all samples)	7 (NIH)
Smalbrugge M. et al., 2005 (Smalbrugge, Jongenelis, Pot, Beekman & Eefsting, 2005)	Cross-sectional	2004	Europe	MDD	DSM-IV	Nursing home resident	Various nursing homes in Netherlands	333	79.3 (9.3)	31.20 %	-	-	4 (NIH)
George K. et al., 2007 (George, Davison, McCabe, Mellor & Moore, 2007)	Cross-sectional	2006	Oceania	MDD	DSM-IV	Nursing home resident	Various residential facilities in Melbourne	300	85.37 (6.44)	23.60 %	-	-	4 (NIH)
Choi N.G. et al., 2008 (Choi, Ransom & Wyllie, 2008)	Cross-sectional	2007	North America	MDD, BD-I, BD-II	ICD-9	Nursing home resident	Five Nursing Homes in Central Texas	65	82.45 (8.44)	23.10 %	Caucasian: 89.2%; Black/African-American: 3.1%; Latinos/Hispanic: 6.1%; Other: 1.5%	-	5 (NIH)
Friedman B. et al., 2009 (Friedman, Delavan, Sheeran & Bruce, 2009)	Prospective OPEN	1997-1999	North America	MDD	DSM-IV	Nursing home resident	Visiting Nurse Service of Westchester City	539	78.4 (7.5)	34.90 %	Caucasian: 85%; Black/African-American: 10.4%; Other: 4.6%	-	5 (NIH)

Volicer L. et al., 2011 (Volicer, Frijters & Van Der Steen, 2011)	Cross-sectional	2009	Europe	MDD	DSM-IV	Nursing home resident	Various nursing homes in Netherlands	741	84.7 (7.1)	29.20 %	-	-	4 (NIH)
Davison T.E. et al., 2012 (Davison, McCabe, Knight & Mellor, 2012)	Cross-sectional	2011	Oceania	MDD	DSM-IV	Nursing home resident	Various nursing homes in Melbourne	100	83.68 (7.2)	20%	-	Diabetes among depressed: 20%; Diabetes among non-depressed: 20%	5 (NIH)
Boorsma M. et al., 2012 (Boorsma et al., 2012)	Cross-sectional	2011	Europe	MDD	DSM-IV	Nursing home resident	Various nursing homes in Netherlands	864	-	32.60 %	-	Diabetes among depressed: 18.5%; Diabetes among non-depressed: 21.3%	6 (NIH)
Leontjevas R. et al., 2012 (Leontjevas, Gerritsen, Vernooij-Dassen, Teerenstra, Smalbrugge & Koopmans, 2012)	Cross-sectional	2011	Europe	MDD	DSM-IV	Nursing home resident	Various nursing homes in Netherlands	72	79.8 (11)	36.10 %	-	-	4 (NIH)
Chu C.L. et al., 2012 (Chu et al., 2012)	Cross-sectional	2011	Asia	MDD	DSM-IV	Veterans' home	Veterans' homes in southern Taiwan	167	81,8 (4,8)	-	-	-	4 (NIH)
Van Asch I. F.M. et al., 2013 (Van Asch, Nuyen, Veerbeek, Frijters, Achterberg & Pot, 2013)	Cross-sectional	2008	Europe	MDD	ICD-9	Nursing home resident	Various nursing homes in the Netherlands	1048	81.9 (7.8)	28.80 %	-	-	4 (NIH)
Allgaier A.K. et al., 2013 (Allgaier, Kramer, Saravo, Mergl, Fejtkova & Hegerl, 2013)	Cross-sectional	The early 2000s	Europe	MDD	DSM-IV	Long-Term Care resident	Various nursing homes in Munich	548	84.5 (8.6)	-	-	-	5 (NIH)
Tiong W.W. et al., 2013 (Tiong, Yap, Huat Koh, Phoon Fong & Luo, 2013)	Cross-sectional	2012	Asia	MDD	DSM-IV	Nursing home resident	Various nursing homes in Singapore	323	77.3 (10.3)	46.10 %	-	-	4 (NIH)
Lee M.J. et al., 2013 (Lee, Hasche, Choi, Proctor & Morrow-Howell, 2013)	Cross-sectional	2003	North America	MDD	DSM-IV	Nursing home resident	Various nursing homes in USA	610	72,6 (8.07)	23.77 %	-	-	4 (NIH)
Drageset J. et al., 2013 (Drageset, Eide & Ranhoff, 2013)	Cross-sectional	2004	North America	MDD	ICD-10	Nursing home resident	Various nursing homes in Bergen	227	85.4	27.80 %	-	-	5 (NIH)
SUMMARY	**Cross-sectional studies, n=31** **Prospective open, n=3** **Prospective controlled (RCT), n=2** **Retrospective, n=0**	-	**North America, n=21** **Europe n=9** **Oceania, n=3** **Asia, n=2** **Other, n=1**	**MDD, n=34** **BD, n=2** **SCZ, n=3** **SCZA, n=0**	**DSM-IV, n=17** **DSM-III, n=13** **ICD-9/10, n=6**	-	-	**Total sample, n=13,754**	**Weighted mean=80.65**	-	-	-	**NIH, n=33** **Cochrane, n=3**

Table 1: Qualitative synthesis of records. Included studies: n=36 (please note that the actual number of studies then included in the meta-analysis exceeded the present one since a couple of original records included multiple multi-diagnostic arms).

Note: studies were sorted based on the year of publication.

Overall, most of the studies were conducted in North America owing to the DSM criteria (either Third or Fourth Editions) and related to MDD samples. In most instance, females were overrepresented among the nursing homes residents without a current diagnosis of dementia (any type). Notably, major non-psychiatric medical comorbidities (e.g. diabetes, other cardio- or cerebrovascular conditions were rarely documented); similarly, prominent cognitive impairment (but not dementia) was relatively uncommon.

Legend: DSM=Diagnostic and Statistical Manual for Mental Disorders; ICD=International Classification of Diseases; BD=Bipolar Disorder; MDD=Major Depressive Disorder; SCZ=Schizophrenia; SCZA=Schizoaffective Disorder; GAD=General Anxiety Disorder; RCT=Randomized Clinical Trial.

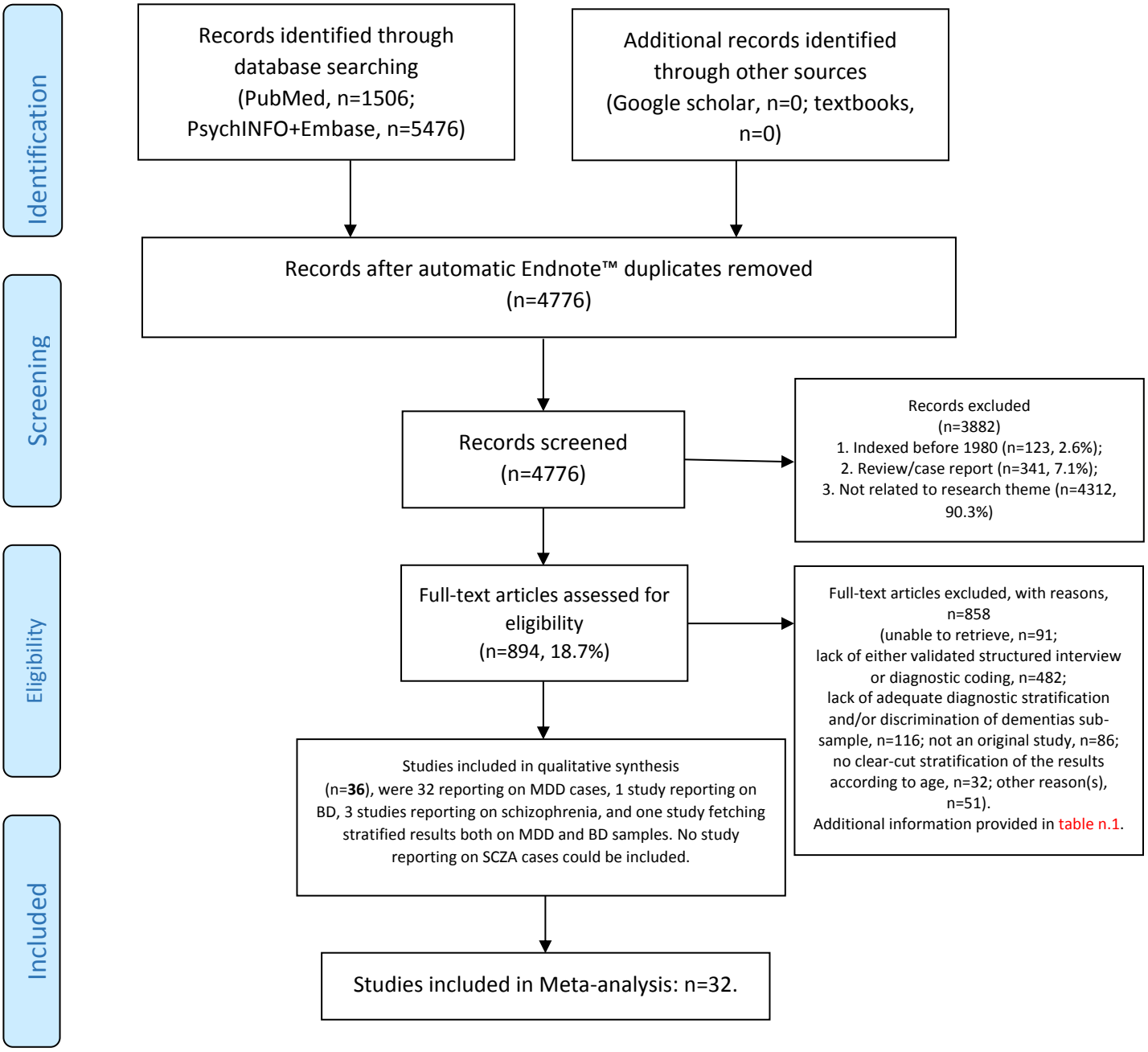
Note: The quality of the 33 out 36 studies assessed using the NIH tool (https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools) has been further appraised by stratification into quartiles as depicted in the boxplot below, whereas score ranging 2-5 (1^{st} and 2^{nd} quartiles merged) were regarded as moderate-poor quality (n=25/33 or 75% of the records) in contrast to higher scores (up to 7) regarded as fair-good quality studies (3^{rd} and 4^{th} quartiles merged), n=9/33 or 24% of the records. Three interventional studies were appraised using the Cochrane tool (13) (two records scored as 7 were considered of fair quality vs. one record scoring 4 considered of poor quality).

Note, 10 out of 36 studies were indexed after the year 2010 (roughly, 27% of the sample); studies indexed after the year 2010 may have nonetheless accounted for data collected earlier in the research process.

MDD nursing homes residents	*Number of studies*	*Prevalence estimate*	*Lower 95%CI*	*Upper 95%CI*	*P value*	*Heterogeneity (I^2 %)*	*Publication bias (Y/N)*	*Subgroup difference (p)*
Whole MDD sample	*32*	18.9%	14.8%	23.8%	<.001	97%	N	-
Geographical region								
Europe	10	16.5%	10.9%	24.1%	<.001	97%	N	<.001
North America	17	25.4%	18%	34.5%	<.001	97%	Y	
Oceania	1	5.7%	3.2%	10%	<.001	0%	-	
Other	4					89%	Y	
Study design-								
Cross-sectional	28	17.2%	13.2%	22%	<.001	97%	Y	<.001
Prospective, open	2	44.1%	33.3%	94.7%	Ns	98%	Y	
Prospective, controlled	2	27.7%	6.1%	69.5%	Ns	98%	Y	
Ethnicity								
Predominantly white/Caucasian	7	35.2%	16.7%	59.7%	Ns	98%	Y	<.001
Predominantly Black or African-American	2	17.5%	11.2%	26.4%	<.001	89%	-	
Predominantly Hispanics	1	5.7%	3.2%	10%	<.001	0%	-	
Diagnostic criteria								
DSM-III	11	12.4%	8.2%	18.2%	<.001	97%	Y	Ns
DSM-IV	16	21.3%	15.2%	29.2%	<.001	94%	Y	
ICD-9 or ICD-10	5	30.9%	13.3%	56.6%	Ns	99%	Y	
Major psychiatric or another medical comorbidity								
Diabetes	3	18.3%	5.8%	44.9%	.023	98%	Y	Ns
Anxiety	4	43.1%	10.8%	82.7%	ns	98%	Y	
Cognitive impairment other than dementia	3	18.5%	6%	44.5%	.021	99%	Y	
NIH quality appraisal								
Poor-moderate quality	14	17.1%	12.1%	23.4%	<.001	95%	Y	Ns
Average-high quality	16	18.3%	12.5%	26%	<.001	98%	Y	

Table 2. Random effect meta-analysis with sensitivity analyses of the prevalence of the major depressive disorder in homes. Note: publication bias could not be evaluated in case of three studies or fewer.

Figure 1: PRISMA 2009 Flow Diagram, adapted



Legend: MDD=Major depressive disorder; BD=Bipolar disorder; SCZA=schizoaffective disorder.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

Figure 1 addendum: PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2 & 5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5

Data collection process	*10*	*Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.*	*5-6*
Data items	*11*	*List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.*	*6*
Risk of bias in individual studies	*12*	*Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.*	*6*
Summary measures	*13*	*State the principal summary measures (e.g., risk ratio, difference in means).*	*6*
Synthesis of results	*14*	*Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.*	*6-7*

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	*15*	*Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).*	*6*
Additional analyses	*16*	*Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.*	*7*
RESULTS			
Study selection	*17*	*Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.*	*8*
Study characteristics	*18*	*For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.*	*8*
Risk of bias within studies	*19*	*Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).*	*9*
Results of individual studies	*20*	*For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.*	*9*
Synthesis of results	*21*	*Present results of each meta-analysis done, including confidence intervals and measures of consistency.*	*8-11*
Risk of bias across studies	*22*	*Present results of any assessment of risk of bias across studies (see Item 15).*	*8-11*
Additional analysis	*23*	*Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).*	*10-11*
DISCUSSION			
Summary of evidence	*24*	*Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).*	*12-15*
Limitations	*25*	*Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).*	*13*
Conclusions	*26*	*Provide a general interpretation of the results in the context of other evidence, and implications for*	*14-15*

		future research.	
FUNDING			
Funding	*27*	*Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.*	*2*

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

*For more information, visit: **www.prisma-statement.org**.*

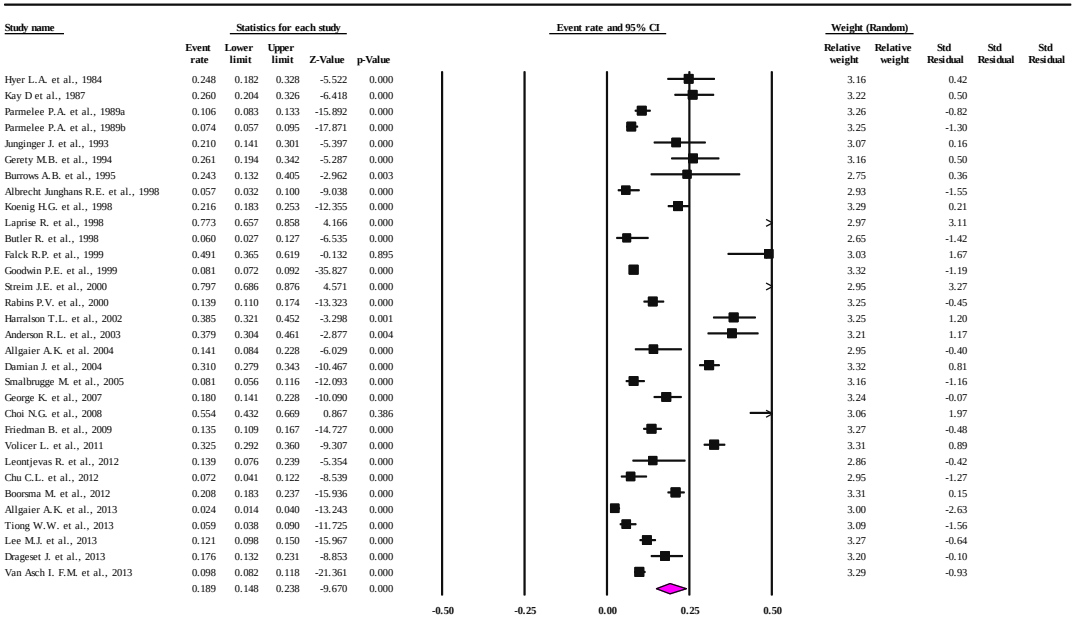


Figure 2: MDD prevalence among nursing homes residents. Random-effect sensitivity meta-analysis. *Studies were ranked from older to most recent indexing.*

Note, 9 out of 32 studies were indexed after the year 2010 (roughly, 28% of the sample).

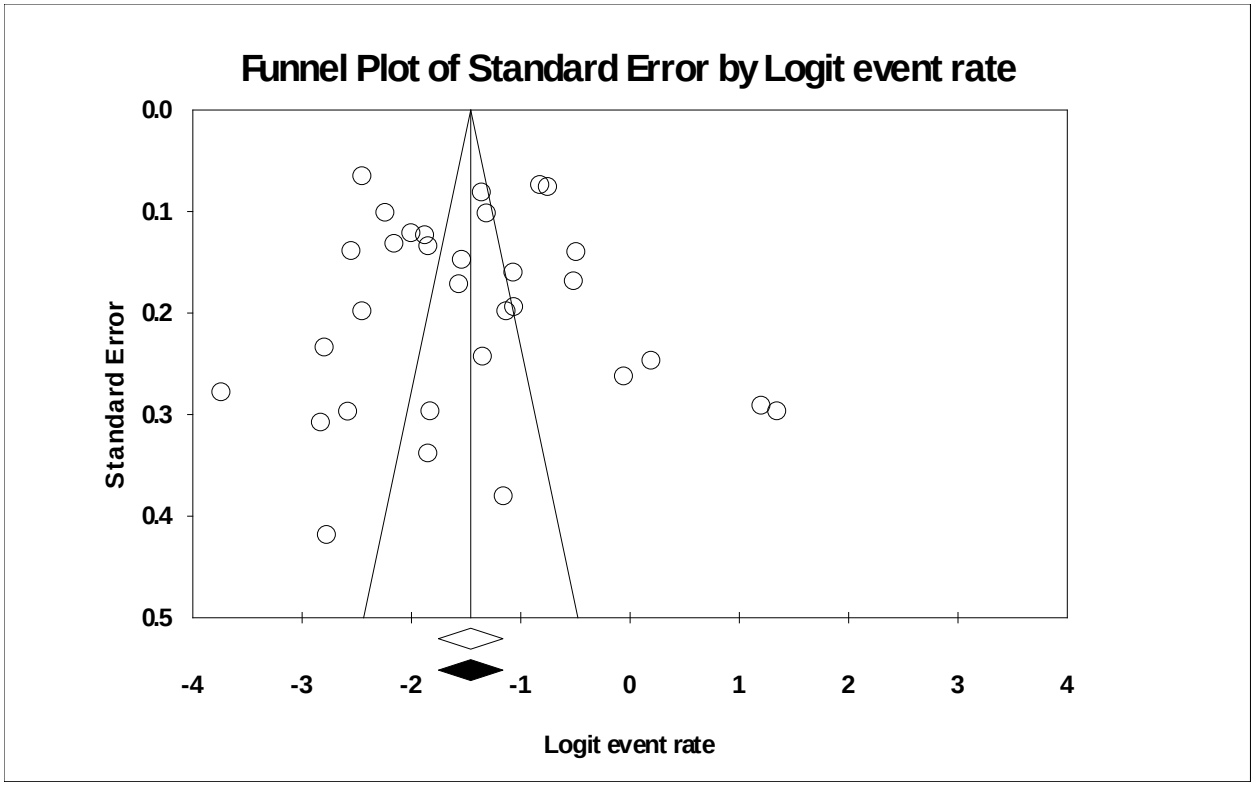


Figure n.3: The visual inspection of the funnel plot would exclude a publication bias since most of the original studies were located in the top tier of the plot, indicating the larger sampled studies with a lower standard error where overrepresented vs. those with smaller sample sizes (bottom of the plot). Notably, the "black diamond" (cumulative effect size) upon trim and fill adjustment substantially overlaps with the non-adjusted one (white color).

Michele Fornaro[1^*], MD, PhD

Marco Solmi[,2,3^], MD, PhD

Brendon Stubbs[4,5], PhD, MSc, BSc

Nicola Veronese[6], MD, PhD

Francesco Monaco[7], MD

Stefano Novello[1], MD

Andrea Fusco[1], MD

Annalisa Anastasia[1], MD

Domenico De Berardis[8], MD, PhD

André F. Carvalho[9,10], MD, PhD

Andrea de Bartolomeis[1], MD, PhD

Eduard Vieta[11], MD, PhD

1 Neuroscience, Reproductive Science and Odontostolmatology, Section of Psychiatry, University School of Medicine "Federico II", Naples, Italy
2 University of Padua, Neuroscience Department, Psychiatry Unit, Padua, IT
3 Azienda Ospedaliera di Padova, Padua Hospital, Psychiatry Unit, Padua, IT
4 Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London SE5 8AZ, UK
5 Health Service and Population Research Department and the Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
6 National Research Council, Ageing Branch, Padua, IT
7 Department of Medicine, Surgery and Dentistry 'Scuola Medica Salernitana', Section of Neuroscience, University of Salerno, Salerno, IT
8 NHS, Department of Mental Health, Psychiatric Service of Diagnosis and Treatment, Hospital "G. Mazzini", ASL 4, Teramo, IT
9 Department of Psychiatry, University of Toronto, Toronto, ON, Canada
10 Centre for Addiction & Mental Health (CAMH), Toronto, ON, Canada
11 Psychiatry and Psychology Department of the Hospital Clínic, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, 170 Villarroel St, 08036, Barcelona, Catalonia, Spain

^joint first authors.

Corresponding author: Dr. Michele Fornaro (via Sergio Pansini n.5, Ospedale Policlinico II di Napoli, Edificio 18, Psichiatria, ZIP 80131, Naples, Italy). Tel/fax:0039-081-7463070. Email: Dott.Fornaro@gmail.com

Full-addresses:

1 Via Sergio Pansini n.5, edificio 18, Ospedale Policlinico II, Naples, Italy.

2 Clinica psichiatrica, via Giustiniani 2, Padova, Italy

3 ULSS 17 Dipartimento Area Salute Mentale - Local Health Unit Psychiatry Department (marco.solmi@unipd.it)

4,5 David Goldberg Centre, Denmark Hill, London, United Kingdom (email: brendon.stubbs@kcl.ac.uk)

6 National Research Council, Neuroscience Institute, Aging Branch, Via Giustiniani, 2, 35128 Padova, Italy (nicola.veronese1@aulss3.veneto.it)

7 Via Allende – 84081 Baronissi, Salerno, Italy (fmonaco1980@gmail.com)

8 Ospedale Mazzini, Teramo, Italy (dodebera@aliceposta.it)

9,10 University of Toronto, Department of Psychiatry, 250 College Street, 8th floor, Toronto, Ontario, M5T 1R8 (andrefc7@terra.com.br)

11 Psychiatry and Psychology Department of the Hospital Clínic, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, 170 Villarroel St, 08036, Barcelona, Catalonia, Spain (EVIETA@clinic.ub.es)