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Research report

The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis

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ABSTRACT

Background: Neuropsychiatric symptoms (NPS) are being increasingly recognized as common serious problems in Alzheimer's disease (AD). However, published data on the prevalence of NPS in persons with AD are conflicting. This meta-analysis aimed to estimate the prevalence of NPS in persons with AD.
Methods: Studies published from 1964 to September 30, 2014, were identified from PubMed and Embase database, reference lists and conference abstracts. We calculated prevalence rates and conducted meta-regression analysis with random-effects model, according to study characteristics, population demographics or condition information.
Results: We identified 48 eligible articles, which provided data for 12 NPS reported in Neuropsychiatric Inventory (NPI). The most frequent NPS was apathy, with an overall prevalence of 49% (95% CI 41–57%), followed by depression, aggression, anxiety and sleep disorder, the pooled prevalence estimates of which were 42% (95% CI 37–46%), 40% (95% CI 33–46%), 39% (95% CI 32–46%) and 39% (95% CI 30–47%), respectively. The less prevalent NPS were irritability (36%, 31–41%), appetite disorder (34%, 27–41%), aberrant motor behavior (32%, 25–38%), delusion (31%, 27–35%), disinhibition (17%, 12–21%) and hallucination (16%, 13–18%). Least common was euphoria, with an overall prevalence of 7% (95% CI 5–9%).
Limitations: Several aspects, such as the quality of included studies were not always optimal and there was significant heterogeneity of prevalence estimate across studies.
Conclusions: NPS were observed to be highly prevalent in AD patients. Disease duration, age, education level, population origin and the severity of cognitive impairment had influence on the prevalence of some NPS.

1. Introduction

Neuropsychiatric symptoms (NPS) are being increasingly recognized as core features of Alzheimer's disease (AD) and related dementias (Petrovic et al., 2007). In this article, we choose 12 neuropsychiatric symptoms reported in Neuropsychiatric Inventory (NPI) to study. It was demonstrated that NPS could be identified as different neuropsychiatric sub-syndromes in diverse studies (Aalten et al., 2007; Cheng et al., 2012). Aalten and colleagues reported the largest European database (EADC), identifying four different NPS sub-syndromes: hyperactivity (aggression, disinhibition, irritability, aberrant motor behavior and euphoria), psychosis (delusion, hallucination and sleep disorder), affective (depression and anxiety,) and apathy (apathy and appetite disorder) (Aalten et al., 2007). More than 80% demented patients exhibit at least one neuropsychiatric symptom, since the onset of cognitive impairment (Lyketsos et al., 2002). However, they are often under-recognized and improperly managed in persons with AD (Chow et al., 2002).

The occurrence of NPS in AD can accelerate disease progression and early institutionalization, and interfere with treatment effects and prognosis (Lyketsos et al., 2002; Steffens et al., 2005).

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Therefore, early and precise recognition of NPS in AD has become urgent as it can be effectively prevented and intervened (Wang et al., 2015). In addition, reliable data on the prevalence of NPS is essential to inform patients and caregivers, ascertain the overall burden of AD, and explore underlying mechanism. Published data on the prevalence rates of NPS in AD patients varied widely. These conflicting results may be attributed to heterogeneity in the study setting, population demographics, evaluation methods or the severity of cognitive impairment (Fuh, 2006; Mega et al., 1996; Teri et al., 1988). A systematic review and meta-analysis could help explain the variability in the existing literature and through pooling, produce more precise estimates of NPS prevalence in AD. The purpose of this systematic review was to investigate the prevalence of NPS in AD.

2. Methods

2.1. Search strategy

We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria for systematic review and meta-analysis (Stroup et al., 2000). The search was executed in PubMed (1964–2014) and Embase (1981–2014) database, and references were exported and managed using EndNote X6. The key words used were: delusion OR hallucination OR apathy OR indifference OR depression OR aggression OR agitation OR anxiety OR euphoria OR elation OR disinhibition OR irritability OR aberrant motor behavior OR sleep disorder OR appetite disorder OR neuropsychiatric symptoms OR behavioral and psychological symptoms of dementia (BPSD) AND Alzheimer disease. The reference lists of suitable retrieved articles and proceedings from the past 3 years of relevant conferences were manually searched for additional studies. The final search was carried out on September 30, 2014.

2.2. Selection criteria

Published studies fulfilling the following inclusion criteria were included in the analysis: were original research; were cross-sectional or longitudinal design; were on patients with probable or possible AD consistent with the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (DSM-IV) or the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA); reported a prevalence of NPS in AD or sufficient information to calculate an estimate; NPS were assessed by validated scale; sample size at least 50; published in English.

We also considered abstracts and unpublished studies, but excluded review articles, editorials, commentaries, hypothesis papers, letters without original data, meta-analyses and papers focused on young-onset AD (YOAD). Where there was more than one publication reported on the same population, we chose data from the most comprehensive report and, where equal, the most recent report. If there was disagreement between authors about the eligibility of studies or data extraction, the articles were discussed in further detail until consensus was reached.

2.3. Data extraction and quality assessment

After the initial assessment for eligibility, two reviewers extracted and reached agreement on data from included articles using a standardized template. From each selected study, we extracted the following data: study characteristics (author, publication year, sample size, setting), population demographics (percentage of female, age, education level, MMSE score), condition information (data sources, AD diagnostic criteria, method of NPS assessment) and reported prevalence or the information needed to calculate an estimate. If a publication involved longitudinal assessment, only the baseline prevalence was included.

The main quality criterion in the evaluation of the prevalence of NPS is using a validated and comprehensive instrument. In this study, only publications that had used Neuropsychiatric Inventory (NPI) or other general scales which assess more than one NPS domain were included in order to ensure high-quality assessment of NPS in the primary studies.

2.4. Statistical analysis

We computed the crude prevalence for each study. Pooled estimates of prevalence and 95% confidence interval (CI) were calculated using random-effects meta-analysis, more robust and appropriate when there was substantial heterogeneity in prevalence between studies. The prevalence of NPS and the total number of included patients for each study population were used as variables. Analyses of the heterogeneity of prevalence across studies were done with I^2 statistic ($I^2 \geq 75\%$ indicating high heterogeneity). Publication bias was investigated using the Egger's test, and where statistically significant bias was found, we used the trim and fill method to adjust for it (Duval and Tweedie, 2000; Egger et al., 1997).

Meta-regression was used to estimate the extent to which measured covariates (publication year, sample size, the method of NPS assessment, study setting, population origin, disease duration, the percentage of female, the mean MMSE score, mean age and mean education level of participants) could explain the observed heterogeneity in prevalence estimates across studies.

For all tests, $p < 0.05$ was deemed to be significant. Combined prevalence was calculated separately for every single NPS. All analyses were carried out using STATA statistical software package, version 12.0.

3. Results

3.1. Identification and description of studies

The literature search yielded a total of 20,424 citations: 13,388 from Embase and 7,036 from PubMed (a total of 16,384 after duplicates removed) (Fig. 1). After the initial screen, 412 studies met the criteria for full-text review, of which 370 were excluded (129 not original research, 85 not AD population, 96 no prevalence or

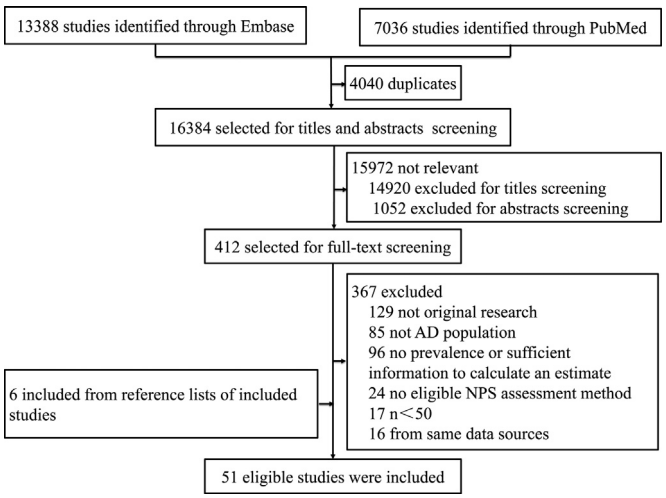

Fig. 1. Flowchart of studies included and excluded. AD=Alzheimer's Disease.

sufficient information to calculate an estimate, 24 no eligible NPS assessment methods, 17 sample size < 50, 19 from same data sources). Additional 6 articles were included by hand-searching from reference lists of potentially eligible studies. Totally, 48 original researches were included in this meta-analysis (Aalten et al., 2007; Bassiony et al., 2000; Binetti et al., 1993; Burns et al., 1990a, 1990b, 1990c, 1990d; Charernboon and Phanasathit, 2014; Cheng et al., 2012; Chiu et al., 2006, 2012; Chow et al., 2002; Cohen et al., 1993; D'Onofrio et al., 2012; Di Iulio et al., 2010; Fernandez et al., 2010; Fernandez Martinez et al., 2008; Fuh et al., 2005; Gormley et al., 1998; Hart et al., 2003; Harwood et al., 2000; Haupt et al., 2000; Hirono et al., 1998; Ikeda et al., 2003; Karttunen et al., 2011; Kwak et al., 2013; Lopez et al., 2005; Lyketsos et al., 1997, 2002, 2001; Mega et al., 1996; Mirakhur et al., 2004; Mizrahi et al., 2006; Moran et al., 2005; Nakaaki et al., 2008; Senanarong et al., 2004; Steffens et al., 2005; Tatsch et al., 2006; Teri et al., 1999; Tractenberg et al., 2003, 2002; Treiber et al., 2008; Tunnard et al., 2011; Van der Mussele et al., 2013; van Vliet et al., 2012; Wilson et al., 2000; Youn et al., 2011; Zhao et al., 2012).

Full details of 48 included studies are presented in Supplementary Table 1 online. Dates of publication ranged from 1990 to 2014. Eighteen studies were based in America, 18 in Europe, and 12 each in Asia. Only 14 studies were in a community setting, the other 34 were in a clinic setting. Forty-four studies offered data on percentage of female, with the percentage ranging from 16% to 86%. The mean age of all participants varied from 67.1 to 85.7 years. Twenty-nine studies reported Data on mean education level, which ranged from 3.5 to 13.8 years. Thirty-three studies provided mean MMSE score, varying from 8 to 23.5. Assessment of neuropsychiatric symptoms varied with studies using NPI, BEHAVE-AD, DSM, CERAD BRSD, CSDD, HRSD or Abbreviated Mental Test Score.

In this meta-analysis, we selected the following 12 NPS reported in MPI to study: delusion, hallucination, apathy, depression, aggression, anxiety, euphoria, disinhibition, irritability, aberrant motor behavior (AMB), sleep disorder and appetite disorder.

3.2. Prevalence of NPS in AD

The twelve neuropsychiatric symptoms were identified as four sub-syndromes, namely hyperactivity (aggression, disinhibition, irritability, aberrant motor behavior and euphoria), psychosis (delusion, hallucination and sleep disorder), affective (depression and anxiety,) and apathy (apathy and appetite disorder) (Aalten et al., 2007). Figs. 2–4 provided the prevalence estimates of most prevalent neuropsychiatric symptoms and the pooled prevalence of all the 12 NPS can be found as Supplementary Figs. 1–12 online. We examined the effects of nine factors on the prevalence of NPS in AD patients found across studies in a meta-regression analysis: (1) publication year (2) sample size (3) method of NPS assessment (4) study setting (5) population origin (6) disease duration (7) the percentage of female (8) the mean MMSE score of participants (9) the mean age of participants (10) the mean education level of participants.

3.2.1. Prevalence of hyperactivity in AD

The prevalence of aggression in AD across the 29 studies reporting on 9,133 persons ranged from 11% to 68%. The overall pooled prevalence of aggression was 40% (95% CI 33–46%) and there was a substantial heterogeneity (I^2=97.7%, P<0.05) between estimates (Supplementary Fig. 1). We then performed meta-regression analyses, which reported that factor of duration (p=0.017) and age (p=0.004) might explain some of the variance across studies (Table 1).

Eighteen studies reported prevalence of disinhibition in AD ranging from 0.6% to 36%. Overall, there were 5,680 AD patients with a pooled prevalence of 17% (95% CI 12–21%) and a high level heterogeneity (I^2=96.4%, P<0.05) across studies (Supplementary

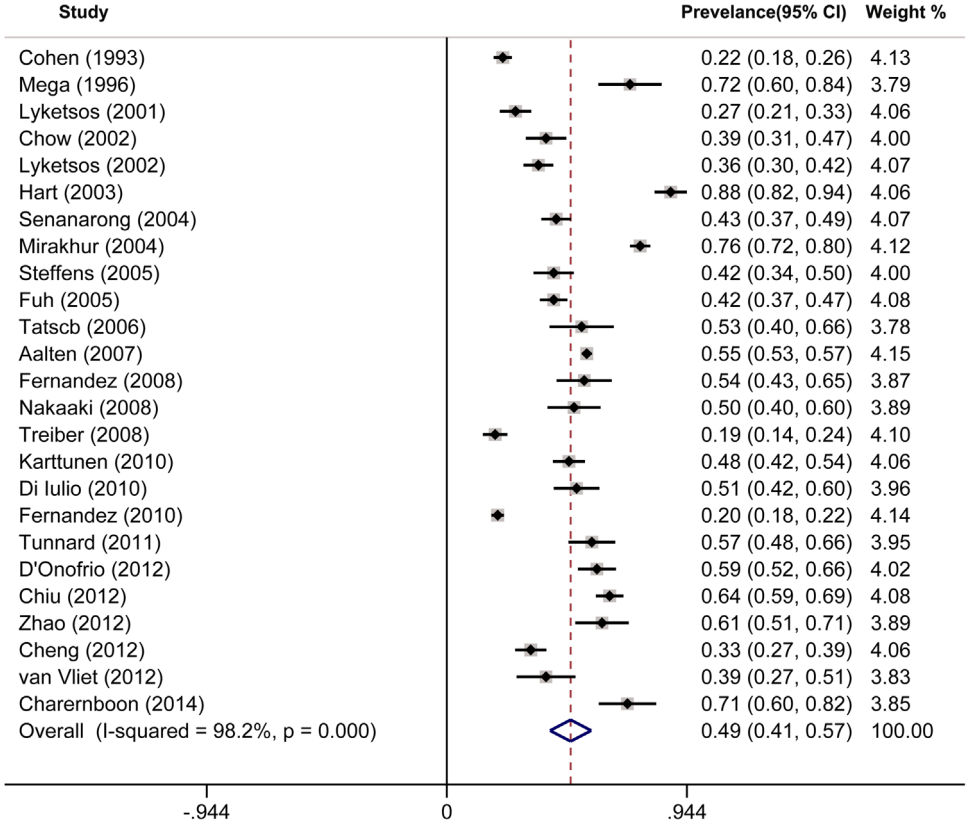

Fig. 2. Overall prevalence of apathy in Alzheimer's disease.

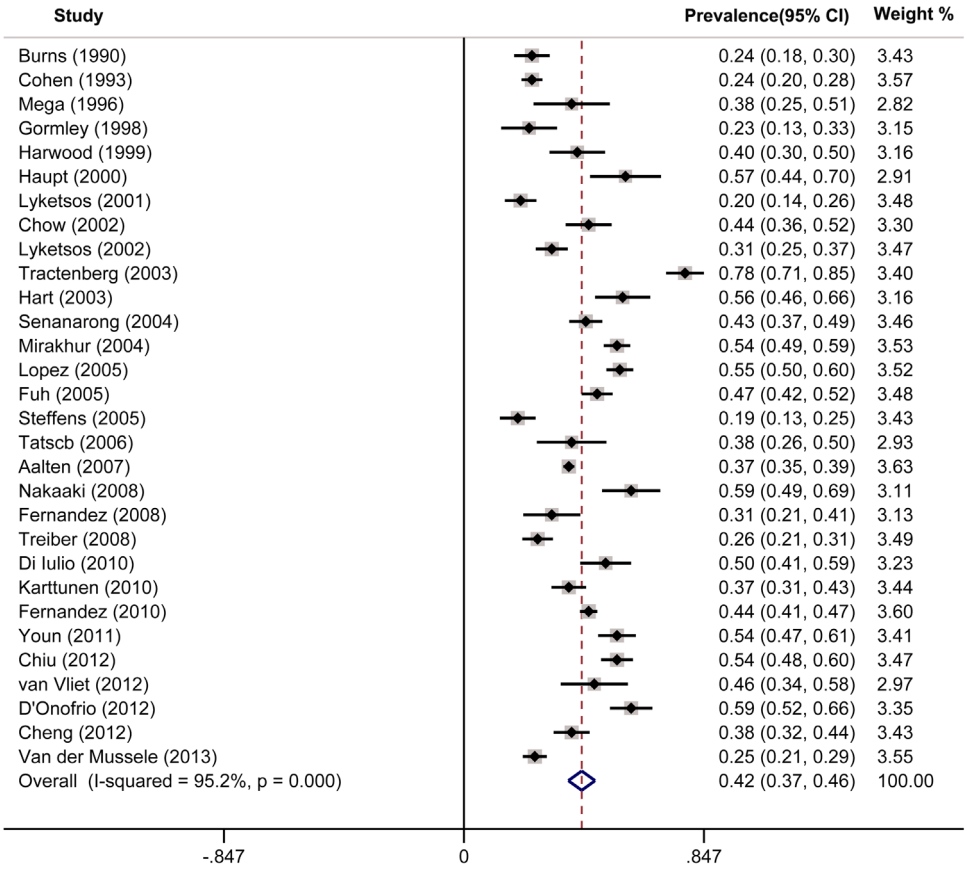

Fig. 3. Overall prevalence of depression in Alzheimer's disease.

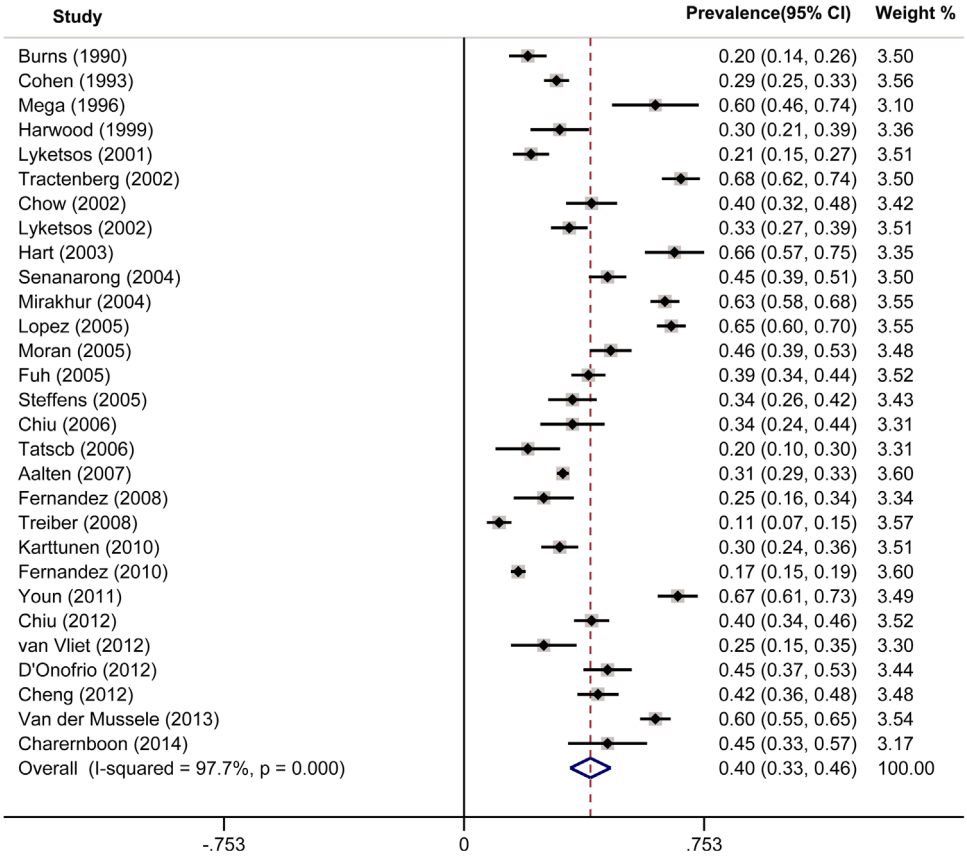

Fig. 4. Overall prevalence of aggression in Alzheimer's disease.

Table 1
Results of meta-regression analyses ($P > |t|$).

Variables	Aggression	Disinhibition	Irritability	AMB	Euphoria	Delusion	Hallucination	Sleep disorder	Depression	Anxiety	Apathy	Appetite disorder
Publication year	0.644	0.009	0.544	0.727	0.307	0.765	0.845	0.653	0.115	0.153	0.493	0.491
Sample size	0.547	0.542	0.877	0.845	0.836	0.461	0.719	0.333	0.696	0.842	0.545	0.456
Evaluation method	0.646	–	0.497	0.877	–	0.117	0.960	0.874	0.661	0.012	0.017	0.895
Study setting	0.210	0.127	0.020	0.035	0.039	0.108	0.760	0.205	0.561	0.200	0.057	0.022
Population origin	0.725	0.820	0.225	0.261	0.804	0.029	0.162	0.563	0.187	0.772	0.433	0.559
Disease duration	0.017	0.009	0.002	0.011	0.085	0.012	0.089	0.604	0.234	0.088	0.001	0.011
Female%	0.502	0.192	0.910	0.319	0.843	0.755	0.585	0.742	0.662	0.731	0.852	0.645
MMSE score	0.322	0.255	0.097	0.077	0.131	0.317	0.084	0.157	0.869	0.682	0.009	0.285
Age	0.004	0.007	0.038	0.064	0.042	0.010	0.664	0.991	0.002	0.012	0.176	0.432
Education level	0.530	0.883	0.299	0.777	0.591	0.946	0.579	0.587	0.636	0.383	0.005	0.763

Note: AMB: Aberrant Motor Behavior; MMSE: Minimum Mental State Examination; NPS: Neuropsychiatric Symptoms.

Fig. 2). The subsequent meta-regression analyses indicated that factors of publication year ($p=0.009$), duration ($p=0.009$) and age ($p=0.007$) might be significant explanations for some of the heterogeneity in the estimates (Table 1).

The prevalence of irritability in AD across the 20 studies reporting on 6,203 persons ranged from 18% to 23%. The overall pooled prevalence of irritability was 36% (95% CI 31–41%) and there was a substantial heterogeneity ($I^2=96.4\%$, $P<0.05$) between estimates (Supplementary Fig. 3). Following the meta-regression analyses revealed that factors of study setting ($p=0.02$), duration ($p=0.002$) and age ($p=0.038$) might be interpretations for some of the variance between estimates (Table 1).

Twenty studies reported the prevalence of aberrant motor behavior in AD ranging from 0.8% to 70%. Overall, these studies reported on 6,756 participants with a pooled prevalence of 32% (95% CI 25–38%) and a significant heterogeneity across individual studies (Supplementary Fig. 4). Afterwards, we conducted the meta-regression analyses, which indicated that factor of study setting ($p=0.035$) and duration ($p=0.011$) might explain some of the variance across studies (Table 1).

The prevalence of euphoria in AD across the 18 studies reporting on 5,488 persons ranged from 0.5% to 20%. The overall pooled prevalence of euphoria was 7% (95% CI 5–9%) and there was a high level heterogeneity between studies (Supplementary Fig. 5). We performed meta-regression analyses, which demonstrated that factors of study setting ($p=0.039$), and age ($p=0.042$) might explain some of the variance across studies (Table 1).

3.2.2. Prevalence of psychosis in AD

The prevalence of delusion in AD across the 34 studies reporting on 10,526 persons ranged from 9% to 59%. The overall pooled prevalence of delusion was 31% (95% CI 27–35%), with a substantial heterogeneity ($I^2=95.9\%$, $P<0.05$) across individual studies (Supplementary Fig. 6). Then we conducted meta-regression analyses, which indicated that factors of age ($p=0.01$), population origin ($p=0.029$) and duration ($p=0.012$) could significantly explain some of the variance in the estimates (Table 1).

Thirty-one studies reported the prevalence of hallucination in AD ranging from 6% to 41%. Overall, these studies reported on 10,123 participants with a pooled prevalence of 16% (95% CI 13–18%) and a high level heterogeneity ($I^2=93.7\%$, $P<0.05$) between estimates (Supplementary Fig. 7). After meta-regression analyses, none of the aforementioned factors could significantly explain any of the variance in the estimates on an individual basis (Table 1).

The prevalence of sleep disorder in AD across the 17 studies reporting on 5,634 persons ranged from 14% to 69%. The overall pooled prevalence of sleep disorder was 39% (95% CI 30–47%), with a substantial heterogeneity ($I^2=97.8\%$, $P<0.05$) across individual studies (Supplementary Fig. 8). After meta-regression analyses, none of the nine factors could significantly explain any of the variance in the estimates on an individual basis (Table 1).

3.2.3. Prevalence of affective AD

Thirty studies reported prevalence of depression in AD ranging from 19% to 78%. Overall, there were 9,012 AD patients with a pooled prevalence of 42% (95% CI 37–46%) and a significant heterogeneity ($I^2=95.2\%$, $P<0.05$) between estimates (Supplementary Fig. 9). The meta-regression analyses of all 9 factors revealed that the factor of age ($p=0.002$) might explain some of the variance in the estimates across studies (Table 1).

The prevalence of anxiety in AD across the 25 studies reporting on 8,109 persons ranged from 12% to 70%. The overall pooled prevalence of anxiety was 39% (95% CI 32–46%), with a substantial heterogeneity ($I^2=97.7\%$, $P<0.05$) across individual studies (Supplementary Fig. 10). Following we conducted meta-regression analyses, indicating that factors of evaluation method ($p=0.012$) and age ($p=0.012$) could be explanations for some of the variance in the estimates (Table 1).

3.2.4. Prevalence of apathy in AD

The prevalence of apathy in AD across the 25 studies reporting on 7,671 persons ranged from 19% to 88%. The overall pooled prevalence of apathy was 49% (95% CI 41–57%) and we observed apparent heterogeneity ($I^2=98.2\%$, $P<0.05$) across studies (Supplementary Fig. 11). Subsequently, we performed meta-regression analyses and it was demonstrated that factors of evaluation method ($p=0.017$), duration ($p=0.001$), education level ($p=0.005$) and MMSE score ($p=0.009$) could be interpretations for some of the variance in the estimates (Table 1).

Seventeen studies reported prevalence of appetite disorder in AD ranging from 11% to 64%. Overall, there were 6,424 AD patients with a pooled prevalence of 34% (95% CI 27–41%) and a significant heterogeneity ($I^2=97.1\%$, $P<0.05$) between estimates (Supplementary Fig. 12). The subsequent meta-regression analyses revealed that the factor of study setting ($p=0.022$) and duration ($p=0.011$) might be interpretation for some of the variance in the estimates across studies (Table 1).

3.3. Assessment of publication Bias

According to the Egger's test, there was evidence of publication bias for the following NPS domains: aggression ($p=0.049$), disinhibition ($p=0.001$), euphoria ($p=0.014$), delusion ($p=0.008$),

hallucination ($p=0.007$), sleep disorder ($p=0.019$). However, using the trim and fill method to account for the bias had no effect on the summary estimate for them.

4. Discussion

This is the first systematic review and meta-analysis designed to assess the prevalence estimates of neuropsychiatric symptoms in persons with AD, which revealed NPS were highly prevalent in AD (Fig. 5). Though the prevalence of NPS varied widely across studies, the most frequent disturbance reported in AD sample was apathy, followed by depression, aggression, anxiety and sleep disorder, while the least common was euphoria. According to meta-regression analyses, age could affect the prevalence of aggression, disinhibition, irritability, euphoria, delusion, depression and anxiety. It was suggested that disease duration had some influence on the occurrence of some NPS: aggression, disinhibition, irritability, AMB, delusion, apathy and appetite disorder. We also observed that study setting affected the prevalence of irritability, AMB, euphoria and appetite disorder. Moreover, the results indicated that evaluation method could have effect on the occurrence of anxiety and apathy. Furthermore, the prevalence of apathy was affected by education level and the severity of cognitive impairment, only delusion was influenced by population origin.

In our study, it was demonstrated that disease duration and age could affect prevalence estimates of aggression, disinhibition and irritability. Yet, further research is needed to illustrate the definite mechanism of these correlations. Additionally, we reported that study setting had influence on the occurrence of irritability and aberrant motor behavior. As aforementioned, some neuropsychiatric symptoms, such as irritability and AMB, were often more bothersome and increase caregiver burden, thus accelerating early institutionalization (Steffens et al., 2005). Moreover, studies conducted in the clinical setting are easily subjected to referral bias, which might overestimate the prevalence (Lyketsos et al., 2002; Reijnders et al., 2008). Euphoria was the least common NPS in AD, which is consistent with numerous studies (Aalten et al., 2007; Cheng et al., 2012; Treiber et al., 2008). In addition, the heterogeneity of prevalence of euphoria was highly correlated with study setting, which might partially due to euphoria is also a notorious disturbance that hard to manage in a home setting. We also found that there was association between the heterogeneity of prevalence of euphoria and age, which requires more studies to illustrate the underlying mechanisms.

Our study revealed that psychotic symptoms were common in persons with AD and there was a significant association between delusion and age. Prior evidences had indicated that delusion was related to age (Bassiony et al., 2000; Hirono et al., 1998), which was consistent with Cooper et al. (Devanand et al., 1992), who had found that delusional patients were older than those without psychotic symptoms. Though we did not find correlation between hallucination and age, Burns et al. had reported that hallucination was associated with a younger age (Burns et al., 1990b). Therefore, further research is needed to gain insight into the mechanisms underlying the association between psychosis and age. In addition, the prevalence of delusion was also found to be influenced by population origin, which was supported by Chow et al., who had reported that Chinese caregivers tend to report higher rates of delusions than Caucasians (Chow et al., 2002). Moreover, we also found that disease duration had affected the heterogeneity of prevalence delusion, which was consistent with the previous study, suggesting that the longer disease duration was associated with the presence of psychosis (Hirono et al., 1998). However, Ikeda et al. had reported that there were no significant differences between those with and without delusions in terms of age, yeas of education, duration of illness and disease severity (Ikeda et al., 2003).

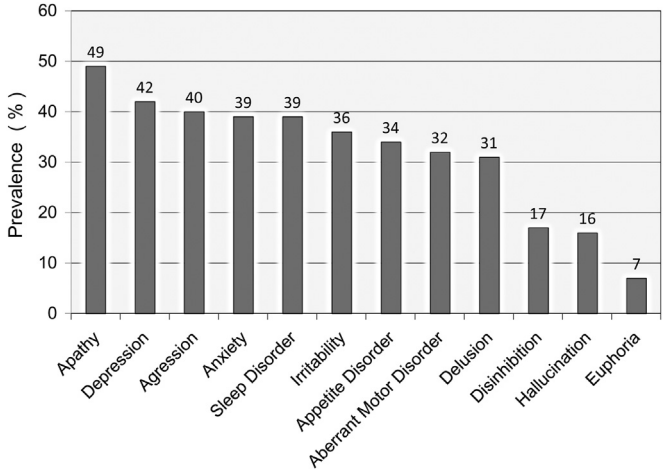

Fig. 5. The prevalence of neuropsychiatric symptoms in Alzheimer's Disease.

As the second most prevalent disturbance, depression was correlated with age. Moreover, we found the effects of evaluation method and age on prevalence estimates of anxiety in AD patients. However, the underlying mechanisms of these associations are ambiguous and additional work is needed to reveal it.

Apathy was the most common disorder among all the NPS in AD, which was supported by other studies (Aalten et al., 2007; Fernandez Martinez et al., 2008; Steffens et al., 2005; Tatsch et al., 2006). A consensus has emerged, supported by this study, that apathy was substantially associated with more severe cognitive impairment (Cheng et al., 2012; Mega et al., 1996; Zhao et al., 2012). We also observed that the prevalence of apathy was influenced by education level, which could be explained by the notion that lower education level contributed to more severe cognitive dysfunction (Chow et al., 2002). Moreover, it was demonstrated that evaluation method and disease duration had effect on the occurrence of apathy, which was in agreement with the previous study (Zhao et al., 2012). Furthermore, there was a substantial relation between the heterogeneity in the prevalence of appetite disorder and study setting and disease duration. Appetite disorder, which may lead to serious consequences including inadequate diet and malnutrition, is notoriously difficult to manage in a home setting and may result in institutionalization (Steffens et al., 2005).

Limitations of this meta-analysis must be considered. Firstly, most of the eligible studies were cross-sectional (75%) in design and clinic-based (69%) in setting which may limit the interpretation of the results with respect to the general population. Secondly, the quality of the included studies was not always optimal, demonstrated by the lack of reporting of non-responders, though the magnitude of this problem may be too small to substantially alter our conclusion. Thirdly, there was significant heterogeneity of prevalence estimate across studies which could be partially due to heterogeneity in publication year, evaluation method, study setting, population origin and disease duration. Fourthly, the possibility of publication bias could not be fully excluded by Egger's test. Finally, though NPI scale is a validated and widely used tool to assess neuropsychiatric symptoms, it could not cover all the NPS. Nevertheless, when the trim and fill analysis was conducted, the overall imputation did not change the general result, which indicated the results are robust to the possibility of unpublished negative studies.

Author disclosures

The authors have nothing to disclose.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2015.09.069.

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