Original Article

Rate of early onset Alzheimer's disease: a systematic review and meta-analysis

Xi-Chen Zhu[1], Lan Tan[1,2], Hui-Fu Wang[1], Teng Jiang[1], Lei Cao[1], Chong Wang[2], Jun Wang[2], Chen-Chen Tan[2], Xiang-Fei Meng[2], Jin-Tai Yu[1,2,3]

[1]Department of Neurology, Qingdao Municipal Hospital, Nanjing Medical University, Qingdao 266071, China; [2]Department of Neurology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, Qingdao 266071, China; [3]Memory and Aging Center, Department of Neurology, University of California, San Francisco, USA

Correspondence to: Jin-Tai Yu. Department of Neurology, University of California, San Francisco, 675 Nelson Rising Lane, Suite 190, Box 1207, San Francisco, CA 94158, USA. Email: jintai.yu@ucsf.edu; Dr. Lan Tan. Department of Neurology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, No. 5 Donghai Middle Road, Qingdao 266071, China. Email: dr.tanlan@163.com.

Abstract: It is generally accepted that the population rate of early onset Alzheimer's disease (EOAD) in Alzheimer's disease (AD) is 1-2%. However, the true population based rate of EOAD has never been verified by a systematic review and meta-analysis. We used electronic searches of Cochrane Library, Embase, Medline and PubMed databases to identify published related studies. The systematic review and meta-analysis was then to be conducted to calculate a pooled rate of EOAD and make comparisons between studies and geographic distribution. A total of 13 papers were included in our systematic review and meta-analysis. The rate of EOAD, 5.5% [95% confidence interval (CI): 0.039-0.079, P<0.001], was generated after pooled analysis of all studies in random effect model. The pooled analysis of the rate in developed country was 5.9% (95% CI: 0.040-0.085, P<0.001). The pooled analysis of the rate in developing countries was 4.4% (95% CI: 0.028-0.066, P<0.001). Our study showed that the rate of EOAD in AD is 5.5%, not 1-2% as usually demonstrated. And our results indicated that the rate in developed countries was relative higher than in developing countries. Further trials with larger samples across more countries and more careful designed of experiments are required to confirm whether our findings are truly significant

Keywords: Early onset Alzheimer's disease (EOAD); rate; Alzheimer's disease (AD); meta-analysis

Submitted Jan 06, 2015. Accepted for publication Jan 06, 2015.
doi: 10.3978/j.issn.2305-5839.2015.01.19
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.01.19

Introduction

Early onset Alzheimer's disease (EOAD), with onset of symptoms at a young age (1,2), usually has a higher prevalence of atypical manifestations with earlier multi domain cognitive impairment when compared to late-onset Alzheimer's disease (LOAD) cases (3). As we all know, Alzheimer's disease (AD) is the most common neurodegenerative dementia (4,5), and it would turn devastated when it occurs at a young age. EOAD disproportionately impacts daily life. In addition, the psychological and medical toll to treat EOAD patients is also significantly.

There is no definitive definition for EOAD. And the cutoff age of EOAD is not definitive, either. EOAD is generally accepted as AD patients with onset before 65 years of age (1). This cutoff point, 65 years old, is generally regarded as a sociological partition according to employment and retirement age. However, the cutoff point has no specific biological significance. But a range of disease features appear across this arbitrary divide. Hence, it is reasonable to choose 65 years of age as the cutoff point of EOAD.

Although more attention has been paid to pathophysiology and treatment of EOAD, epidemiological data for rate of EOAD is sparse. It is generally accepted that EOAD

accounts for 1% to 2% of AD cases (6). However, the percentage needs to be affirmed further. Hence, we performed a systematic review and meta-analysis of all studies that presented original data to calculate a rate of EOAD in AD. Then analysis of the population based rate was undertaken to make a geographic comparison.

Methods

Systematic search

Electronic searches of Cochrane Library, Embase, Medline and PubMed databases were used to identify published articles and studies. Medical Subject Headings (MeSH) terms and keywords included "EOAD", "Early Onset Alzheimer Disease", "Presenile Alzheimer Dementia", "Alzheimer Disease, Early Onset", "incidence", "prevalence" and "epidemiology" were used to look for related studies. Additional trials were searched from previous related reviews and reference lists of included papers. These included studies were published in the period from 1985 to 2013. When no information reported on the rate of EOAD in a population based study, we tried to contact the corresponding author to get data.

Study selection

The eligible studies for our meta-analysis from the initial search were all according to the following criteria: (I) Participants: the definition of EOAD is defined as AD patients with onset before 65 years of age. The diagnosis of AD can follow many criteria, such as the National Institute of Neurological Disorders and Stroke-Alzheimer Diseases and Related Disorders Association Working Group criteria (NINCDS-ADRDA) (7,8), the Diagnostic and Statistical Manual of Mental Disorders (DSM) (9), the Clinical Dementia Rating Scale (CDR) (10,11), or the International Classification of Diseases, 9th edition (ICD-9) (12), and Mini-Mental State Examination (MMSE) score (13). In addition, AD can be diagnosed by Clinical manifestations (14). Our diagnostic criteria of EOAD participants have two points: firstly, they were diagnosed as AD patients; secondly, they were younger than 65 years old. (II) Outcome: we included studies which presented original data with the count of EOAD and total AD cases. We excluded the studies that did not contain statistical information. The participants with front-temporal dementia, vascular dementia, or other rarer forms of dementia were also excluded. In addition, studies with non-random enrolment for EOAD participants were also excluded from our analysis.

Data extraction and quality assessment

Two reviewers independently read the appropriate articles and extracted data according to predefined criteria. The final valid statistics of each outcome were the count of EOAD and AD cases. Additionally, data for country of study origin and characteristics of participants (number, age, female, and diagnostic criteria) were also extracted. When conflicts appeared in inclusion, exclusion or data extraction, disagreement was resolved with the third author through review and discussion. The Agency for Healthcare Research and Quality (AHRQ) evaluation standard was a common tool for observational studies to assess the quality of prevalence studies in a meta-analysis (http://www.ncbi.nlm.nih.gov/books/NBK35156/). Our meta-analysis was assessed by AHRQ, which totally had 11 items to evaluate the quality of these included studies.

Statistical analysis

We use the Meta function of the Meta Analyst 3.13 software to combine proportions. Random effect model was performed in our meta-analysis. According to the heterogeneity, fixed or random effect model was then performed in our meta-analysis. The effect of heterogeneity was quantified using I^2 =100% × (Q – df)/Q (15). When a significant I^2-statistic (I^2>50%) appeared, heterogeneity was thought existed in studies, then meta-analysis was conducted in random effect model (15).

Results

Literature search and characteristics of included study

Finally, a total of 15 relevant articles seemed to fulfill the inclusion criteria after the application of search strategy, and the search strategy was presented in *Figure 1*. Among the 15 trials, two trials were from Zhang group and these two trials contained same amounts of EOAD and AD patients, hence we only included one in our meta-analysis. In addition, two studies performed by V. Chandra were conducted among the same cohort (a rural Hindi-speaking population in Ballabgarh in northern India) (16,17), we chose the one with higher quality in our meta-analysis (16). These included articles were published between 1985 and

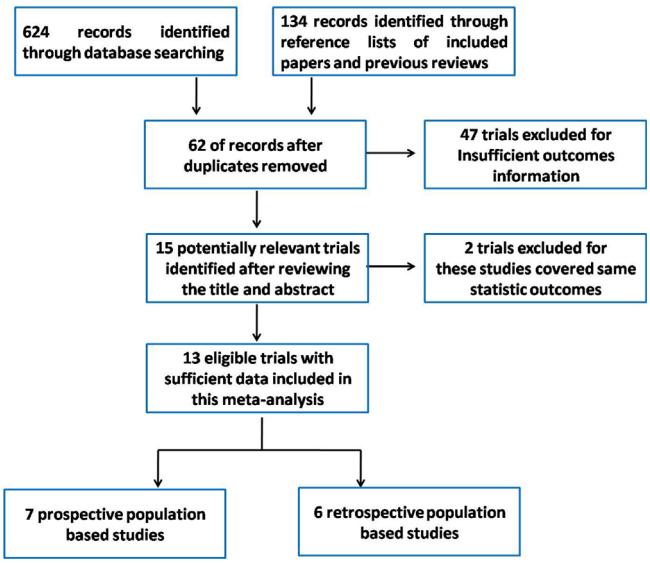

Figure 1 Flow diagram of study identification process.

2013. In addition, these included trials were all sporadic forms of EOAD. These included trials were conducted in Europe, America and Asia. Finally, our study included a total of 1,274 EOAD patients and 11,982 AD cases. Data details of the included studies are presented in *Table 1*.

Methodological quality and data available for analysis

In our meta-analysis, we used AHRQ evaluation standard to assess the quality of included trials. There are 11 items to assess the quality of these included studies, and *Table S1* showed these results by presenting the main statistical results on every measurement scale.

Meta-analysis

The rate of EOAD in AD, 5.5% [95% confidence interval (CI): 0.039-0.079, P<0.001], was generated after pooled analysis of all studies. We chose the outcome analyzed in random effect model, and the Forrest plot of the results in random effect model was demonstrated in *Figure 2*. The value of I^2 is 0.486 indicating low heterogeneity exists in this study. In addition, the funnel plot of the results was seen in *Figure S1*. There were eight countries included in our meta-analysis. Among these six were developed countries, two were developing countries. After analysis, the rate of EOAD in AD is 6.9% (95% CI: 0.044-0.107) in Russia, 5.7% (95% CI: 0.019-0.160) in USA, 1.2% (95% CI: 0.006-0.023) in Netherlands, 6.8% (95% CI: 0.042-0.110) in Sweden, 14.8% (95% CI: 0.057-0.335) in Spain and 9.7% (95% CI: 0.090-0.105) in UK. The pooled analysis of the rate in developed country was 5.9% [95% CI: (0.040-0.085), P<0.001]. This result of the meta-analysis shows low heterogeneity (I^2=0.487) about the rate of EOAD in developed countries. The rate of EOAD was 5.9% (95% CI: 0.020-0.159) in India and 4.0% (95% CI: 0.028-0.056) in China. The pooled analysis of the rate in developing countries was 4.4% [95% CI: 0.028-0.066, P<0.001]. In addition, the result of meta-analysis indicates low heterogeneity (I^2=0.101) about the rate of EOAD in developing countries. The individual rate of EOAD for each country was demonstrated in *Figure 3*. In addition, we found P value of the rate of EOAD between developing countries and developed countries was less than 0.05, indicating that significant difference of the rate of EOAD exits between developing countries and developed countries.

Discussion

Numerous studies have paid attention to examine the incidence of LOAD. However, there seems to be a paucity of epidemiologic data about the frequency of EOAD, not to mention the epidemiological research which explored the rate of EOAD cases among AD cases. EOAD is a devastating condition for the patients and their families. Hence, more attention should be paid to EOAD and it is necessary to figure out the answer of the matter about the rate of EOAD cases in AD cases.

This systematic review and meta-analysis is made up of 13 studies. According to our meta-analysis based on population enriched studies, generally reported rates of EOAD (1-2%) from previous studies are likely biased. Since our study was conducted by population based studies in a defined geographic area during a given period of time, the final population based rate, 6.1%, is likely to represent more accurate estimation about the rate of EOAD.

As shown in *Figure 3*, we notice that the rate of EOAD varies among different countries. These geographic differences may result from variability in the underlying genetic structure. In addition, the pooled analyses of the rate in developed and developing countries are significant different. Moreover, the rate in developed countries consistent with the finally pooled analysis of all countries, and the rate in developed countries are relative higher than in developing countries. These outcomes may result from that developed countries have more robust basic medical

Table 1 Characteristics of the included studies for the meta-analysis

Reference	Author	Year	Country	Methods	Diagnositic criteria	Gender (female %)	Female EOAD	EOAD Total	Total female AD	Total AD	Total N
(18)	AV Suhanov	2006	Russia	A prospective population based study	NINCDS-ADRDA	72.00	5	18	73	260	520
(19)	AE Molero	2007	USA	A prospective population based study	CDR-4	66.90	3	6	73	97	2,438
(20)	A Ott	1995	Netherlands	A prospective population based study	NINCDS-ADRDA	NA	2	4	263	339	7,528
(21)	A Ruitenberg	2001	Netherlands	A prospective population based study	NINCDSADRDA, DSM-III-R	60.32	2	5	270	395	40,441
(22)	BS Schoenberg	1987	USA	A prospective population based study	Based on insidious onset and slow progression of dementia	64.70	2	3	76	117	42,000
(23)	CJ Vas	2001	India	A prospective population based study	DSM-IV	51.51	NA	2	NA	62	24,488
(16)	V Chandra	1998	India	A prospective population based study	NINCDS-ADRDA and CDR	46.92	2	3	11	32	5,126
(14)	BS Schoenberg	1985	USA	A retrospective population based study	NA	56.38	1	2	52	80	8,925
(24)	F Coria	1993	Spain	A retrospective population based study	DSM-IIIR	51.89	3	4	21	27	503
(25)	G McGonigal	1993	United Kingdom	A retrospective population based study	NINCDS-ADRDA			569		5,874	6,581
(26)	N Andreasen	1999	Sweden	A retrospective population based study	NINCDS-ADRDA	59.94	NA	15	NA	220	619
(27)	PK Panegyres	2013	Native American Indians, Alaskans and Hawaiians	A retrospective population based study	MMSE and -ADAS-Cog at 9 of 10	55.38	327	614	2,075	3,747	3,747
(28)	Z Zhang	2005	China	A retrospective population based study	NINCDS-ADRDA	53.80	21	29	514	732	34,807

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; CDR-4, the Clinical Dementia Rating Scale; DSM, the Diagnostic and Statistical Manual of Mental Disorders; EOAD, early onset Alzheimer's Disease; MMSE, Mini-Mental State Examination; NA, not available; NINCDS-ADRDA, the National Institute of Neurological Disorders and Stroke-Alzheimer Diseases and Related Disorders Association Working Group criteria.

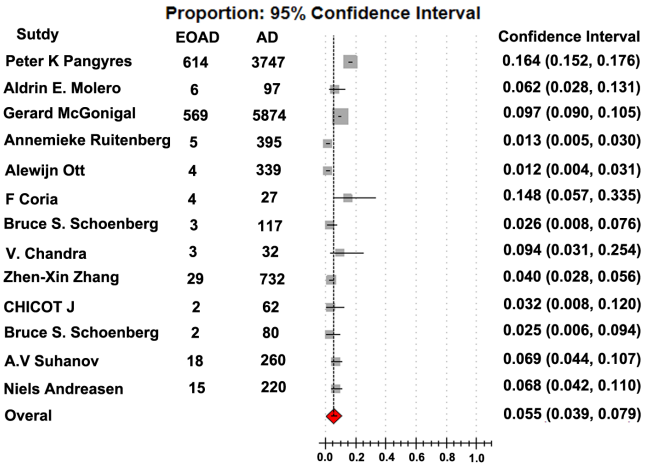

Figure 2 Forest plots show population based studies included in pooled analysis.

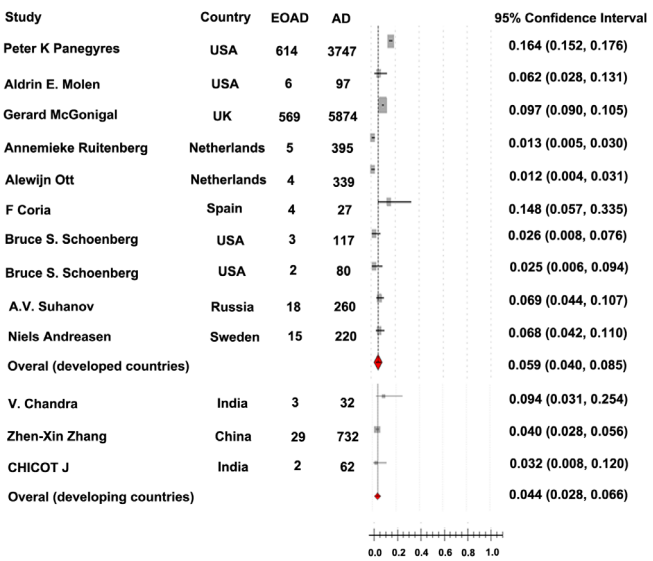

Figure 3 Forest plots show the pooled analysis of included studies across different countries.

care, hence, more EOAD population in developed countries would be discovered and diagnosed timely. Maybe the rate in developed counties is more close to the accurate prevalence of EOAD in world, and this is consistent with our outcomes.

Our meta-analysis still has several potential limitations. First, the account of the trials included in our meta-analysis was relatively small, and the included trials only covered eight countries. Therefore, it is a weak argument to reveal the accurate rate over the world. Second, *APOE*, age, and sex play a vital role in EOAD. Hence, more studies are needed to perform to explore the possible *APOE*-, age- and gender-dependent effect. Lastly, our included trials were all sporadic EOAD, we did not figure out the difference between sporadic and familial forms of EOAD.

In summary, our meta-analysis first offered some evidence of the potential rate of EOAD among AD cases. And the present rate (6.1%) is higher than the generally accepted rate (1-2%). The result of our meta-analysis draws more attention to EOAD. But our meta-analysis still has several limitations. Therefore, further trials with larger samples across more countries and careful design of experiment are required to confirm whether our findings are truly significant.

Acknowledgements

Funding: This work was supported by grants from the National Natural Science Foundation of China (81471309, 81371406, 81171209), the Shandong Provincial Outstanding Medical Academic Professional Program, Qingdao Key Health Discipline Development Fund, and Qingdao Outstanding Health Professional Development Fund.
Disclosure: The authors declare no conflict of interest.

References

1. Rossor MN, Fox NC, Mummery CJ, et al. The diagnosis of young-onset dementia. Lancet Neurol 2010;9:793-806.
2. Jiang T, Yu JT, Tan L. Novel disease-modifying therapies for Alzheimer's disease. J Alzheimers Dis 2012;31:475-92.
3. Smits LL, Pijnenburg YA, Koedam EL, et al. Early onset Alzheimer's disease is associated with a distinct neuropsychological profile. J Alzheimers Dis 2012;30:101-8.
4. Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med 2010;362:329-44.
5. Jiang T, Yu JT, Tian Y, et al. Epidemiology and etiology of Alzheimer's disease: from genetic to non-genetic factors. Curr Alzheimer Res 2013;10:852-67.
6. Sassi C, Guerreiro R, Gibbs R, et al. Exome sequencing identifies 2 novel presenilin 1 mutations (p.L166V and p.S230R) in British early-onset Alzheimer's disease. Neurobiol Aging 2014;35:2422.e13-6.
7. Lopez OL, Swihart AA, Becker JT, et al. Reliability of NINCDS-ADRDA clinical criteria for the diagnosis of Alzheimer's disease. Neurology 1990;40:1517-22.
8. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the

NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734-46.
9. Gomez R, Harvey J, Quick C, et al. DSM-IV AD/HD: confirmatory factor models, prevalence, and gender and age differences based on parent and teacher ratings of Australian primary school children. J Child Psychol Psychiatry 1999;40:265-74.
10. Miller JM, Pliskin NH. The clinical utility of the Mattis Dementia Rating Scale in assessing cognitive decline in Alzheimer's disease. Int J Neurosci 2006;116:613-27.
11. Juva K, Sulkava R, Erkinjuntti T, et al. Usefulness of the Clinical Dementia Rating scale in screening for dementia. Int Psychogeriatr 1995;7:17-24.
12. ICD-9-CM. International Classification of Diseases, 9th revision, Clinical Modification. 3d edition, volumes 1, 2 and 3. Official authorized addendum effective October 1, 1990--HCFA. J Am Med Rec Assoc 1990;61:suppl 1-35.
13. Squitti R, Barbati G, Rossi L, et al. Excess of nonceruloplasmin serum copper in AD correlates with MMSE, CSF [beta]-amyloid, and h-tau. Neurology 2006;67:76-82.
14. Schoenberg BS, Anderson DW, Haerer AF. Severe dementia. Prevalence and clinical features in a biracial US population. Arch Neurol 1985;42:740-3.
15. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
16. Chandra V, Ganguli M, Pandav R, et al. Prevalence of Alzheimer's disease and other dementias in rural India: the Indo-US study. Neurology 1998;51:1000-8.
17. Chandra V, Pandav R, Dodge HH, et al. Incidence of Alzheimer's disease in a rural community in India: the Indo-US study. Neurology 2001;57:985-9.
18. Suhanov AV, Pilipenko PI, Korczyn AD, et al. Risk factors for Alzheimer's disease in Russia: a case-control study. Eur J Neurol 2006;13:990-5.
19. Molero AE, Pino-Ramirez G, Maestre GE. High prevalence of dementia in a Caribbean population. Neuroepidemiology 2007;29:107-12.
20. Ott A, Breteler MM, van Harskamp F, et al. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. BMJ 1995;310:970-3.
21. Ruitenberg A, Ott A, van Swieten JC, et al. Incidence of dementia: does gender make a difference? Neurobiol Aging 2001;22:575-80.
22. Schoenberg BS, Kokmen E, Okazaki H. Alzheimer's disease and other dementing illnesses in a defined United States population: incidence rates and clinical features. Ann Neurol 1987;22:724-9.
23. Vas CJ, Pinto C, Panikker D, et al. Prevalence of dementia in an urban Indian population. Int Psychogeriatr 2001;13:439-50.
24. Coria F, Gomez de Caso JA, Minguez L, et al. Prevalence of age-associated memory impairment and dementia in a rural community. J Neurol Neurosurg Psychiatry 1993;56:973-6.
25. McGonigal G, Thomas B, McQuade C, et al. Epidemiology of Alzheimer's presenile dementia in Scotland, 1974-88. BMJ 1993;306:680-3.
26. Andreasen N, Blennow K, Sjodin C, et al. Prevalence and incidence of clinically diagnosed memory impairments in a geographically defined general population in Sweden. The Pitea Dementia Project. Neuroepidemiology 1999;18:144-55.
27. Panegyres PK, Chen HY. Differences between early and late onset Alzheimer's disease. Am J Neurodegener Dis 2013;2:300-6.
28. Zhang ZX, Zahner GE, Roman GC, et al. Dementia subtypes in China: prevalence in Beijing, Xian, Shanghai, and Chengdu. Arch Neurol 2005;62:447-53.

Cite this article as: Zhu XC, Tan L, Wang HF, Jiang T, Cao L, Wang C, Wang J, Tan CC, Meng XF, Yu JT. Rate of early onset Alzheimer's disease: a systematic review and meta-analysis. Ann Transl Med 2015;3(3):38. doi: 10.3978/j.issn.2305-5839.2015.01.19

Supplementary

Table S1 The Agency for Healthcare Research and Quality (AHRQ) evaluation standard of included studies

Items	References												
	(29)	(30)	(31)	(32)	(33)	(34)	(35)	(36)	(37)	(38)	(39)	(40)	(41)
Define the source of information (survey, record review)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Indicate time period used for identifying patients	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Indicate whether or not subjects were consecutive if not population-based	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	No	No	No	No	No	No	No	No	No	No	No	No	No
Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	Yes	Yes	Yes	Not clear	Not clear	Not clear	No	Not clear	Not clear	Not clear	No	Not clear	Yes
Explain any patient exclusions from analysis	Yes	Yes	No	Not clear	Yes	No	Yes	No	Yes	Yes	Not clear	Yes	Yes
Describe how confounding was assessed and/or controlled	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
If applicable, explain how missing data were handled in the analysis	No	Yes	Not clear	No	No	No	No	Not clear	Not clear	Yes	Not clear	No	Yes
Summarize patient response rates and completeness of data collection	No	Not clear	Not clear	No	No	No	No	No	No	Yes	No	No	Not clear
Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	No	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Not clear	Not clear	Yes

The AHRQ evaluation standard has 11 items to assess the quality of included studies, and each item has three grades: yes, no or not clear.

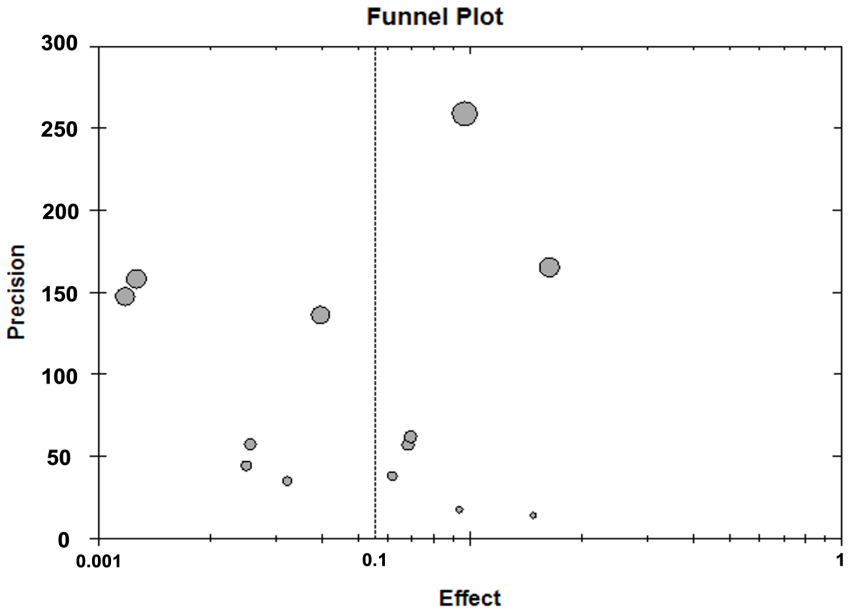

Figure S1 Funnel plots of population based studies included in pooled analysis.

References

29. Schoenberg BS, Anderson DW, Haerer AF. Severe dementia. Prevalence and clinical features in a biracial US population. Arch Neurol 1985;42:740-3.
30. Chandra V, Ganguli M, Pandav R, et al. Prevalence of Alzheimer's disease and other dementias in rural India: the Indo-US study. Neurology 1998;51:1000-8.
31. Suhanov AV, Pilipenko PI, Korczyn AD, et al. Risk factors for Alzheimer's disease in Russia: a case-control study. Eur J Neurol 2006;13:990-5.
32. Molero AE, Pino-Ramirez G, Maestre GE. High prevalence of dementia in a Caribbean population. Neuroepidemiology 2007;29:107-12.
33. Ott A, Breteler MM, van Harskamp F, et al. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. BMJ 1995;310:970-3.
34. Ruitenberg A, Ott A, van Swieten JC, et al. Incidence of dementia: does gender make a difference? Neurobiol Aging 2001;22:575-80.
35. Schoenberg BS, Kokmen E, Okazaki H. Alzheimer's disease and other dementing illnesses in a defined United States population: incidence rates and clinical features. Ann Neurol 1987;22:724-9.
36. Vas CJ, Pinto C, Panikker D, et al. Prevalence of dementia in an urban Indian population. Int Psychogeriatr 2001;13:439-50.
37. Coria F, Gomez de Caso JA, Minguez L, et al. Prevalence of age-associated memory impairment and dementia in a rural community. J Neurol Neurosurg Psychiatry 1993;56:973-6.
38. McGonigal G, Thomas B, McQuade C, et al. Epidemiology of Alzheimer's presenile dementia in Scotland, 1974-88. BMJ 1993;306:680-3.
39. Andreasen N, Blennow K, Sjodin C, et al. Prevalence and incidence of clinically diagnosed memory impairments in a geographically defined general population in Sweden. The Pitea Dementia Project. Neuroepidemiology 1999;18:144-55.
40. Panegyres PK, Chen HY. Differences between early and late onset Alzheimer's disease. Am J Neurodegener Dis 2013;2:300-6.
41. Zhang ZX, Zahner GE, Roman GC, et al. Dementia subtypes in China: prevalence in Beijing, Xian, Shanghai, and Chengdu. Arch Neurol 2005;62:447-53.