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

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

\textsuperscript{1}Department of Neurology, Qingdao Municipal Hospital, Nanjing Medical University, Qingdao 266071, China; \textsuperscript{2}Department of Neurology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, Qingdao 266071, China; \textsuperscript{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 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 $I^2 = 100\% \times (Q - df)/Q$ (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
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.

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.

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>
<thead>
<tr>
<th>Reference</th>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Methods</th>
<th>Diagnostic criteria</th>
<th>Gender (female %)</th>
<th>Female EOAD</th>
<th>EOAD Total</th>
<th>Female Total</th>
<th>AD Total</th>
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<td>(18)</td>
<td>AV Suhanov</td>
<td>2006</td>
<td>Russia</td>
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<td>CDR-4</td>
<td>66.90</td>
<td>3</td>
<td>6</td>
<td>73</td>
<td>97</td>
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<td>(20)</td>
<td>A Ott</td>
<td>1995</td>
<td>Netherlands</td>
<td>A prospective population based study</td>
<td>NINCDS-ADRDA</td>
<td>NA</td>
<td>2</td>
<td>4</td>
<td>263</td>
<td>339</td>
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<td>A Ruitenberg</td>
<td>2001</td>
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<td>5</td>
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<td>A prospective population based study</td>
<td>Based on insidious onset and slow progression of dementia</td>
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<td>2</td>
<td>3</td>
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<td>India</td>
<td>A prospective population based study</td>
<td>DSM-IV</td>
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<td>2</td>
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<td>(16)</td>
<td>V Chandra</td>
<td>1998</td>
<td>India</td>
<td>A prospective population based study</td>
<td>NINCDS-ADRDA and CDR</td>
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<td>3</td>
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<td>(14)</td>
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<td>(24)</td>
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<td>1993</td>
<td>Spain</td>
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<td>3</td>
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<td>NA</td>
<td>15</td>
<td>NA</td>
<td>220</td>
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<td>(27)</td>
<td>PK Panegyres</td>
<td>2013</td>
<td>Native American Indians, Alaskans and Hawaiians</td>
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<td>MMSE and -ADAS-Cog at 9 of 10</td>
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<td>(28)</td>
<td>Z Zhang</td>
<td>2005</td>
<td>China</td>
<td>A retrospective population based study</td>
<td>NINCDS-ADRDA</td>
<td>53.80</td>
<td>21</td>
<td>29</td>
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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.
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


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.


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.
References


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