ORIGINAL ARTICLE

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The Prevalence and Incidence of Dementia Due to Alzheimer's Disease: a Systematic Review and Meta-Analysis

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ABSTRACT: ***Background:*** Updated information on the epidemiology of dementia due to Alzheimer's disease (AD) is needed to ensure that adequate resources are available to meet current and future healthcare needs. We conducted a systematic review and meta-analysis of the incidence and prevalence of AD. ***Methods:*** The MEDLINE and EMBASE databases were searched from 1985 to 2012, as well as the reference lists of selected articles. Included articles had to provide an original population-based estimate for the incidence and/or prevalence of AD. Two individuals independently performed abstract and full-text reviews, data extraction and quality assessments. Random-effects models were employed to generate pooled estimates stratified by age, sex, diagnostic criteria, location (i.e., continent) and time (i.e., when the study was done). ***Results:*** Of 16,066 abstracts screened, 707 articles were selected for full-text review. A total of 119 studies met the inclusion criteria. In community settings, the overall point prevalence of dementia due to AD among individuals 60 + was 40.2 per 1000 persons ($CI_{95\%}$: 29.1-55.6), and pooled annual period prevalence was 30.4 per 1000 persons ($CI_{95\%}$: 15.6-59.1). In community settings, the overall pooled annual incidence proportion of dementia due to AD among individuals 60 + was 34.1 per 1000 persons ($CI_{95\%}$: 16.4-70.9), and the incidence rate was 15.8 per 1000 person-years ($CI_{95\%}$: 12.9-19.4). Estimates varied significantly with age, diagnostic criteria used and location (i.e., continent). ***Conclusions:*** The burden of AD dementia is substantial. Significant gaps in our understanding of its epidemiology were identified, even in a high-income country such as Canada. Future studies should assess the impact of using such newer clinical diagnostic criteria for AD dementia such as those of the National Institute on Aging–Alzheimer's Association and/or incorporate validated biomarkers to confirm the presence of Alzheimer pathology to produce more precise estimates of the global burden of AD.

RÉSUMÉ: Prévalence et incidence de la démence due à la maladie d'Alzheimer : revue systématique et méta-analyse. ***Contexte:*** Nous avons besoin d'informations sur l'épidémiologie de la démence due à la maladie d'Alzheimer (MA) afin de nous assurer que des ressources adéquates sont disponibles pour satisfaire les besoins actuels et futurs de la population en soins de santé. Nous avons effectué une revue systématique et une méta-analyse de l'incidence et de la prévalence de la MA. ***Méthodologie:*** Nous avons effectué une recherche dans les bases de données MEDLINE et EMBASE de 1985 à 2012 ainsi que dans la liste de références d'articles retenus. Les articles retenus devaient fournir des estimations de l'incidence et/ou de la prévalence populationnelle de la MA. Deux évaluateurs ont revu indépendamment les résumés et le texte intégral ainsi que l'extraction des données des publications et en ont évalué la qualité. Nous avons utilisé des modèles à effets aléatoires pour générer des estimations regroupées stratifiées par âge, sexe, critères diagnostiques, lieu (continent) et temps (moment où l'étude a été réalisée). ***Résultats:*** Parmi les 16 066 résumés examinés, 707 articles ont été retenus pour une revue du texte intégral. En tout, 119 études rencontraient les critères d'inclusion. Dans la communauté, la prévalence ponctuelle globale de la démence due à la MA chez les individus de 60 ans et plus était de 40,2 par 1 000 (IC à 95%: 29,1 à 55,6) et la prévalence annuelle pour les données regroupées était de 30,4 par 1 000 (IC à 95%: 15,6 à 59,1). Dans la communauté, la proportion d'incidence annuelle globale regroupée de la démence due à la MA chez les individus de 60 ans et plus était de 34,1 par 1 000 (IC à 95%: 16,4 à 70,9) et le taux d'incidence était de 15,8 par 1 000 personnes-années (IC à 95%: 12,9 à 19,4). Les estimations variaient significativement selon l'âge, les critères diagnostiques utilisés et le lieu (continent). ***Conclusions:*** Le fardeau de la démence dû à la MA est considérable. Nous avons identifié des lacunes importantes dans notre compréhension de son épidémiologie, même dans un pays à revenu élevé comme le Canada. Des études ultérieures devraient évaluer l'impact de l'utilisation de critères diagnostiques plus récents pour identifier la démence due à la

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MA tels ceux du National Institute on Aging-Alzheimer's Association et/ou incorporer des biomarqueurs validés pour confirmer la présence de la pathologie de la MA et fournir des estimations plus précises de son fardeau global.

Keywords: Alzheimer's, dementia, meta-analysis, systematic review

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder leading to cognitive impairment, neuropsychiatric symptoms, disability, dependency, caregiver burden, substantial healthcare expenditures and premature death.[1-3] Up to 70% of the dementias occurring in older adults are attributed in whole or in part to AD.[4] Though described more than a century ago,[5] treatment options remain limited. Available pharmacotherapies provide modest symptomatic benefits[6] of debatable cost-effectiveness.[7]

Updated information on the epidemiology of dementia due to AD is needed if we are to ensure that adequate resources are mobilized to deal with the needs of those with this condition and their families. Such studies can also inform prevention strategies and approaches to management. Systematic reviews on the epidemiology of dementia generally do not deal with specific causes such as AD, but rather provide estimates of overall dementia.[8,9] The last systematic review of the global incidence of dementia specifically due to AD was published in 2008.[10] While the age-specific incidence rate of AD dementia doubles approximately every 5.5 years in older populations[11] and several studies have produced estimates stratified by sex and geographic region,[10,12-14] an unexplored issue is the heterogeneity produced by differing diagnostic criteria and study setting. In a majority of the more recent reviews, either a systematic methodology was not utilized[10,12,15] or it was uncertain whether one was.[14,16,17]

In this report, we present an updated systematic review and meta-analysis of population-based studies of the incidence and prevalence of dementia due to AD. We also examine the extent and causes of heterogeneity in these estimates.

Methods

This is one in a series of systematic reviews on the prevalence and incidence of priority neurological conditions as part of the National Population Health Study of Neurological Conditions.[18]

Search Strategy

The systematic review and meta-analysis were conducted according to a predetermined protocol based on the PRISMA statement for systematic reviews and meta-analyses.[19] The search strategy (Appendix A) was developed by the study authors (who have expertise in dementia and/or disease epidemiology) in consultation with a research librarian with systematic review expertise. The primary search was conducted in the MEDLINE and EMBASE databases in February of 2011 and updated in July of 2012. References were exported and managed using EndNote X5.[20] International studies published before the year 2000 and Canadian studies published prior to 1985 were excluded because of the availability of prior meta-analyses summarizing earlier work. The earlier date for Canadian studies was to ensure that all relevant national work was included, as this was part of a nationally funded study examining the burden of neurological conditions in Canada. The review was restricted to articles published in English or French. The reference lists of included articles were manually searched for additional articles.

Study Selection

Two reviewers independently examined the titles and abstracts of all retrieved references in order to identify papers likely reporting original population-based data on the prevalence and/or incidence of AD dementia. Two reviewers also independently examined the full-text papers identified during the first phase. To be included in the systematic review, reviewed papers had to: (1) report original research; (2) be population-based; and (3) provide an incidence and/or prevalence estimate of dementia due to AD. Disagreements about the inclusion of articles were resolved by consensus or involvement of a third author if necessary.

Data Extraction and Study Quality

Two reviewers extracted data from included articles using a standard data collection form. Any disagreement was resolved by consensus. When multiple articles reported data on the same study population, the most accurate and comprehensive data as determined by the reviewers were used. In cases where the studies reported on different data collection years or subgroups (e.g., by sex and/or age), all data were included. The demographic data recorded included age, sex, setting (community-only, both community and institution, institution-only) and study location (i.e., Africa, Asia, Australia, Europe, North America, South America). The approach to ascertain cases was noted, as were sources of data and definitions/diagnostic criteria used. Incidence and prevalence estimates of AD dementia from each study were recorded, along with any stratification by age, sex or year of data collection. The quality of the included studies was evaluated using an assessment tool[21,22] (Appendix B), with each study given a quality score that ranged from 0 to 8 (higher scores indicating a higher-quality assessment).

Data Synthesis and Analysis

The significance of age, sex, diagnostic criteria, location (i.e., continent) and time (i.e., when the study was conducted) on incidence and prevalence estimates was assessed using meta-regression. Age was examined using the youngest-aged person in the study as a continuous factor of potential heterogeneity (note that few studies provided data on mean or median age). Sex, diagnostic criteria and geographic location were treated as categorical variables. Changes over time were examined using the study start, midpoint and end-years as potential sources of heterogeneity. All pooled estimates were restricted to studies reporting on older individuals (i.e., aged 60+, 65+, 70+) to mitigate the potential confounding effects of age. All period estimates were converted to annual estimates (e.g., period prevalence represents the annual period prevalence). Studies were also stratified by the location of participants (i.e., community-only, community and institution, institution-only) to minimize

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confounding by disease severity. Studies were included in the meta-analysis if they reported the estimate with 95% confidence intervals ($CI_{95\%}$), the number of AD cases along with overall sample size, or the information with which to calculate an estimate. Additionally, subgroup meta-analysis was only performed if more than one study was available for each subgroup (e.g., a region could have been omitted from this analysis if only one study was available in a region; however, if more than one study was included in the other regions, these data were then analyzed).

To compare study quality characteristics across groups (i.e., continent), ANOVA testing was utilized to determine differences. To assess for significant between-study heterogeneity, the Cochrane Q statistic was calculated and I^2 was employed to quantify the magnitude. All the pooled estimates and 95% confidence intervals were calculated using random-effects models. Publication bias was investigated visually using funnel plots and statistically using Begg's,[23] Egger's[24] and the trim-and-fill tests. The trim-and-fill method identifies funnel plot asymmetry by imputing the effect estimates of potentially missing studies and assessing the influence of these studies on the pooled estimate. For all tests, a value of p less than 0.05 was deemed to be significant. All statistical analyses were carried out in *R* version 2.14.[25] The *meta* package was used to produce the pooled estimates, forest plots and publication bias assessments.[26] The *metafor* package was used to conduct the meta-regression using restricted maximum-likelihood estimation.[27]

Results

Identification and Description of Studies

The search strategy yielded a total of 16,066 citations, including duplicates (8743 from MEDLINE, 7323 from EMBASE) (Figure 1). After screening titles and abstracts, 707 articles were selected for full-text review. Of them, 547 were excluded (230 international studies were published before 2000, 164 did not report incidence or prevalence of dementia, 114 were not population-based, 39 did not report original data). The updating of the search and hand searching the references led to an additional 4 and 12 articles, respectively. Among the 176 eligible papers meeting the inclusion criteria, 57 were excluded, as they did not report on the incidence or prevalence of AD dementia. A total of 119 papers reported on AD dementia.

The characteristics of the 119 included studies are shown in Tables 1-3. Seventy-five reported on prevalence, 43 on incidence and 1 on both. Forty-four studies provided data from Europe,

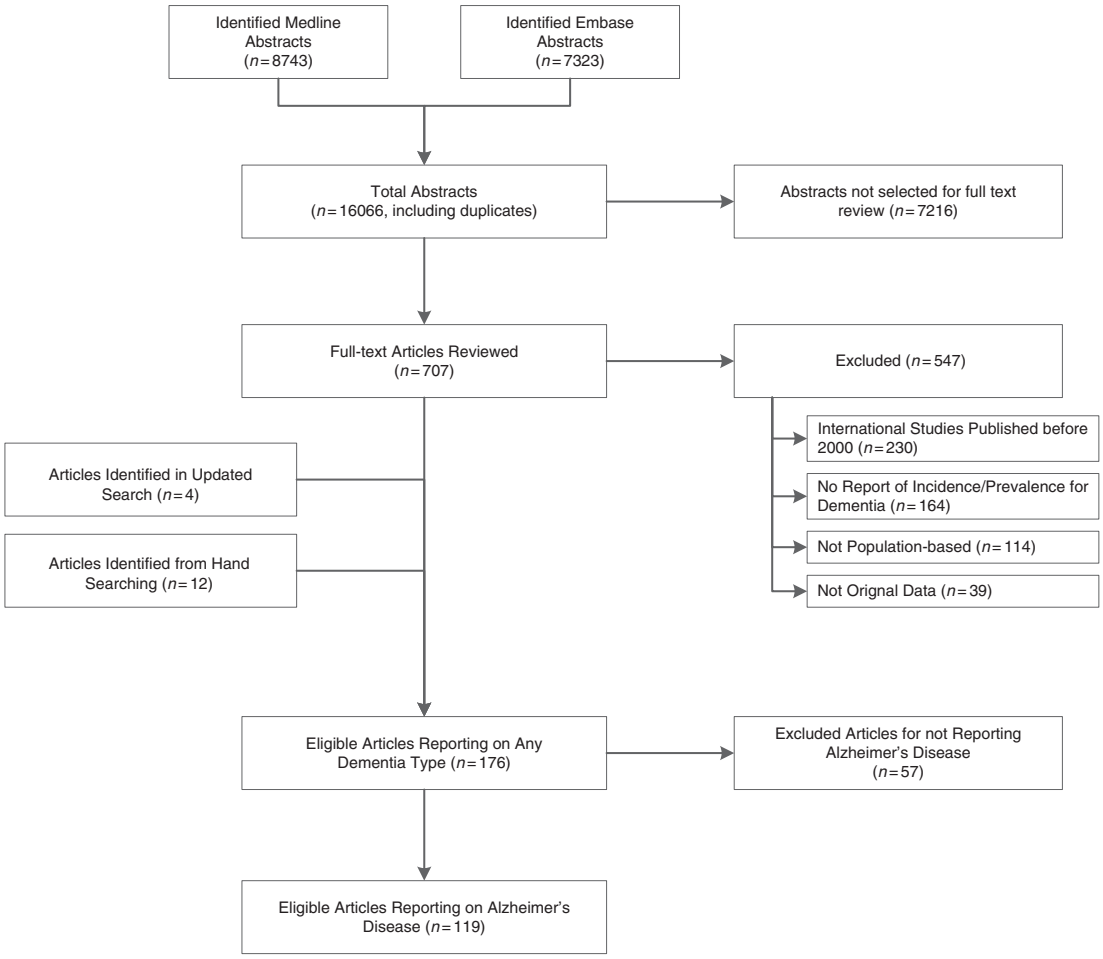

Figure 1: *Study flow diagram.*

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Table 1: Studies Reporting on the Prevalence of Alzheimer's Disease

Author, Date	Country and Region	Age Range Studied	Data Source	Diagnosis Established by	Diagnostic Criteria	Years of Data Collection	Groups Studied
Community Only							
Anttila (2004)	FINLAND *Kupio and Joensuu*	65-79	Cannot determine	Health professional	NINCDS-ADRDA	1998	Overall
Banerjee (2008)	INDIA *Kolkata*	50+	Door-to-Door survey	Health professional	NINCDS-ADRDA	2002-2003	Overall
Bermejo-Pareja (2009)	SPAIN *Las Margaritas, Lista, Arevalo*	65+	Telephone Survey Mailed survey	Health professional Administrative data codes Medical chart review	NINCDS-ADRDA	1994-1998	Overall
Borjesson-Hanson (2004)	SWEDEN *Goteborg*	95	Census	Health professional Medical chart review	NINCDS-ADRDA	1996-1998	Male Overall Female Overall Overall
Bottino (2008)	BRAZIL *Sao Paulo*	60+	Door-to-Door survey	Health professional Imaging test	DSM-IV	2002-2003	Overall
Bowirrat (2001)	ISRAEL *Wadi Ara*	60+	Door to Door Survey	Health professional	DSM-IV	1995	Overall
Bowirrat (2002)	ISRAEL *Wadi Ara*	60+	Door to Door Survey	Health professional	DSM-IV	1995	Male Overall Female Overall Overall
Bowirrat (2002)	ISRAEL *Wadi Ara*	60+	Door to Door Survey	Health professional	DSM-IV	1995	Male Overall Female Overall Overall
Canadian Study of Health and Aging Working Group (1994)	CANADA	65+	Administrative Database	Health professional	NINCDS-ADRDA	1991	Male 85+ Female 85+ 85 + Male 65-74 Male 75-84 Male 85+ Male Overall Female 65-74 Female 75-84 Female 85+ Female Overall 65-74 75-84 85+ Overall
Dahl (2007)	SWEDEN	70-81	Registry	Health professional Administrative data codes	DSM-IV	2001-2005	Overall
Das (2006)	INDIA *Kolkata*	50+	Door-to-Door survey	Health professional	NINCDS-ADRDA	2003-2004	Overall
Das (2008)	INDIA *Kolkata*	60+	Door-to-Door survey	Health professional	NINCDS-ADRDA	2003-2004	Overall
de Jesus Llibre (2009)	CUBA	65+	Door-to-Door survey Registry	Health professional Imaging test Other	NINCDS-ADRDA	2003	Overall

de Silva (2003)	SRI LANKA *Ragama*	65+	Public Health Midwife Records	Health professional	NINCDS-ADRDA	2000	Overall
Demirovic (2003)	USA	65+	Door-to-Door survey Census	Health professional Imaging test	NINCDS-ADRDA	1993-1996	Male Overall Female Overall
Fish (2008)	WALES *Caerphilly*	65-84	Electoral egister Hospital/Clinic review	Health professional Medical chart review Imaging test Other	NINCDS-ADRDA	2002-2004	Overall
Fujishima (2002)	JAPAN *Hisayama*	65+	Registry	Health professional	NINCDS-ADRDA	1985 and 1992	Overall Overall
Ganguli (2000)	USA	65+	Door-to-Door survey Registry	Health professional Medical chart review	NINCDS-ADRDA	1997-1999	Overall
Guerchet (2010)	CONGO	65+	Door-to-Door survey	Health professional Medical chart review	NINCDS-ADRDA	2008-2009	65-74 75-84 85+ Male 65-74 Male 75-84 Male 85+ Female 65-74 Female 75-84 Female 85+ Male Overall Female Overall
Gurvit (2008)	TURKEY *Instabul* Kad-koy	70+	Door-to-Door survey	Health professional	NINCDS-ADRDA	-	Overall Male Overall Female Overall 70-74 75-79 80+ Male 70-74 Male 75-79 Male 80+ Female 70-74 Female 75-79 Female 80+
Hall (2009)	USA	65+ (1992) 70+ (2001)	Door-to-Door survey	Health professional Medical chart review	NINCDS-ADRDA	1992 and 2001	70-74 75-79 80-85 85+ Overall
Herrera (2002)	BRAZIL *Sao Paulo* Catanduva	65+	Door-to-Door survey Census	Health professional Imaging test Other	NINDS-AIREN	_	Overall
Ikeda (2001)	JAPAN *Nakayama*	65+	Door-to-Door survey	Health professional Medical chart review Imaging test Other	NINCDS-ADRDA	1997-1998	Overall
Ikeda (2004)	JAPAN *Nakayama*	65+	Door-to-Door survey	Health professional Medical chart review Imaging test Other	DSM-III-R	1997-1998	65+

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Table 1. *(Continued)*

Author, Date	Country and Region	Age Range Studied	Data Source	Diagnosis Established by	Diagnostic Criteria	Years of Data Collection	Groups Studied
Jhoo (2008)	KOREA *Seongnam*	65+	Mailed survey Telephone survey	Health professional Imaging test Other	NINCDS-ADRDA	2005-2006	65-69 70-74 75-79 80+ Male Overall Female Overall Overall
Kivipelto (2001)	FINLAND *Kupio and Joensuu*	65-79	Census	Health professional Self-report	NINCDS-ADRDA	1998	Overall
Kivipelto (2002)	FINLAND *Kupio and Joensuu*	65-79	Census	Health professional	NINCDS-ADRDA	1998	Overall
Lee (2002)	KOREA	65+	Door-to-Door survey	Health professional Medical chart review Imaging test	NINCDS-ADRDA	1999-2000	65-69 70-74 75-79 80-84 85+ Overall
Li (2007)	USA *Chicago*	65+	Health Maintenance Organization	Health professional Imaging test	NINCDS-ADRDA	1994-1996	Overall
Lopez (2003)	USA *Pittsburgh, Sacramento, Winston-Salem, Hagerstown*	65+	Administrative databases Other	Health professional	NINCDS-ADRDA	1998-1999	Overall
Maneno (2006)	USA	60+	Administrative databases	Administrative data codes	ICD-9	2000-2002	Overall
Mathuranath (2010)	INDIA *Kerala*	55+	Door-to-Door survey	Health professional	NINCDS-ADRDA DSM-IV	2001	55-59 60-64 65-69 70-74 75-79 80-84 85+ 65+ Overall Male 55-59 Male 60-64 Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male 85+ Male 65+ Male Overall Female 55-59 Female 60-64 Female 65-69 Female 70-74 Female 75-79 Female 80-84 Female 85+ Female 65+ Female Overall

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Meguro (2002)	JAPAN *Tajiri*	65+	Other	Health professional Imaging	NINCDS-ADRDA	1998	Overall
Molero (2007)	VENEZUELA *Maracaibo*	55+	Door-to-Door survey	Health professional Imaging	NINCDS-ADRDA	1998-2001	Male 55-64 Male 65-74 Male 75-84 Male 85+ Male Overall Female 55-64 Female 65-74 Female 75-84 Female 85+ Female Overall 55-64 65-74 75-84 85+ Overall
Nunes (2010)	PORTUGAL	55-79	Other	Health professional Medical chart review Imaging test Other	DSM-IV-TR	2003	Overall
Perkins (2002)	USA	65+	Door-to-Door survey	Health professional	NINCDS-ADRDA	1997-1998	Overall
Plassman (2007)	USA	71+	Door-to-Door survey	Health professional Medical chart review Other	DSM-III-R; DSM-IV	2002	71-79 80-89 90+ Overall Male Overall Female Overall
Polvikoski (2001)	FINLAND *Vantaa*	85+	Cannot determine	Health professional Medical chart review	NINCDS-ADRDA	1991	85-89 90+ Overall
Rovio (2005)	FINLAND	65-79	Cannot determine	Health Professional	DSM-IV	1998	Overall
Scazufca (2008)	BRAZIL *Sao Paulo*	65+	Door-to-Door survey	Health professional	DSM-IV	2003-2005	Overall
Sekita (2010)	JAPAN *Hisayama*	65+	Registry	Health professional Medical chart review	DSM-III; DSM-III-R; Hachinski	1985 1992 1998 2005	Overall Overall Overall Overall
Shaji (2005)	INDIA *Cochin*	65+	Door-to-Door survey	Health professional	ICD-10 DSM-IV	-	Overall
Spada (2009)	ITALY *Sicily* San Teodoro	60-85	Door-to-Door survey Other	Health professional Other	NINCDS-ADRDA	2005	Overall
Suh (2003)	KOREA *Yonchon County*	65+	Door-to-Door survey	Health professional Medical chart review	NINCDS-ADRDA	1996-1997	Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male 85-89 Male 90-94 Male Overall Female 65-69 Female 70-74

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Table 1. *(Continued)*

Author, Date	Country and Region	Age Range Studied	Data Source	Diagnosis Established by	Diagnostic Criteria	Years of Data Collection	Groups Studied
							Female 75-79 Female 80-84 Female 85-89 Female 90-94 Female Overall 65-69 70-74 75-79 80-84 85-89 90-94 Overall
Vanhanen (2006)	FINLAND *Kuopio*	69-78	Cannot determine	Health Professional Imaging	NINCDS-ADRDA	1990-1991	Overall
Vas (2001)	INDIA *Bombay*	40+	Door-to-Door survey Mailed survey Other	Health professional Imaging test	NINCDS-ADRDA	1991	Overall
Wada-Isoe (2009)	JAPAN *Amino-Cho*	65+	Door-to-Door survey	Health professional Imaging	NINCDS-ADRDA	2008	65-69 70-74 75-79 80-84 85-89 90+ Overall Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male 85-89 Male 90+ Male Overall Female 65-69 Female 70-74 Female 75-79 Female 80-84 Female 85-89 Female 90+ Female Overall
Wakutani (2007)	JAPAN *Daisen-Cho*	65+	Hospital/ clinic chart review Administrative databases	Health professional	DSM-III; Hachinski	1980 1990 2000	Overall Overall Overall
Wangtongkum (2008)	THAILAND *Chian Mai province*	45+	Door-to-Door survey	Health professional Imaging test Other	DSM-IV	2004-2005	Overall
Xu (2009)	SWEDEN	65+	Registry Telephone survey	Health professional	NINCDS-ADRDA	1998-2001	Overall
Yamada (2001)	JAPAN *Amino-Cho*	65+	Door-to-Door survey	Health professional Imaging test Other	NINCDS-ADRDA	1998	Male Overall Female Overall Overall

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Zhao (2010)	CHINA *Shanghai*	55+	Door-to-Door survey Census	Health professional Medical chart review	NINCDS-ADRDA	1997-1998	Male 55-59 Male 60-64 Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male 85-89 Male 90+ Male Overall Female 55-59 Female 60-64 Female 65-69 Female 70-74 Female 75-79 Female 80-84 Female 85-89 Female 90+ Female Overall Overall Male 60+ Male 65+ Male 70+ Male 75+ Male 80+ Male 85+ Female 60+ Female 65+ Female 70+ Female 75+ Female 80+ Female 85+
Zhou (2006)	CHINA	50+	Other	Health professional	NINCDS-ADRDA	1999	Male 50-54 Male 55-59 Male 60-64 Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male Overall Female 50-54 Female 55-59 Female 60-64 Female 65-69 Female 70-74 Female 75-79 Female 80-84 Female Overall 50-54 55-59 60-64 65-69 70-74 75-79 80-84 Overall

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Table 1. *(Continued)*

Author, Date	Country and Region	Age Range Studied	Data Source	Diagnosis Established by	Diagnostic Criteria	Years of Data Collection	Groups Studied
Community & Institution							
Arslantas (2009)	TURKEY *Eskisehir*	55+	Door-to-Door survey	Health professional Imaging test	NINCDS-ADRDA	2002-2004	Overall
Benedetti (2002)	ITALY	75+	Door-to-door survey	Health professional	NINCDS-ADRDA	1996	Female 75-79 Female 80-84 Female 85-89 Female 90-97 Female Overall Male 75-79 Male 80-84 Male 85-89 Male 90-97 Male Overall 75-79 80-84 85-89 90-97 Overall
Borroni (2011)	ITALY	45-65	Registry	Health professional Imaging Other	None	2009	Overall Male Overall Female Overall
Camicioli (2000)	USA	65+	Registry Chart Review	Medical Chart review	NINCDS-ADRDA	1994	Overall
Canadian Study of Health and Aging Working Group (1994)	CANADA	65+	Administrative Databases	Health professional	NINCDS-ADRDA	1991	Male 85+ Female 85+ 85 + Male 65-74 Male 75-84 Male 85+ Male Overall Female 65-74 Female 75-84 Female 85+ Female Overall 65-74 75-84 85+ Overall 65-74 75-84
Chen (2007)	TAIWAN	65+	Other: Nursing Home Records	Health professional	NINCDS-ADRDA	2004	Male Overall Female Overall Overall
Ebly (1994)	CANADA	85+	Other	Health professional	NINCDS-ADRDA	1990-1992	Male 85-89 Male 90-94 Male 95+ Male Overall Female 85-89 Female 90-94

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							Female 95+ Female Overall 85-89 90-94 95+ Overall
Gascon-Bayarri (2007)	SPAIN *Catalonia* El Prat del Llobregat	70+	Door-to-Door survey Mailed survey Telephone survey	Health professional Imaging test	NINCDS-ADRDA	2002-2003	Male 70-74 Male 75-79 Male 80-84 Male 85-89 Male 90+ Male Overall Female 70-74 Female 75-79 Female 80-84 Female 85-89 Female 90+ Overall Female 70-74 75-79 80-84 85-89 90+ Overall
Gavrila (2009)	SPAIN	65-96	Door-to-Door survey Registry	Health professional Imaging	NINCDS-ADRDA	2003-2005	Male Overall Female Overall 65-69 70-74 75-79 80-84 85+ Overall
Gislason (2003)	SWEDEN *Gothenburg*	85	Registry	Health professional Imaging test	NINCDS-ADRDA	1986-1987	Overall
Harvey (2003)	ENGLAND	30-64	Registry Administrative Databases	Health professional Medical chart review Imaging test	NINCDS-ADRDA	–	40-44 45-49 50-54 55-59 60-64 Overall 45-64
Ikejima (2009)	JAPAN	20-64	Mailed survey	Medical chart review	DSM-III-R	2006	20-24 25-30 30-34 35-39 40-44 45-49 50-54 55-59 60-64 Overall 45-64
Landi (2005)	ITALY	80+	Registry	Health professional	MDS-HC	2003-2004	Male Overall Female Overall Overall

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Table 1. *(Continued)*

Author, Date	Country and Region	Age Range Studied	Data Source	Diagnosis Established by	Diagnostic Criteria	Years of Data Collection	Groups Studied
Lovheim (2008)	SWEDEN	85+	Other	Health professional Medical chart review Other	DSM-IV	2005-2006	Overall
Manton (2005)	USA	65+	Registry	Cannot determine	SPMSQ or MMSE	1982-1999	Overall 65-79 80+ Male Overall Male 65-79 Male 80+ Female Overall Female 65-79 Female 80+
Phung (2010)	DENMARK	40+	Registry	Administrative data codes	ICD-8/10	1970-2004	Overall
Rahkonen (2003)	FINLAND *Kuopio*	75+	Cannot determine	Health professional Medical chart review Other	DSM-IV	1998	Overall Male Overall Female Overall 75-79 80-84 85-89 90+
Rockwood (2000)	CANADA	65+	Other	Health professional	NINCDS-ADRDA	1991-1992, 1996	65-74 75-84 85+ Overall Male Overall Female Overall
Sahadevan (2008)	SINGAPORE	50+	Door-to-Door survey	Health professional Other	NINCDS-ADRDA	2001-2003	Overall Male Overall Female Overall 50-59 60-69 70-79 80+
Stevens (2002)	UK *London* Islington	65+	Door-to-Door survey	Health professional Medical chart review Other	NINCDS-ADRDA DSM-IV	-	Overall
Zhang (2005)	CHINA	55+	Door-to-Door survey Census	Health professional	NINCDS-ADRDA	1997	Male 55-64 Male 65-74 Male 75-84 Male 85+ Male Overall Female 55-64 Female 65-74 Female 75-84 Female 85+ Female Overall 55-64 65-74 75-84 85+ Overall

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Institution Only								
Andreasen (1999)	SWEDEN	42-92	Hospital/Clinic review	Health professional Imaging test Other	NINCDS-ADRDA	1990-1995	Overall	
Canadian Study of Health and Aging Working Group (1994)	CANADA	65+	Administrative Databases	Health professional	NINCDS-ADRDA	1991-1992	Male 85+ Female 85+ 85 + Male 65-74 Male 75-84 Male 85+ Male Overall Female 65-74 Female 75-84 Female 85+ Female Overall 65-74 75-84 85+ Overall	
Magaziner (2000)	USA *Baltimore* Maryland	65+	Other: Nursing Home Records	Health professional Medical chart review	DSM-III-R	1992-1995	Overall	
Rosenblatt (2004)	USA *Central Maryland*	58+	Other: Nursing Home Records	Health Professional Medical chart review	NINCDS-ADRDA	-	Overall	

36 from Asia, 32 from North America, 5 from South America, 2 from Africa and 2 from Australia (2 studies reported data from more than one continent). Nine studies reported on those aged 60+, 68 on those 65+ and 19 on those 70+.

Prevalence of AD

Forty-five articles[28-72] reported on the point prevalence of AD dementia, with 20 eligible for inclusion in the meta-analysis of those aged 60+.[28,29,31,33,35,36,38,39,42,45,46,48,57,60-63,65,67,70] In community-only settings, the point prevalence among those 60+ years of age was 40.19 ($CI_{95\%}$: 29.06-55.59) per 1000 (Figure 2). Point prevalence estimates in the community ranged from a low of 15.51 per 1000 in one study from India[60] to a high of 204.13 per 1000 in a study from Israel.[70] The pooled point prevalence in those 60+ in combined community and institution studies was 26.57 ($CI_{95\%}$: 11.83-59.69) per 1000. In community and institution studies, point prevalence estimates ranged from a low of 12.34 per 1000 in a study from the United States[35] to a high of 51.00 per 1000 in a study from Canada.[28] The pooled point prevalence of AD among those 60+ in institution-only settings was 226.97 ($CI_{95\%}$: 88.23-583.87).

Thirty studies reported on the period prevalence of AD,[73-103] with 10 eligible for inclusion in the meta-analysis of those 60+.[77,82,83,87,89-91,99,100,102] In community settings, the pooled annual period prevalence among those aged 60+ was 30.4 ($CI_{95\%}$: 15.6-59.1) per 1000 (Figure 3). In combined community and institution settings, the pooled annual period prevalence was 44.0 ($CI_{95\%}$: 19.9-97.1) per 1000. A single study from an institution in the United States reported an annual period prevalence of 101.0 ($CI_{95\%}$: 89.4-114.1) per 1000.[93] Annual period prevalence estimates for any setting ranged from 1.1 per 1000 in a community study from India[77] to 123.0 in a community study from the United States.[91]

Incidence of AD

Fourteen studies reported on the incidence proportion of AD,[104-117] with six included in the meta-analysis of 60+ studies.[107,108,111,113,114,116] In community settings, the pooled annual incidence proportion among those aged 60+ was 34.1 ($CI_{95\%}$: 16.4-70.9) per 1000 (Figure 4). A single U.S. study reported on the annual incidence proportion in combined community and institution settings with an estimate of 27.2 ($CI_{95\%}$: 22.2-33.3) per 1000.[105] There were no studies from an institution-only setting. Annual incidence proportion estimates for any setting ranged from 11.5 per 1000 in a community study from Nigeria[108] to 97.8 per 1000 in a community study from the United States.[111]

Thirty studies reported on the incidence rate of AD,[72,118-146] with 11 eligible for inclusion in the meta-analysis of those 60+.[118,122,126-129,136,140,143-145] In community-only settings, the pooled incidence rate of AD among those 60+ was 15.8 ($CI_{95\%}$: 12.9-19.4) per 1000 person-years (Figure 5). A single Italian study reported on the incidence rate in combined community and institution settings with an estimate of 7.0 ($CI_{95\%}$: 5.5-8.9) per 1000 person-years.[120] There were no studies from an institution-only setting. The lowest estimate for any setting was 7.0 ($CI_{95\%}$: 4.8-10.3) per 1000 person-years in a community study from the Netherlands[145] and the aforementioned study from Italy, and the highest 30.0 ($CI_{95\%}$: 25.4-35.5) per 1000 person-years in a community study from the United States.[143]

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Table 2: Studies Reporting on the Incidence Rate of Alzheimer's Disease

Author, Date	Country and Region	Age Range Studied	Data Source	Diagnosis Established by	Diagnostic Criteria	Years of Data Collection	Groups Studied
Community Only							
Bermejo-Pareja (2008)	SPAIN *Las Margaritas, Lista, Arevalo*	65+	Door-to-Door survey Mailed survey	Health professional Administrative data codes Medical chart review	NINCDS-ADRDA	1997-1998	Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male 85-90 Male 90+ Male Overall Female 65-69 Female 70-74 Female 75-79 Female 80-84 Female 85-90 Female 90+ Female Overall 65-69 70-74 75-79 80-84 85-90 90+ Overall
Chandra (2001)	INDIA	55+	Door-to-Door survey Registry	Health professional	NINCDS-ADRDA	-	Male 55-64 Male 65-74 Male 75-84 Male 85+ Male 65+ Male Overall Female 55-64 Female 65-74 Female 75-84 Female 85+ Female 55+ 65+ 55-64 65-74 75-84 85+ Overall
Fitzpatrick (2004)	USA	65+	Door-to-Door survey	Health professional Imaging	NINCDS-ADRDA	1992-1994	Overall < 75 75-79 80-84 85+
Fuhrer (2003)	FRANCE *Gironde and Dordogne*	65+	Door-to-Door survey Registry	Health professional Imaging test	NINCDS-ADRDA	1988-1997	Overall
Kukull (2002)	USA *Washington* Seattle	65+	Door-to-Door survey Other	Health professional Imaging test Other	NINCDS-ADRDA	1994	65-69 70-74 75-79 80-84 85-89 90+ Overall

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Larrieu (2002)	FRANCE	65+	Registry	Health professional	NINCDS-ADRDA	1993-1998	Overall
Larrieu (2004)	FRANCE	65+	Registry	Health professional	NINCDS-ADRDA	1993-1998	Overall
Lee (2002)	KOREA *Seoul* Kwanak District	65+	Door-to-Door survey	Health professional Medical chart review Imaging test	NINCDS-ADRDA	1999-2000	65-69 70-74 75-79 80-84 85+ Overall Male Overall Female Overall
Li (2007)	CHINA	60+	Door-to-Door survey	Health professional	NINCDS-ADRDA	1997 1999	Overall Overall
Matsui (2009)	JAPAN	65+	Registry	Health professional	NINCDS-ADRDA	1985-2002	Overall
Meguro (2007)	JAPAN *Tajiri*	65+	Door-to-Door survey	Health professional	NINCDS-ADRDA	2003	Overall
Mercy (2008)	UK	45+	Other	Health professional Imaging test	NINCDS-ADRDA	2000-2006	Overall
Nitrini (2004)	BRAZIL *Sao Paulo* Catanduva	65+	Door-to-Door survey	Health professional Imaging test Other	NINCDS-ADRDA	1997-2000	Female 70-74 Female 75-79 Female 80-84 Female 85-89 Female 90+ Male 70-74 Male 75-79 Male 80-84 Male 85-89 70-74 75-79 80-84 85-89 90+ Overall
Perez (2010)	FRANCE	65+	Other: Electoral Rolls	Health professional Self-report diagnosed by a health professional	NINCDS-ADRDA	-	65-69 70-74 75-79 80-84 85+ Overall
Polvikoski (2006)	FINLAND *Vantaa*	85+	Cannot determine	Health professional Medical chart review	DSM-III-R	2001	Overall
Ravaglia (2007)	ITALY *Conselice* *Ravenna* *Emilia Romagna region*	65+	Door-to-Door survey	Health professional Medical chart review Imaging test	NINCDS-ADRDA	2003-2004	Overall
Ravaglia (2005)	ITALY *Conselice* *Ravenna* *Emilia Romagna region*	65+	Door-to-Door survey	Health professional Medical chart review Imaging test	NINCDS-ADRDA	1999-2004	Male 65-74 Male 75-84 Male 85-94 Male Overall Female 65-74 Female 75-84 Female 85-94 Female Overall

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Table 2. *(Continued)*

Author, Date	Country and Region	Age Range Studied	Data Source	Diagnosis Established by	Diagnostic Criteria	Years of Data Collection	Groups Studied
							65-74 75-84 85-94 Overall
Ravalglia (2008)	ITALY *Conselice* *Ravenna* *Emilia Romagna region*	65+	Door-to-Door survey Registry	Health professional Medical chart review Imaging test	NINCDS-ADRDA	1999-2004	Overall
Tang (2001)	USA	65+	Administrative databases	Health professional Imaging test	NINCDS-ADRDA	1992-1999	65-74 75-84 85+ Overall
Tyas (2006)	CANADA *Manitoba*	65+	Registry Administrative databases	Health professional Other	NINCDS-ADRDA	1991-1997	Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male 85-89 Male 90+ Male Overall Female 65-69 Female 70-74 Female 75-79 Female 80-84 Female 85-89 Female 90+ 65-69 70-74 75-79 80-84 85-89 90+ Overall
Waite (2001)	AUSTRALIA *Sydney*	75+	Door-to-Door survey Census	Health professional	NINCDS-ADRDA	1991-1994	Female 75-79 Female 80-84 Female 85-89 Female 90+ Female Overall Male 75-79 Male 80-84 Male 85-89 Male 90+ Male Overall 75-79 80-84 85-89 90+ Overall

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Community & Institution

Di Carlo (2002)	ITALY *Genoa, Segrate (Milan), Selvazzano-Rubano (Padua), Impruneta (Florence), Fermo (Ascoli Piceno), Naples, Casamassima (Bari), and Catania*	65-84	Door-to-Door survey Registry	Health professional Medical chart review	NINCDS-ADRDA	1995	Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male Overall Female 65-69 Female 70-74 Female 75-79 Female 80-84 Female Overall 65-69 70-74 75-79 80-84 Overall
Edland (2002)	UNITED STATES *Minnesota* Rochester	50+	Hospital/Clinic chart review Administrative Databases	Medical chart review	DSM-IV	1985-1989	Female 50-54 Female 55-59 Female 60-64 Female 65-69 Female 70-74 Female 75-79 Female 80-84 Female 85-89 Female 90-94 Female 95-99 Female Overall Male 50-54 Male 55-59 Male 60-64 Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male 85-89 Male 90-94 Male 95-99 Male Overall 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89 90-94 95-99 Overall
Garre-Olmo (2010)	SPAIN *Catolonia*	30-64	Registry	Health professional Medical chart review Imaging test	DSM-IV-TR	2007-2009	30-64 65+ Overall
Knopman (2004)	USA	40-70	Administrative Databases	Medical chart review	DSM-IV	1990-1994	40-49 50-59 60-69

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Table 2. *(Continued)*

Author, Date	Country and Region	Age Range Studied	Data Source	Diagnosis Established by	Diagnostic Criteria	Years of Data Collection	Groups Studied
McDowell (2007)	CANADA	65+	Other: Canadian Study of Health and Aging	Health professional	NINCDS-ADRDA	1991-2001	Overall
Ruitenberg (2001)	NETHERLANDS *Rotterdam* Ommoord	55+	Door-to-Door survey	Health professional Medical chart review Imaging test	NINCDS-ADRDA	1990-1999	Female 55-59 Female 60-64 Female 65-69 Female 70-74 Female 75-79 Female 80-84 Female 85-89 Female 90-94 Female 95+ Female Overall Male 55-59 Male 60-64 Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male 85-89 Male 90-94 Male 95+ Male Overall 55-59 60-64 65-69 70-74 75-79 80-84 85-89 90-94 95+ Overall

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Table 3: Studies Reporting on the Incidence Proportion of Alzheimer's Disease

Author, Date	Country and Region	Age Range Studied	Data Source	Diagnosis Established by	Diagnostic Criteria	Years of Data Collection	Groups Studied
Community Only							
Cornelius (2004)	SWEDEN *Stockholm* Kungsholmen district	75+	Other: Prescription Records	Health professional	Hachinski Scale	1991-1993 1994-1996	Overall Overall
Forti (2010)	ITALY	65+	Registry	Health professional Imaging test	NINCDS-ADRDA	2003-2004	< 75 75+
Ganguli (2000)	USA *Pennsylvania*	65+	Door-to-Door survey Registry	Health professional Medical chart review	NINCDS-ADRDA	1997-1999	65-69 70-74 75-79 80-84 85-89 90+ Overall Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male 85-89 Male 90+ Male Overall Female 65-69 Female 70-74 Female 75-79 Female 80-84 Female 85-89 Female 90+ Female Overall
Hendrie (2001)	NIGERIA *Ibadan* Idkan area	65+	Door-to-Door survey	Health professional Imaging test	NINCDS-ADRDA	1997-1998	65-74 75-84 85+ Overall
Kawas (2000)	USA	55+	Cannot determine	Health professional Medical chart review Imaging Other	NINCDS-ADRDA	1985-1998	Male 55-59 Male 60-64 Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male 85+ Male Overall Female 55-59 Female 60-64 Female 65-69 Female 70-74 Female 75-79 Female 80-84 Female 85+ Female Overall 55-59 60-64 65-69

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Table 3. *(Continued)*

Author, Date	Country and Region	Age Range Studied	Data Source	Diagnosis Established by	Diagnostic Criteria	Years of Data Collection	Groups Studied
							70-74 75-79 80-84 85+ Overall
Knopman (2003)	USA	50-100	Door-to-Door Survey Registry	Health professional Imaging test	DSM-IV	1985-1989	Overall
Kuller (2005)	USA	<70-80+	Administrative Databases	Health professional Medical chart review Imaging test	NINCDS-ADRDA	1998-1999	Overall
Lopez (2005)	USA	65+	Administrative Databases	Health professional Medical chart review Imaging test	NINCDS-ADRDA	1994-1999	Overall
Lopez-Pousa (2004)	SPAIN	75+	Door-to-Door survey	Health professional	DSM-II-R	1990-1991	Male 75-79 Male 80-84 Male 85-89 Male 90+ Male Overall Female 75-79 Female 80-84 Female 85-89 Female 90+ Female Overall 75-79 80-84 85-89 90+ Overall
Miech (2002)	USA	65+	Door-to-Door survey	Health professional Imaging test	NINCDS-ADRDA	1998-1999	Overall Male Female
Morris (2002)	USA	65+	Census	Health professional Imaging test	NINCDS-ADRDA	1993-2000	Overall
Piguet (2003)	AUSTRALIA *Sydney*	75+	Registry	Health professional	NINCDS-ADRDA	1997-2000	Overall
Seshadri (2002)	USA	68-97	Other	Health professional Medical chart review Imaging test	NINCDS-ADRDA	1986-1990	Overall Male Overall Female Overall
Vermeer (2003)	NETHERLANDS *Rotterdam*	60-90	Other: Previous survey participants	Health professional Imaging test	NINCDS-ADRDA	1999-2000	Overall
Zandi (2002)	USA	65+	Door-to-Door survey	Health professional Imaging test	DSM-III-R	1998-2000	Male Overall Female Overall
Community & Institution							
Evans (2003)	USA	65+	Census	Health professional	NINCDS-ADRDA	-	Overall

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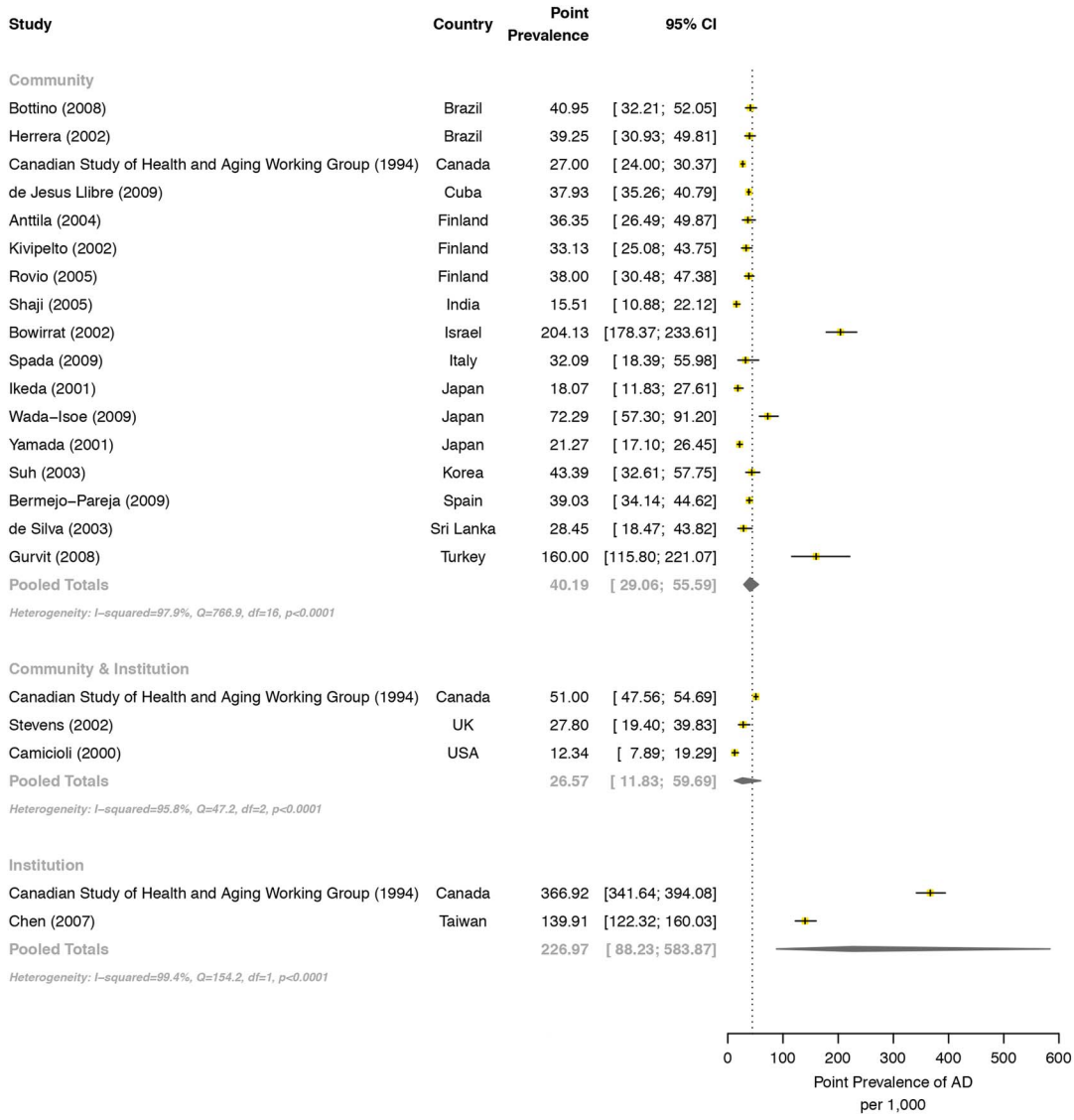

Figure 2: *Pooled point prevalence of Alzheimer's Disease.*

Sources of Heterogeneity

The effect of important potential sources of heterogeneity (i.e., age, sex, diagnostic criteria, location [continent], time [when the study was done]) on incidence and prevalence estimates in those aged 60+ was assessed using univariate meta-regressions.

Age

Increasing age was associated with increasing point prevalence, period prevalence, incidence rate and incidence proportion estimates ($p < 0.001$).

Sex

Though the differences did not reach statistical significance (p values ranged from 0.102 to 0.582), estimates of incidence and prevalence by sex of the subjects were higher in females than in males, in the 22 studies that reported on this.

Diagnostic Criteria for AD

Within community settings, DSM–IV criteria[147] ($n = 2$) produced a statistically significant ($p = 0.044$) higher estimate for AD dementia point prevalence (91.7 [$CI_{95\%}$: 19.0-442.8] per 1000) than those based on NINCDS–ADRDA criteria for probable AD[148] ($n = 14$; 38.2 [$CI_{95\%}$: 31.3-46.6] per 1000). No statistically significant differences between the aforementioned criteria were seen for period prevalence in the community ($p = 0.065$), though the association was in the same direction as seen in the pooled point prevalence. All incidence studies used NINCDS–ADRDA criteria for probable AD.

Location

Within community settings, the estimated annual period prevalence for North America ($n = 2$; 103.6 [$CI_{95\%}$: 73.4-146.1] per 1000) was significantly higher than those for Asia ($n = 4$; 11.7 [$CI_{95\%}$: 2.8-48.5] per 1000; $p = 0.017$) and Europe ($n = 2$; 31.3 [$CI_{95\%}$: 14.4-67.7] per 1000; $p = 0.006$). The estimates

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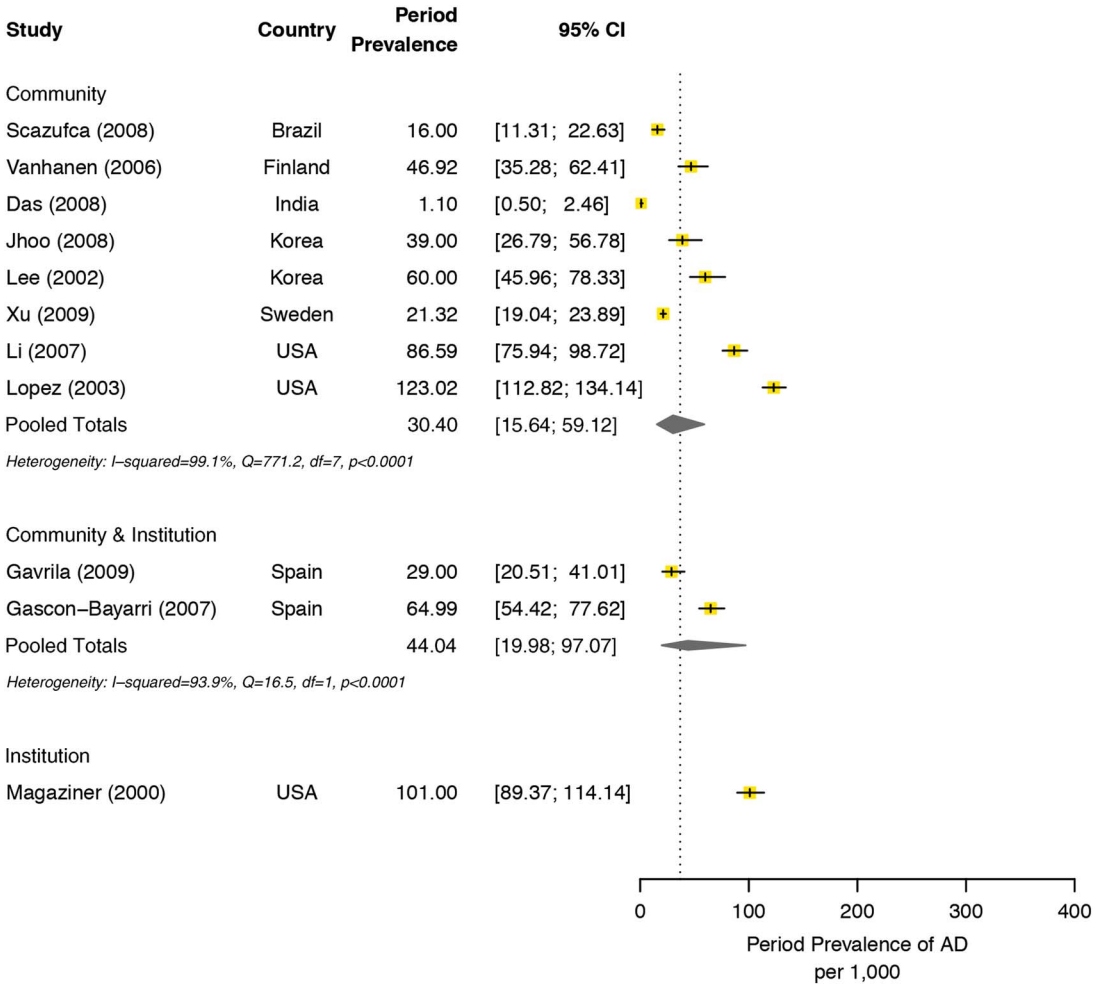

Figure 3: *Pooled period prevalence of Alzheimer's disease.*

for single studies for continents were: South America (16.0 [$CI_{95\%}$: 11.3-22.6] per 1000) and Australia (88.0 [$CI_{95\%}$: 82.7-93.7] per 1000). The incidence proportion estimate in a single-community African study (11.5 [$CI_{95\%}$: 9.70-13.64] per 1000) was lower than the estimated incidence proportion from five North American community studies (42.6 [$CI_{95\%}$: 23.0-78.8] per 1000) but could not be subjected to a meta-analysis as we required at least two estimates from a single region to be included.

Time

There was no effect of the time of study initiation, midpoint or conclusion on point prevalence, period prevalence, incidence rate or incidence proportion estimates.

Publication Bias

For the period prevalence, point prevalence, incidence rate and incidence proportion of AD dementia, significant funnel plot asymmetry was not found using Begg's or Egger's test ($p > 0.05$). Upon visual inspection, the funnel plots appeared symmetrical.

Study Quality

The median study quality score for studies reporting on the incidence or prevalence of AD dementia was 6/8 (range 3-8) (Table 4). Study quality did not vary by continent based on the results of ANOVA analyses.

Discussion

A substantial societal burden from AD dementia was demonstrated in our systematic review and meta-analyses. In community settings, the point prevalence of AD dementia among those 60 + was 40.2 per 1000, while its incidence proportion was 34.1 per 1000 and incidence rate was 15.8 per 1000 person-years. Despite the large number of studies included in our meta-analysis, the resulting estimates lacked precision at times due to significant statistical heterogeneity. Our finding that the period prevalence of AD dementia in community settings (30.4 per 1000 persons) was lower than the point prevalence (40.2 per 1000 persons) was unexpected and should be interpreted with caution. You would typically expect the opposite finding (i.e., a higher pooled estimate from the period prevalence studies). This was likely due to the significant heterogeneity (i.e., >99% for period prevalence studies) that existed between these two pools of studies, leading to wide confidence intervals. In addition, there were several outliers, particularly in the period prevalence estimates, which ranged from a low of 1.1 in India[77] to a high of 123.0 per 1000 persons in a U.S. study.[91]

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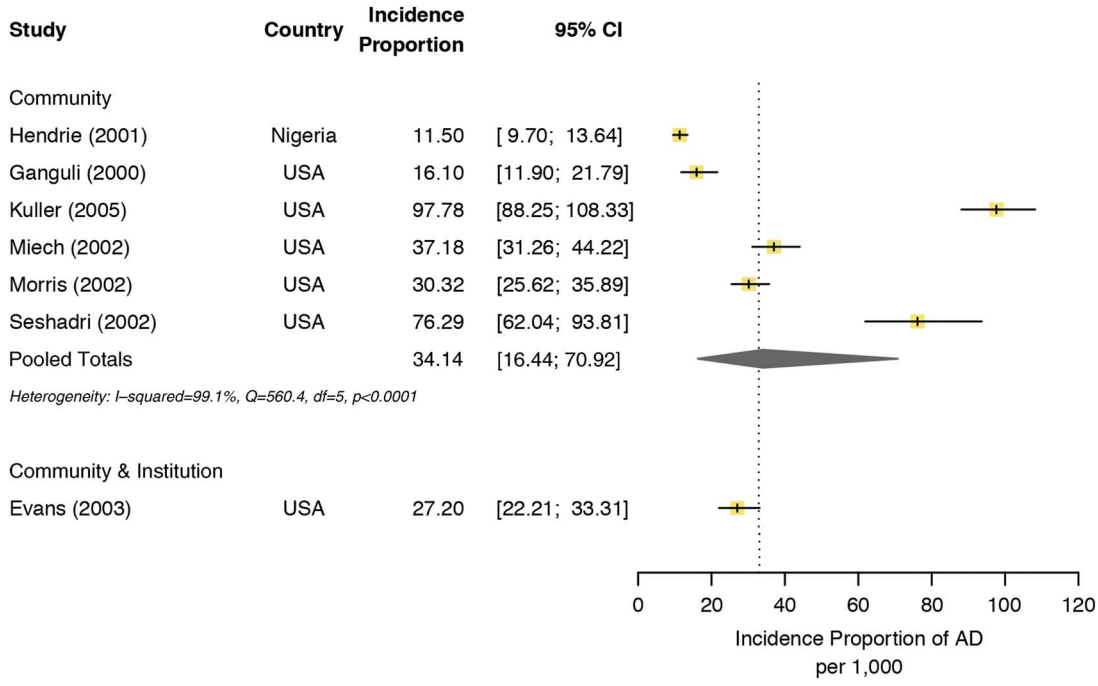

Figure 4: *Pooled incidence proportion of Alzheimer's disease.*

Our exploration of the sources of this heterogeneity led to several interesting findings. There was an insufficient number of population-based institution studies to do meta-analyses for this setting, but our descriptive analysis indicated that incidence rate for AD dementia is higher in the community while prevalence is greater in institutions. This is not surprising. There are few at-risk individuals within institutions, and the high mortality rate from other causes in the small at-risk institutional group likely means that they will likely die from another cause before they have time to develop AD. The inclusion of an institutionalized sample as well as region-specific variation in the availability of facility-based care and/or likelihood for institutionalization can have a substantial impact on the estimated prevalence of AD dementia in a community.[149] Institutionalization typically occurs as a result of the functional impairments, behavioural challenges and associated burden on family caregivers that arise as the disease progresses and largely explain the high prevalence in this setting. Information on the incidence and prevalence of AD stratified by setting is particularly relevant for planning resource allocation. We identified a significant gap when it comes to the population-based epidemiology of AD dementia in institutional and residential settings. Future studies are required to understand the true burden of AD dementia in long-term and supportive care facilities. The use of standardized assessments based on data abstracted from interRAI instruments to provide estimates for the prevalence of dementia in these settings holds promise, but it is unclear whether they could be utilized for estimates of dementia arising specifically from AD.[150]

All estimates of incidence and prevalence were higher for females compared to males, though the differences were not statistically different. In economically developed nations, about two-thirds of individuals diagnosed with AD dementia are women.[151] This is primarily due to the fact that women on average live longer than men, and increasing age is the most important non-genetic risk factor for AD dementia. Incidence studies suggest an age-dependent relationship between sex and likelihood of developing AD dementia. One of the studies we included noted differences in incidence rates by sex after 90 years of age.[142] Other reports indicate that the incidence of AD dementia increases with age in both sexes until 85-90 years of age, after which it plateaus for men but continues to increase among women.[152,153] A prior meta-analysis reported slightly longer doubling times with increasing age for AD dementia in men compared to women,[10] while another study reported that women tend to have a higher incidence at very advanced ages.[12] These noted differences between the sexes could be due to methodological issues, the differential impact of historical environmental risk factors, or true biological differences in disease susceptibility between the sexes.[154] Interestingly, recent data suggest that, relative to women, men who survive to older ages may exhibit a lower risk for developing AD because of a healthier cardiovascular risk profile.[155]

Difficulties examining the effect of the diagnostic criteria utilized to diagnose AD cases were encountered due to the ubiquitous use of NINCDS–ADRDA criteria. However, for point prevalence in community-only settings, DSM–IV criteria were found to produce significantly higher estimates than studies utilizing NINCDS–ADRDA criteria for probable AD (and possibly ICD–10 criteria[156]); a trend in the same direction was also shown in community period prevalence estimates. The choice and operationalization of diagnostic criteria can have a large effect on estimated incidence and/or prevalence.[157,158] In one study, the use of DSM–III criteria led to 29.1% of subjects receiving a dementia diagnosis compared to 13.7% when DSM–IV criteria were employed.[157] Newer diagnostic criteria for

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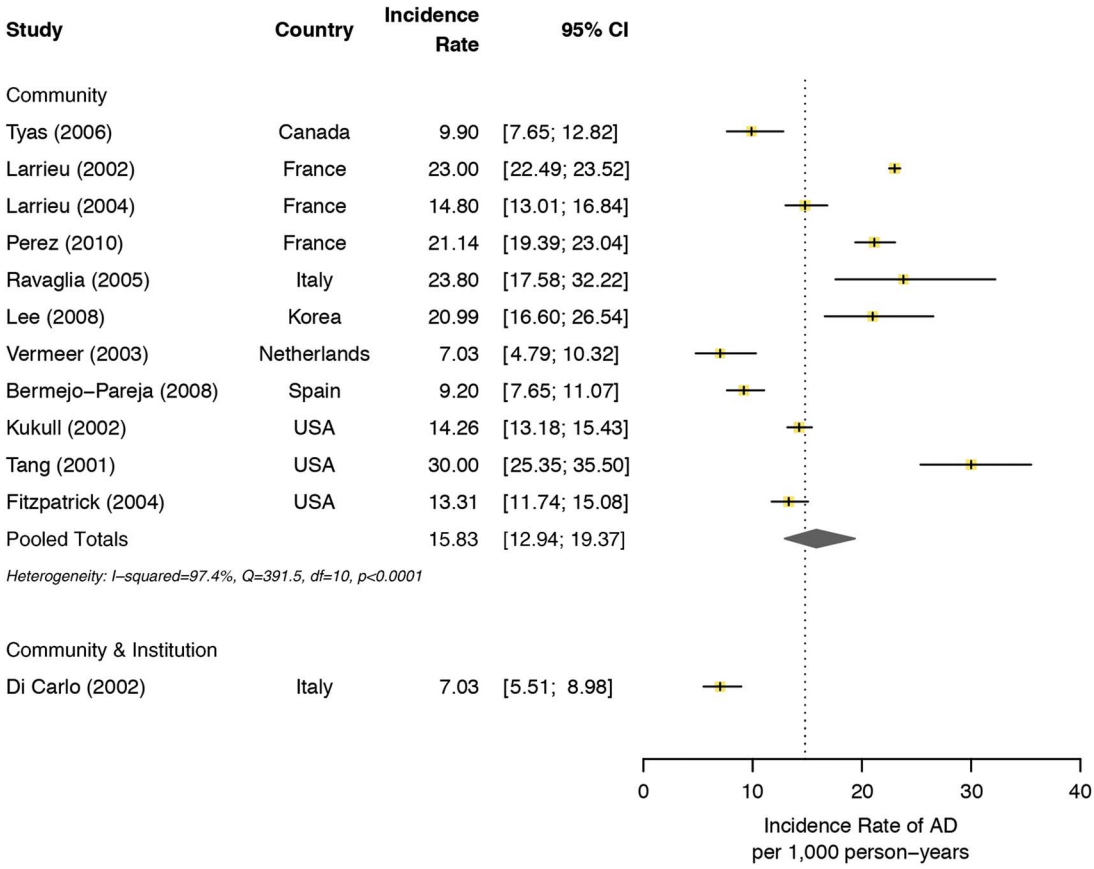

Figure 5: *Pooled incidence rate of Alzheimer's disease.*

AD decouple AD from the presence of a dementia and no longer require the presence of a memory impairment, the impact of which on epidemiological estimates of the incidence and prevalence of AD is yet unknown.[159] In the future, a diagnosis of preclinical AD may be made on the basis of biomarkers, though clinical criteria will be required to diagnose symptomatic (i.e., mild cognitive impairment or dementia) AD.[160] We suspect that the National Institute on Aging–Alzheimer's Association clinical diagnostic criteria for dementia due to AD[161] will be used in future incidence and prevalence studies of AD. Studies are needed to assess the potential impact of using these newer diagnostic approaches compared to the criteria that have been used to date on the estimated incidence and prevalence of AD and trends over time.

Estimates of AD dementia incidence and prevalence tended to be higher in North America as compared to Asia, but these differences were not statistically different except for estimates of period prevalence in community settings. Geographical differences in epidemiological estimates of AD could be due to a variety of factors other than true differences in age-specific disease risk, such as differing screening methods and thresholds for diagnosis, age distribution of the assessed population, duration of survival after the onset of AD dementia, overall life expectancy and competing risks.[17] Nonetheless, the possibility of true regional differences in AD incidence and prevalence has important implications. It is unlikely that the observed findings can be fully explained by differences in life expectancy. While North America has a relatively high life expectancy, estimates of life expectancy are similar or even higher in several Asian countries (e.g., Japan).[162] Similar findings (i.e., lower estimates in Asia) have been reported for Huntington's disease and Parkinson's disease, where it is felt that differences in the distribution, life expectancy and degree of stigmatization associated with a diagnosis of the condition may contribute to variations in disease reporting.[163,164]

The methodology utilized for this systematic review and meta-analysis closely followed established guidelines. We feel we were able to identify most eligible studies as multiple sources of study ascertainment were employed. We found no evidence for publication bias. We did, however, find a good deal of statistical heterogeneity.

In order to accurately plan for future needs, there remains an ongoing requirement to provide accurate estimates of the incidence and prevalence of AD. Relying on older data may lead to either over- or underestimating the resources required if incidence and prevalence rates are changing over time. Though, using meta-regression analysis, we did not find that time had an effect on the incidence or prevalence of AD, this does not preclude the possibility of true changes in age-standardized incidence and/or prevalence rates for dementia from AD occurring either now or in the near future due to changes in the presence of risk factors at a population level.[165] There could well be rising and/or falling rates of AD within specific nations or regions that could be obscured by looking at international changes. For dementia overall, as an example, there is a suggestion that

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Table 4: Quality assessment scores of Alzheimer's Disease incidence and prevalence studies

Study (Year)	Q1: Target population described?	Q2: Cases from entire population or probability sampling?	Q3: Response rate >70%?	Q4: Non-responders clearly described?	Q5: Sample representative of population?	Q6: Data collection methods standardized?	Q7: Validated criteria to assess disease?	Q8: Were estimates given with confidence intervals or subgroups?	Total Quality Score (/8)
Andreasen (1999)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Anttila (2004)	Yes	Yes	Yes	NR	NR	Yes	Yes	No	5
Arslantas (2009)	Yes	Yes	NC	No	NC	Yes	Yes	Yes	5
Banerjee (2008)	Yes	Yes	NR	NR	NC	Yes	Yes	Yes	5
Benedetti (2002)	Yes	Yes	Yes	Yes	NC	Yes	Yes	Yes	7
Bermejo-Pareja (2008)	Yes	Yes	Yes	Yes	NC	Yes	Yes	Yes	7
Bermejo-Pareja (2009)	Yes	Yes	Yes	Yes	NC	Yes	Yes	Yes	7
Borjesson-Hanson (2004)	Yes	Yes	No	No	NC	Yes	Yes	Yes	5
Borroni (2011)	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	5
Bottino (2008)	Yes	No	No	No	NC	Yes	Yes	Yes	4
Bowirrat (2001)	Yes	Yes	NR	Yes	Yes	No	No	No	4
Bowirrat (2001)	Yes	Yes	NR	Yes	Yes	No	No	No	4
Bowirrat (2001)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Camicioli (2000)	Yes	Yes	Yes	Yes	NC	Yes	Yes	No	6
Canadian Study of Health and Aging Working Group (1994)	Yes	Yes	Yes	NR	NC	Yes	Yes	Yes	6
Chandra (2001)	Yes	Yes	Yes	No	NR	Yes	Yes	Yes	6
Chen (2007)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Cornelius (2004)	Yes	NC	NR	NR	NR	Yes	Yes	Yes	4
Dahl (2007)	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	5
Das (2006)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Das (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
de Jesus Llibre (2009)	Yes	Yes	Yes	No	NR	Yes	Yes	Yes	6
de Silva (2003)	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	5
Demirovic (2003)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	6
Di Carlo (2002)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	6
Ebly (1994)	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	6
Edland (2002)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Evans (2003)	Yes	Yes	NR	NR	NC	Yes	Yes	Yes	5
Fish (2008)	Yes	Yes	Yes	Yes	NC	Yes	Yes	Yes	7
Fitzpatrick (2004)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Forti (2010)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Fuhrer (2003)	Yes	Yes	Yes	No	Yes	Yes	Yes	No	6

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Table 4. *(Continued)*

Study (Year)	Q1: Target population described?	Q2: Cases from entire population or probability sampling?	Q3: Response rate > 70%?	Q4: Non-responders clearly described?	Q5: Sample representative of population?	Q6: Data collection methods standardized?	Q7: Validated criteria to assess disease?	Q8: Were estimates given with confidence intervals or subgroups?	Total Quality Score (/8)
Fujishima (2002)	No	NC	Yes	NR	NC	Yes	Yes	Yes	4
Ganguli (2000)	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	5
Ganguli (2000)	Yes	Yes	NC	NR	NR	Yes	Yes	No	4
Garre-Olmo (2010)	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	6
Gascon-Bayarri (2007)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Gavrila (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Gislason (2003)	Yes	Yes	No	No	NC	Yes	Yes	Yes	5
Guerchet (2010)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Gurvit (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Hall (2009)	Yes	Yes	No	Yes	NC	Yes	Yes	Yes	6
Harvey (2003)	Yes	Yes	NA	No	NC	Yes	Yes	Yes	5
Hendrie (2001)	Yes	Yes	NR	NR	Yes	Yes	Yes	Yes	6
Herrera (2002)	Yes	Yes	Yes	No	NC	Yes	Yes	Yes	6
Ikeda (2001)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Ikeda (2004)	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	6
Ikejima (2009)	Yes	Yes	NR	NR	NC	Yes	Yes	Yes	5
Jhoo (2008)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	6
Kawas (2000)	Yes	NC	NR	NR	No	Yes	Yes	Yes	4
Kivipelto (2001)	Yes	Yes	Yes	No	NR	Yes	Yes	No	5
Kivipelto (2002)	Yes	Yes	Yes	No	NR	Yes	Yes	No	5
Knopman (2003)	Yes	Yes	Yes	Yes	NC	Yes	Yes	Yes	7
Knopman (2004)	No	NC	Yes	Yes	Yes	Yes	Yes	Yes	6
Kukull (2002)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	6
Kuller (2005)	No	Yes	NR	NR	NC	Yes	Yes	Yes	4
Landi (2005)	Yes	Yes	Yes	No	NR	Yes	No	Yes	5
Larrieu (2002)	Yes	Yes	No	No	NR	Yes	Yes	Yes	5
Larrieu (2004)	Yes	Yes	No	No	NR	Yes	Yes	Yes	5
Lee (2002)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7
Lee (2008)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Li (2007)	Yes	No	No	No	Yes	Yes	Yes	Yes	5
Li (2007)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	7
Lopez (2003)	Yes	NR	NR	NR	NR	Yes	Yes	Yes	4
Lopez (2005)	Yes	Yes	NR	NR	NR	Yes	Yes	No	4
Lopez-Pousa (2004)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Lovheim (2008)	Yes	Yes	Yes	Yes	No	Yes	No	Yes	6

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Magaziner (2000)	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	7
Maneno (2006)	Yes	No	Yes	Yes	Yes	NC	No	No	4
Manton (2005)	Yes	Yes	NA	NR	NA	NR	No	Yes	3
Mathuranath (2010)	Yes	Yes	NA	NA	NC	Yes	Yes	Yes	5
Matsui (2009)	Yes	Yes	Yes	No	NC	Yes	Yes	No	5
McDowell (2007)	Yes	Yes	NR	NR	NR	Yes	Yes	No	4
Meguro (2002)	Yes	Yes	No	No	NR	NR	Yes	Yes	4
Meguro (2007)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	6
Mercy (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Miech (2002)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Molero (2007)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	6
Morris (2002)	Yes	Yes	Yes	No	NR	Yes	Yes	No	5
Nitrini (2004)	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	7
Nunes (2010)	Yes	Yes	No	No	NR	Yes	Yes	Yes	5
Perez (2010)	Yes	Yes	No	No	NR	Yes	Yes	Yes	5
Perkins (2002)	Yes	Yes	NR	NR	Yes	Yes	Yes	Yes	6
Phung (2010)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Piguet (2003)	Yes	Yes	Yes	No	NC	Yes	Yes	No	5
Plassman (2007)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7
Polvikoski (2001)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	7
Polvikoski (2006)	Yes	Yes	Yes	No	Yes	Yes	Yes	No	6
Rahkonen (2003)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Ravaglia (2005)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Ravaglia (2005)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Ravalglia (2008)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Rockwood (2000)	No	Yes	No	No	NR	Yes	Yes	Yes	4
Rosenblatt (2004)	Yes	Yes	Yes	No	NR	Yes	Yes	No	5
Rovio (2005)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	6
Ruitenberg (2001)	Yes	Yes	Yes	No	NC	Yes	Yes	Yes	6
Sahadevan (2008)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	6
Scazufca (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Sekita (2010)	Yes	Yes	NC	No	NC	Yes	Yes	Yes	5
Seshadri (2002)	Yes	Yes	Yes	No	NC	Yes	Yes	No	5
Shaji (2005)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Spada (2009)	Yes	Yes	Yes	No	NR	Yes	Yes	No	5
Stevens (2002)	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	7
Suh (2002)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Tang (2001)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7
Tyas (2006)	No	Yes	No	Yes	NC	Yes	Yes	Yes	5

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Table 4. *(Continued)*

Study (Year)	Q1: Target population described?	Q2: Cases from entire population or probability sampling?	Q3: Response rate > 70%?	Q4: Non-responders clearly described?	Q5: Sample representative of population?	Q6: Data collection methods standardized?	Q7: Validated criteria to assess disease?	Q8: Were estimates given with confidence intervals or subgroups?	Total Quality Score (/8)
Vanhanen (2006)	Yes	Yes	Yes	No	NR	Yes	Yes	No	5
Vas (2001)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	6
Vermeer (2003)	Yes	Yes	No	Yes	No	Yes	Yes	No	5
Wada-Isoe (2009)	Yes	Yes	NR	No	Yes	Yes	Yes	Yes	6
Waite (2001)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Wakutani (2007)	Yes	Yes	Yes	No	NR	Yes	Yes	Yes	6
Wangtongkum (2008)	Yes	Yes	NR	No	No	Yes	Yes	No	4
Xu (2009)	Yes	Yes	Yes	No	NR	Yes	Yes	No	5
Yamada (2001)	No	Yes	NR	No	NR	Yes	Yes	Yes	4
Zandi (2002)	Yes	Yes	NR	NR	NR	Yes	Yes	No	4
Zhang (2005)	Yes	Yes	Yes	No	NR	Yes	Yes	Yes	6
Zhao (2010)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	6
Zhou (2006)	Yes	Yes	Yes	No	NR	Yes	Yes	Yes	7

*Note: NR = Not reported; NC = Not clear

rates are falling in high-rate areas (often high-income countries) and might be rising in low- and middle-income countries, where premature mortality is decreasing.[166,167] This underscores the need for future studies on the epidemiology of this important condition.

Disclosures

Kirsten Fiest, Jodie Roberts, Colleen Maxwell, Eric Smith, Alexandra Frolkis, Adrienne Cohen, Andrew Kirk, Dawn Pearson, Tamara Pringsheim, and Andres Venegas-Torres have nothing to disclose.

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Statement of Authorship

KMF, JIR, CJM, DBH, TP and NJ contributed to study conception and design. KMF, JIR, CJM, DBH, EES, AC, AK, DP, AV-T and NJ contributed to the acquisition of data. KMF and AF conducted the data analysis. KMF, JIR, CJM, DBH, EES and NJ participated in the interpretation of study data. All authors participated in critically revising the manuscript for important intellectual content and gave final approval for the submission of this manuscript and any further submissions of this work.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/cjn.2016.36

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