Published in final edited form as:

J Am Geriatr Soc. 2019 July ; 67(7): 1361–1369. doi:10.1111/jgs.16027.

Incidence of Dementia and Alzheimer's Disease Over Time: a Meta-Analysis

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Abstract

Background/Objectives: Population-based incidence estimates of dementia and Alzheimer's disease (AD) provide important information for public health policy and resource allocation. We conducted a meta-analysis of published studies that reported age-specific incidence rates of dementia and AD to determine whether dementia and AD incidence rates are changing over time.

Design: PubMed and MEDLINE were searched for publications through June 30, 2017 using keywords dementia, Alzheimer, and incidence. Inclusion criteria for the meta-analysis are: (1) population-based studies using personal interviews and direct examinations of the study subjects, (2) Standardized clinical diagnosis criteria, (3) Reporting age-specific incidence rates, (4) Published in English, and (5) Sample size greater or equal to 500 and length of follow-up greater or equal than two years. Mixed effects models were used to determine the association between birth year and incidence rates.

Measurements: Age-specific dementia/AD incidence rates and their standard errors reported in each study.

Results: Thirty-eight articles with 53 cohorts on dementia incidence and 31 articles with 35 cohorts on AD incidence met the inclusion criteria. There were significant associations between later birth years and decreased dementia incidence rates in all three age groups (65-74, 75-84 and 85+). There were no significant associations between birth year and AD incident rates in any of the three age groups. In particular, AD incidence rates reported from Western countries stayed steady in all age groups while studies in non-Western countries showed significantly increased AD

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Author Contributions: Sujuan Gao and Hugh C. Hendrie were responsible for the concept and design of the work. Heather N. Burney and Christianna E. Purnell performed the data collection. Sujuan Gao and Heather Burney completed the data analysis. Sujuan Gao, Heather Burney, Hugh C Hendrie, Christianna E. Purnell, and Chris M. Callahan participated in the manuscript preparation.

Conflict of Interest: The authors have no conflicts of interest.

incidence rates for the 65-74 age group (OR=2.78, p=0.04), but non-significant association for the 75-84 or 85+ groups.

Conclusion: Dementia incidence declined over the last four decades, but AD incidence did not decline. Further research, especially from non-Western countries, is needed to elucidate the mechanism underlying the trends in dementia and AD incidence over time.

Keywords

dementia; Alzheimer's disease; incidence; trend

Introduction

With the increase in the older adult population in the world, Alzheimer's disease (AD) and related dementia is becoming a major global public health challenge. It is projected that the prevalence of dementia will nearly quadruple in the next 40 years, by which time approximately 1 in 45 Americans and 1 in 85 people worldwide will be affected by the disease.[1] Population-based prevalence and incidence estimates of dementia and AD provide important information for public health policy and resource allocation. Findings from these cohort studies can also reveal disparities in disease risk in different study populations that may lead to the identification of potential risk or protective factors.

Over the last several decades, many epidemiological studies have reported dementia and AD incidence rates in populations across the world. Several population-based studies that enrolled multiple cohorts over time have reported declining AD and dementia incidence rates,[2–5] while other studies found no change in disease risk.[6,7] Two recent reviews of dementia incidence included data from a few studies each enrolling at least two birth cohorts over time and found substantial heterogeneity in the time trend of dementia incidence.[8,9] Since most of the studies that reported incidence decline were from the United States or Europe, it has been suggested that rising education levels and aggressive treatment of cardiovascular diseases in these countries may have contributed to the decline in dementia and AD incidence.[10] No meta-analysis has been conducted to examine AD incidence over time.

We note that previous reviews that included only studies with multiple birth cohorts did not capture information from the vast majority of studies that published incidence rates, and many of these were from non-Western countries. Combining data from all studies on dementia and AD incidence over the last four decades will provide a more complete synthesis of the changing trends of dementia and AD risk.

We conducted a systematic search of published studies through June 30, 2017 and a meta-analysis of age-specific incidence of dementia and AD. Our objective is to determine whether there is a change in dementia and AD incidence rates over time and whether trends of dementia and AD incidence over time differed by study populations from Western countries versus non-Western countries and by sex.

Methods

Data Sources

We (HB and SG) conducted searches both directly and via EndNote X8 in PubMed and MEDLINE for publications in English through June 30, 2017. PubMed was searched using terms “Alzheimer” AND “incidence” OR title “Alzheimer incidence” for Alzheimer’s disease and terms “dementia” AND “incidence” OR title “dementia incidence” for dementia. MEDLINE Ovid was searched using text word “Alzheimer” AND text word “incidence” OR title “Alzheimer incidence” for Alzheimer’s disease and text word “dementia” AND text word “incidence” OR title “dementia incidence” for dementia. In addition to articles from the search, we also reviewed reference lists from identified articles to locate potential published studies. The analyses were conducted using published results. Therefore, conference proceedings, abstract, and unpublished studies were not included. No contact with authors was attempted.

Selection of Studies

All abstracts from the search were reviewed to determine study selection. Since our objective is to ascertain trends in incidence rates over time, the following inclusion criteria were used to select studies that employed vigorous methodology in the meta-analysis: (1) The study was population-based using personal interviews and direct examinations of the study subjects. (2) The study used standardized clinical diagnosis criteria. Specifically, DSM-III, DSM-III-R or DSM-IV[11–13] for the diagnosis of dementia, NINCDS/ADRDA[14] for the diagnosis of AD. Eight publications that used other diagnostic criteria but stated equivalency to the standard criteria we specified were also included. (3) Age-specific incidence rates were reported. This is necessary given both dementia and AD incidence rates were age dependent to ensure fair comparisons. (4) The study was published in English. (5) Sample size for each cohort was greater or equal to 500 and length of follow-up greater or equal than two years. The restriction on sample size and length of follow-up is to ensure that each included study identifies sufficient numbers of incident cases to ensure the accuracy of reported incidence rates. Since dementia/AD incidence rates were about 1 to 2% per year for individuals younger than 75[8], a study with sample size less than 500 would be expected to identify only 10 to 20 incident cases during a 2 year follow-up thus introducing large variations in rate estimates.

For incidence of dementia, 103 articles were identified for full-text review as the result of the literature search and abstract review. Thirty-eight articles with 53 cohorts met the inclusion criteria for the meta-analysis on the incidence of dementia with several articles reporting incidence rates for multiple cohorts. For incidence of AD, 70 articles were identified for full-text review. Thirty-one articles with 35 cohorts met the inclusion criteria for the meta-analysis on the incidence of AD. For studies reporting incidence rates in the same cohort in multiple publications, data from the most recent publication were used. Many studies were excluded for not reporting age-specific incidence rates or not being population-based. Figures 1 and 2 provide flow charts for the selection of studies and the numbers of excluded studies by reasons of exclusion.

Data Extraction

For each included study, we recorded age-specific incidence rates, standard error estimates, and 95% confidence intervals of the rates, if reported. We also recorded sex-specific incidence rates whenever these were available. In cases where only sex-specific incidence rates were reported, we combined the sex-specific rates using information and methods provided in the articles. In addition, we recorded the calendar year for the beginning and the end of follow-up for each study cohort. Two people (HB and CP) independently reviewed the articles and extracted the data included in the meta-analysis.

Statistical Analysis

All extracted age-specific dementia/AD incident rates and standard error estimates for the rates were standardized to per person-year. For a given age group, we calculated average birth year as the median study year minus the median age in the particular age group. For example, for a study conducted during 1991-1999, the average birth year of 1925 for participants in the 65-74 age group was used. If a study was conducted from 2001 to 2009, we would use an average birth year of 1935 for participants in the same age group. Therefore, each age-specific incidence rate extracted from the included studies was aligned with an estimated average birth year for participants in the age group. We are interested in estimating the association between birth year and dementia/AD incidence rates for individuals of similar age, *i.e.* whether individuals born in a later birth year had lower dementia or AD incidence when they reach certain age. We examined the time trends of incidence rates for three age groups (65-74, 75-84, and 85+) separately. Since some studies reported incidence rates using 5-year age groups, while others used 10 year intervals, we chose to conduct our models using the 10 year interval in order to include as many studies as possible. Therefore, studies reporting incidence rates for 65-69 and 70-74 will contribute two observations to the model for age group 65-74. Analyses were carried out for the incidence of dementia and for the incidence of AD separately.

For each age group, a mixed effects model was used to determine the association between birth year and incidence rates of dementia/AD. The outcome variable for the mixed effects model was the logit function of the standardized incidence rates and the independent variable was the average birth year for the age group. In the mixed effects model, we assumed a random study effect and fixed the variance of the random measurement errors to be the variance of the logit rate based on standard error estimates reported from each study.[15] Details of the mixed effects model specification are described in the Supplementary Text.

We further explored whether the association between birth year and incidence rates differed between studies conducted in Western countries (Europe, the United States, and Canada) and non-Western countries by conducting separate mixed effects models in the two sub-groups. In the subset of studies reporting sex-specific incidence rates, we used similar models for males and females, separately. Additional sensitivity analyses were conducted to determine the robustness of results. As alternatives to the mixed effects models, we used both generalized logistic and Poisson models in the subset of studies that reported number of incident cases and person-year at risk for each age group. Since median study time was used to estimate birth year which may lead to potential bias especially for longer studies, we also

fitted the models to only studies with follow-up longer than 5 years. We also restricted the models to those with large sample sizes (n≥2000) to examine the robustness of our study findings. Details of the sensitivity analyses are described in the Supplementary Text. The statistical software SAS version 9.4 was used for the analyses.

Results

Description of Data

We present summary information on the cohorts included in the meta-analysis in Table 1. Fifty three cohorts with a total of 123,335 individuals reported age-specific incidence rates for dementia; 37 of these were from Western countries (Europe, U.S. and Canada). The median length of follow-up was 5 years and the median study sample size was 1730. There were 35 cohorts with 89,376 individuals reporting age-specific incidence rates of AD; 25 of the cohorts were from Western countries. The median length of follow-up for AD studies was 4.5 years and the median study sample size was 1835. Summary information for each study included for dementia and AD incidence in the meta-analysis is presented in Supplementary Tables S1 and S2, respectively. For each cohort, we included study names, sample size, country, and age range of the study population. We also included the following information: (a) diagnostic criteria; (b) whether screening was used; (c) years of study collection; (d) length of follow-up; and (e) whether sex-specific rates were reported. Since our inclusion criteria required the use of standardized diagnosis criteria, all studies included in the meta-analysis were published after 1990.

Incidence of Dementia

In Table 2 we present the results of mixed effects models for the association between birth year and dementia incidence rates in age groups of 65-74, 75-84 and 85+, separately. Significant associations were seen between later birth years and decreased incidence rates for all age groups. Specifically, each 10-year increase in birth year was associated with 80% reduction in the odds of incident dementia for individuals reaching age 65-74 (Odds Ratio (OR)=0.20, $p<0.0001$). The reduction in the odds of incident dementia was 80% for individuals reaching age 75-84 (OR=0.20, $p<0.0001$) and 28% for those 85 or older (OR=0.72, $p=0.01$) for each 10-year increase in birth year. For each age group, we illustrate the time trend in dementia incidence in Figures 3a–3c where logit incidence rates are shown as dots with their sizes proportional to the inverse of the study variance. Regression lines based on parameter estimates from the mixed effects models are also shown in these figures. When the mixed effects models were conducted in studies from Western countries only, we observed similar trends between later birth year and decreased dementia incidence as in all studies. However, when we restricted the models to studies from non-Western countries, a significant decreasing dementia incidence was only seen in individuals reaching age 65-74 (OR=0.44, $p<0.0001$), not for those in age groups 75-84, or 85+. Using studies that reported sex-specific incidence rates showed similar trends of dementia incidence decline in males and females.

Incidence of AD

In Table 2 we also present results from mixed effects models for incident AD. There were no significant associations between birth year and AD incident rates for any of the three age groups. The time trends for AD incidence rates are illustrated in Figures 3d–3f. Analysis using studies from Western countries suggested steady AD incidence rates for individuals in all three age groups (OR≥0.91, p≥0.68) with each 10 year increase in birth year. Studies in non-Western countries showed significantly increased AD incidence rates for age group 65-74 (OR=2.78, p=0.04), but non-significant association for age 75-84 or 85+ groups. Analysis using sex-specific incidence rates did not reveal significant differences in AD incidence trends between male and female subjects.

Additional sensitivity analyses were conducted and are described in more detail in the Supplement (Supplementary Tables S3 and S4). We found similar results using generalized logistic or Poisson models in subsets of studies that reported numbers of cases and person-years at risk, in studies with follow-up longer than 5 years and those with sample sizes larger than 2000. Similar trends in dementia incidence decline were seen in the subset of studies that enrolled multiple birth cohorts. However, in the subset of studies that reported both dementia and AD incidence rates, we found no decline in dementia incidence and an increasing, albeit non-significant, trend for AD incidence. This is perhaps due to the exclusion of many large studies of dementia incidence and some loss of power. In the Supplementary materials, we present results in dementia incidence rates by whether a study included a separate diagnosis for cognitive impairment (Supplementary Figure S1), used a screening instrument (Supplementary Figure S2), and ascertained dementia cases in deceased participants (Supplementary Figure S3). The decline in dementia incidence rates was consistently seen for the younger age groups.

Discussion

This meta-analysis found that dementia incidence rates declined for individuals born in later birth years compared to earlier birth cohorts and the decline was seen in populations from both Western and non-Western countries. In contrast, AD incidence rates did not decline over time in all studies included in the meta-analysis. AD incidence rates remained constant over time in studies from Western countries, while an increasing AD incidence was actually seen in studies from non-Western countries.

Our finding of declining dementia incidence rates was consistent with a recent review that included five studies each with multiple birth cohorts.[9] Our meta-analysis included two additional multiple-cohort studies,[16–18] and 35 single cohort studies in addition to the studies in the previous review. Studies of a single cohort of each age group still offer information on incidence for individuals in those age groups and should be included in systematic reviews. Our mixed-effects model approach is a part of meta-regression models used in meta-analysis and allows the estimation of time trend using results from both multiple cohorts and single cohort studies. Thus our results were able to provide more comprehensive synthesis of published results on dementia and AD incidence.

Several factors have been postulated to account for the decline in dementia incidence. The first is the improvement of early childhood environment from the early 1900's to the 1940's, the range of birth years covered by the studies included in this analysis. This time period has seen the greatest reduction in infant mortality rates,[19] coupled with the steepest increase in life expectancy.[9] Studies of historical cohorts have shown that as childhood mortality improved, those born in later birth cohorts also had lower rates of mortality and disease in adulthood.[20] While better sanitation, nutrition, income, and medicine are generally thought to contribute to the reduction in childhood mortality and increase in life expectancy, there is also the theory by Finch and Crimmins that "lifetime exposure to infectious diseases and inflammation" impacts individuals' overall health status throughout their lifetime.[20] Higher levels of education, particularly in childhood, have also been associated with lower rates of dementia in both Western and non-Western nations in some studies.[21–23]

The second factor that may be related to the decline in dementia incidence is the reduction in cardiovascular risk over the last several decades. Rates of smoking in adults in the U.S. have declined since the 1960's.[24] Stroke incidence[25] and mortality from cardiovascular disease globally[26,27] have also decreased over the same time. Thus the decline in dementia incidence may reflect the reduction in vascular dementia as results of aggressive efforts in the prevention and treatment of cardiovascular risk factors over the last several decades. However, since many studies did not report incidence rates for vascular dementia, we did not conduct a separate meta-analysis of vascular dementia incidence.

The decline in dementia incidence could also be due to a shift in dementia diagnosis criteria over time. We attempted to minimize the heterogeneities in results by including only studies using standard diagnostic criteria. If there were an increasing awareness in dementia identification, higher incidence rates over time rather than declining trends would be a more anticipated result.

In contrast to the decline of dementia incidence, we found no decline of AD incidence over time. As a large percentage of dementia cases involve vascular pathology, this would suggest that the decline in dementia rates is primarily due to a decline in cerebrovascular disease rather than specific AD-related pathologies. Apart from the very recent effort in using neuroimaging techniques for AD diagnosis, clinical diagnostic criteria for AD have been relatively consistent and no effective treatment or prevention for AD has been identified. The same set of cardiovascular risk factors found to be associated with increased dementia risk have also been implicated as risk factors for AD, but not consistently established.[28] The reported associations between cardiovascular risk factors and AD seem to depend on the timing of risk exposure measures with those measured at midlife conferring the higher risk and those measured in late life having no risk or even being protective.[29]

There have been no previous meta-analyses on AD incidence with which to compare our results. Results from studies enrolling multiple birth cohorts have not been consistent. The Rochester, Minnesota study and the Chicago Health and Aging Project found no birth cohort effects in AD incidence from 1975-1994 or 1997-2008, respectively.[7,30] The Indianapolis-Ibadan Dementia Project reported significant decline in AD incidence rates in an African American cohort enrolled in 2001 compared to those enrolled in 1992, but no change in AD

incidence in Nigerians enrolled in 2001 compared to those enrolled in 1992.[2] There are important methodologic differences among these studies. The Rochester Study used medical record based diagnosis, thus was not included in this meta-analysis. The 2010 publication from the Chicago study used rolling enrollment and analyzed time trend using logistic regression models without reporting age-specific incidence rates. Therefore, an earlier publication from the study with estimated incidence rates was included in the meta-analysis.[31] Results from the Indianapolis-Ibadan study were included in the meta-analysis.

It is worth noting that only 10 out of the 35 cohorts for the AD incidence analyses were from non-Western countries (five countries in Asia, one in South America and one in Africa). This could be due to the requirement of English publications. Our results indicated that for the younger age groups there was an increasing trend toward higher AD incidence with later birth years in non-Western cohorts. Compared to European and American populations, studies from non-Western countries had reported lower AD incidence rates. The increase in AD incidence may be due to a number of factors. One factor may be improved survival so that carriers of AD risk genes were more likely to survive to older age with higher risk for developing AD.[32] Another factor could be a more aggressive AD identification process over time. However, the fact that our models for dementia incidence in the non-Western countries did not find an increasing trend seem to suggest that a shifting diagnosis is unlikely to account for the higher AD incidence over time in non-Western countries.

We note that many factors contribute to the heterogeneities in incidence rate estimates and were not fully accounted for in our meta-analysis. These factors include refusal rate, attrition rate during follow-up, mortality rate, whether a study ascertained dementia/AD cases for deceased subjects, whether a study include a separate diagnosis for cognitive impairment, and whether a study included individuals living in nursing homes. Since many of these factors are not included in many studies, our analyses were unable to fully account for these factors.

There were a number of strengths in this analysis. The identification of studies included in our meta-analysis was systematic and comprehensive ensuring all relevant publications were included. The use of standardized diagnostic criteria for inclusion reduced potential heterogeneity in study results due to differences in diagnoses. The mixed effects models used for analyses accounted for estimation precision reported from each study. Extensive sensitivity analyses were conducted to ensure robust results.

There were also a number of limitations. Due to the nature of meta-analysis, we relied on aggregated data rather than individual data, thus our analysis lacks the ability to adjust for individual characteristic information. Second, our analyses included only studies published in English, thus it is possible that publications in non-English journals were excluded. Third, our results may be subject to publication bias, although perhaps to a lesser extent than meta-analyses evaluating treatment efficacies, as incidence studies tended to be more descriptive in nature and were less likely to be rejected for non-significant findings. Fourth, we estimated birth year based on median study time for each age group, thus leading to some loss of precision in defining birth years, especially for studies with relatively long follow-up. Nevertheless, sensitivity analyses limiting analyses by length of follow-up produced similar

results. Lastly, our meta-analyses identified only studies that published population-based age-specific incidence rates. Thus it is possible that we may have excluded studies investigating time trends through various modeling approaches without presenting age-specific incidence rates.

In summary, this meta-analysis found that incidence rates of dementia declined over the last four decades, but AD incidence rates did not decline in Western countries, and actually increased for younger age groups in non-Western countries. These results emphasize the need for more research into the specific etiology and risk factors for Alzheimer Disease in order to develop a comprehensive treatment and prevention strategy for this devastating disease.[33] Future research would be enhanced by including studies from non-Western as well as Western countries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

Sponsor's Role: This research was funded in part by NIH grant RO1 AG045350 and NIH grant P30 AG010133. The funders had no influence on the design, methods, data collection, or analysis of this study or in the preparation of this paper.

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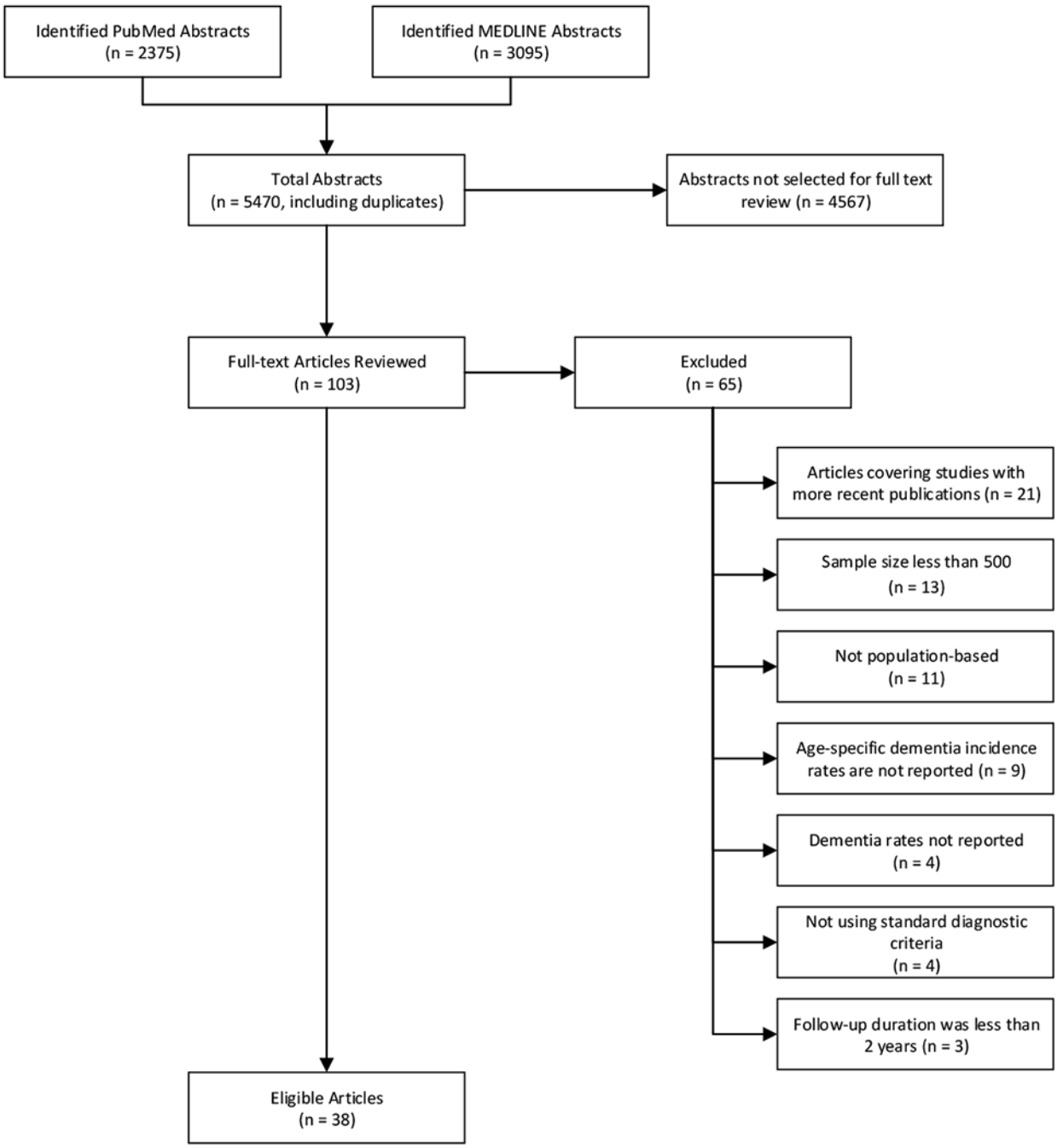

Figure 1.
Dementia study flow diagram

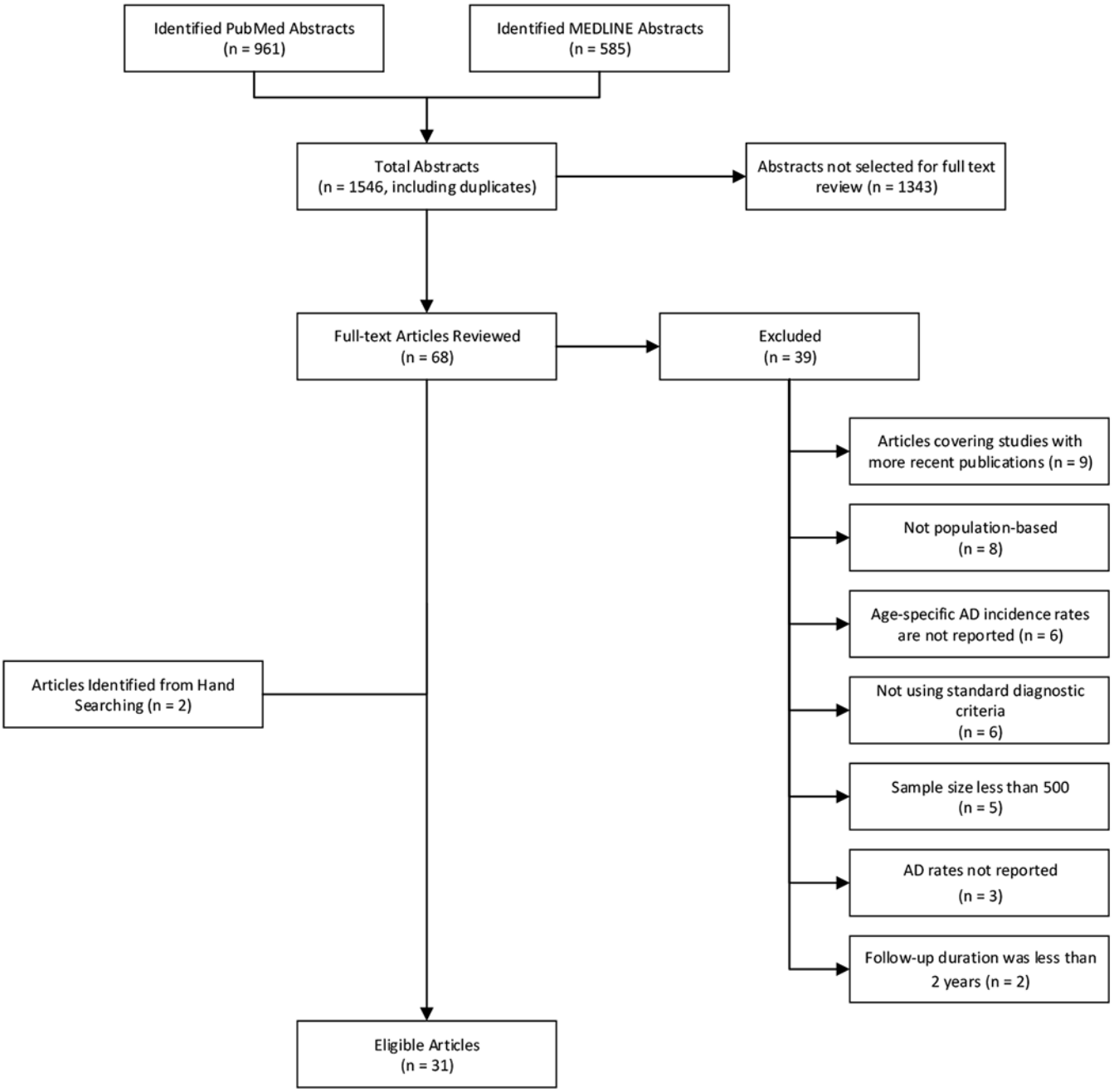

Figure 2.
Alzheimer's disease study flow diagram

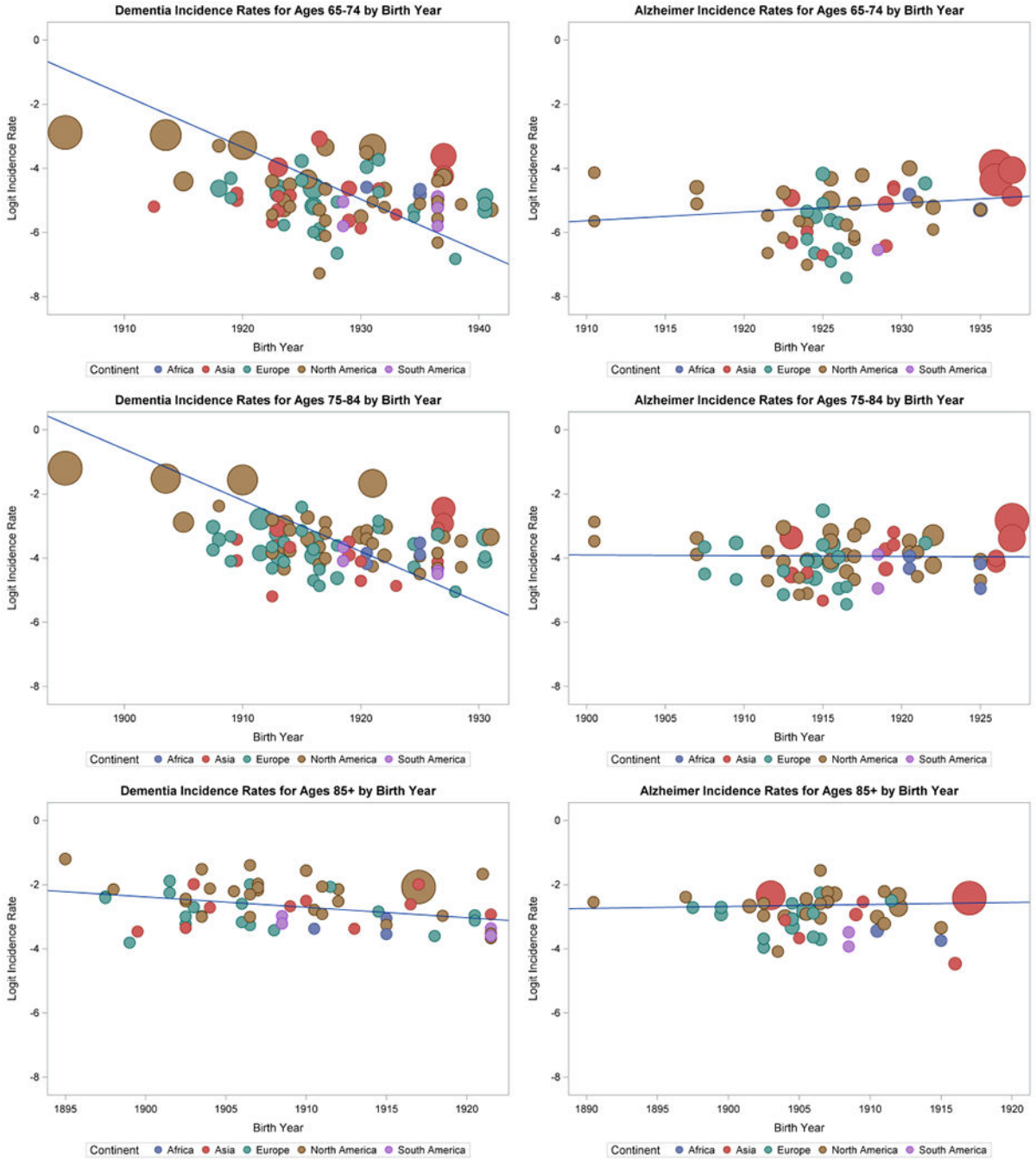

Figure 3.

Time trend for dementia or Alzheimer's disease incidence rates by birth year. The sizes of the dots are proportional to the inverse of the variances of incidence rates reported by each study.

3a. Time trend for dementia incidence rates for ages 65-74 ($p<0.0001$).

3b: Time trend for dementia incidence rates for ages 75-84 ($p<0.0001$).

3c: Time trend for dementia incidence rates for ages 85+ ($p=0.01$).

3d: Time trend for Alzheimer's disease incidence rates for ages 65-74 ($p=0.26$).

3e: Time trend for Alzheimer's disease incidence rates for ages 75-84 (p=0.90).
3f: Time trend for Alzheimer's disease incidence rates for ages 85+ (p=0.54).

Table 1:

Descriptive summary for studies included in the meta-analyses.

	Outcomes	
Characteristics	**Incident Dementia**	**Incident Alzheimer's Disease**
Total number of cohorts	53	35
Total sample size	123,335	89,376
Number of cohorts by continent		
Africa	3	2
Asia	10	7
Europe	17	10
North America	20	15
South America	3	1
Number of cohorts with sex-specific rates	32	21
Median length of follow-up (interquartile range)	5 (3 – 7)	4.5 (3.2 – 8)
Median Study Sample Size (interquartile range)	1730 (1192 – 2507)	1835 (1173 – 3308)

Table 2.

Results of mixed effects models: estimated association of birth year with the log odds of dementia and Alzheimer's disease incidence. The estimated odds ratio represents the change in odds for incident dementia or Alzheimer's disease with 10 year increase in birth year.

		Dementia Incidence					Alzheimer's Disease Incidence				
Cohorts	**Age Group**	**Number of Cohorts**	**Odds Ratio**	**95% Confidence Interval**		**p-value**	**Number of Cohorts**	**Odds Ratio**	**95% Confidence Interval**		**p-value**
All cohorts	65-74	49	0.20	0.18	0.22	<0.0001	32	1.31	0.83	2.08	0.26
	75-84	53	0.20	0.19	0.21	<0.0001	35	0.98	0.70	1.36	0.90
	85+	50	0.72	0.58	0.90	0.01	33	1.06	0.87	1.30	0.54
Western Countries	65-74	29	0.17	0.15	0.19	<0.0001	22	0.99	0.53	1.83	0.97
	75-84	33	0.20	0.19	0.21	<0.0001	25	0.91	0.60	1.40	0.68
	85+	30	0.79	0.58	1.06	0.15	23	0.99	0.70	1.40	0.94
Non-Western Countries	65-74	20	0.44	0.35	0.56	<0.0001	10	2.78	1.33	5.79	0.04
	75-84	20	1.06	0.67	1.69	0.81	10	1.41	0.66	3.04	0.40
	85+	20	0.77	0.53	1.13	0.41	10	0.91	0.63	1.29	0.60
Asian Countries	65-74	10	0.47	0.26	0.85	0.04	7	3.11	1.55	6.26	0.02
	75-84	10	1.34	0.63	2.86	0.49	7	1.72	0.72	4.09	0.28
	85+	10	0.97	0.77	1.21	0.78	7	0.91	0.61	1.36	0.66
Studies with sex-specific rates											
Female	65-74	29	0.18	0.16	0.20	<0.0001	17	1.61	0.85	3.06	0.17
	75-84	31	0.20	0.19	0.21	<0.0001	20	0.95	0.67	1.33	0.75
	85+	29	0.80	0.55	1.17	0.27	19	0.78	0.51	1.18	0.26
Male	65-74	30	0.21	0.19	0.24	<0.0001	18	1.07	0.67	1.72	0.78
	75-84	32	0.22	0.21	0.24	<0.0001	21	0.75	0.47	1.18	0.23
	85+	29	0.84	0.62	1.15	0.30	20	0.87	0.51	1.49	0.63