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REVIEW ARTICLE

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Sex differences in the incidence and prevalence of young-onset Alzheimer's disease: A meta-analysis

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Abstract

Objectives: The lifetime incidence of Alzheimer's disease is higher in women than in men, but it remains unclear if similar sex differences exist in young-onset Alzheimer's disease (YOAD). This systematic review test the hypothesis that women have a higher prevalence and incidence of YOAD than men.

Methods: We searched Pubmed and Embase (inception to 11 June 2020) for original publications of population-based observational studies with data on the prevalence and/or incidence of YOAD, defined as a medical diagnosis of Alzheimer's disease before the age of 65 years. Data on cross-sectional and/or prospective numbers, percentages, incidences, and incidence rates (in person-years) were derived from included studies. Quality assessment was done using the Nottingham Ottawa Scale. Meta-analyses were done to test the hypothesis that women have a higher prevalence and incidence of YOAD than men.

Results: After screening of 3252 titles, 12 articles were included. The pooled prevalence was 0.4% (confidence interval [CI] = 0.1–2.1) in women and 0.2% (CI = 0–1.2) in men (six studies, relative risk [RR] = 1.54, CI = 0.69–3.44, I^2 = 38%). The pooled incidence was 0.02% (CI = 0.01–0.08) in women and 0.01% (CI = 0–0.05) in men (five studies, RR = 1.50, CI = 0.91-2.48, I^2 = 0%). The incidence rates per 100,000 person-years ranged from 0 to 132 in women and from 0 to 42 in men.

Conclusions: Given the low prevalence and wide CIs, no firm conclusions can be drawn. Large-scale studies are required to verify that women are more likely than men to develop YOAD.

KEYWORDS
Alzheimer's disease, incidence, prevalence, sex characteristics, systematic review

Key points

- This review examined whether women are more likely than men to develop young-onset Alzheimer's disease (YOAD)
- Prevalence and incidence of YOAD appeared higher in women than in men
- Sex differences in prevalence and incidence of YOAD were not statistically significant

1 | INTRODUCTION

Young-onset Alzheimer's disease (YOAD) is classified as Alzheimer's disease (AD) with an onset before the age of 65 years, and it constitutes 5% of all AD diagnoses. While similar brain pathologies such as beta-amyloid accumulation and brain atrophy are found in YOAD and late-onset AD (LOAD, onset after the age of 65 years), these pathologies are present at a younger age in YOAD patients than in AD patients in general.[1] Over the life course, women are more likely than men to develop AD.[2] Whether this sex difference exists mainly in LOAD or also in YOAD remains unclear. A better understanding of sex-differences in the incidence of AD and YOAD can inform personalized medicine.

Both sex and gender have an impact on the prevalence of AD. "Sex" refers to biologically determined characteristics of women and men.[3] "Gender" refers to the socially and culturally determined meaning of being a man or a woman.[3] Across the lifespan, both sex and gender may influence the incidence of AD via genetic, hormonal, and lifestyle mechanisms. Sex-stratified genome-wide association studies have shown differences in loci associated with AD in men and women.[4,5] The female sex hormone estrogen may serve as a protector against neural degeneration.[6] As women age, estrogen levels decrease and the exposure to mitochondrial toxicity and beta-amyloid accumulation increases, resulting in a greater risk of AD.[7] This is supported by evidence from neuroimaging studies showing that post-menopausal women have lower gray matter density than perimenopausal women.[8] Moreover, women taking hormone replacement therapy have lower incidence of AD than women not taking hormone replacement therapy.[9,10] Sex/gender differences in lifestyle-related AD risk factors, such as diet[11] and physical activity,[12] may also contribute to differences in AD incidence. Finally, men and women also differ in health-seeking behavior,[13–15] which could influence the timing of diagnosis and therefore incidence of AD.

Another potential explanation for the higher lifetime incidence of AD in women than men is the longer life expectancy of women.[16] The longer life expectancy means that women simply have more time to develop AD than men. If differences in life expectancy forms the dominant explanatory mechanism for sex/gender differences in AD incidence, one would expect to find greater sex differences in the incidence of LOAD than in the incidence of YOAD. While sex differences in LOAD have been well established,[2,17] this is less clear for YOAD. To date, observational studies have shown inconsistent results, with some studies showing higher prevalence of YOAD in women[18,19] and others showing higher prevalence men[20] or no difference.[21,22] Given the low overall prevalence of YOAD, a meta-analysis may provide more robust sex-specific estimates of the prevalence and incidence of YOAD.

The aim of this systematic review and meta-analysis is to examine whether there are sex/gender differences in the prevalence and incidence or YOAD. We hypothesize that women have a higher prevalence and incidence of YOAD than men.

2 | METHODS

The protocol for this review was registered in PROSPERO (CRD42020197312) and the PRISMA recommendations for reporting were followed to write this manuscript.

2.1 | Search strategy

The search was conducted in two electronic databases, Pubmed and Embase, covering the period from inception to the 11 June 2020. The search strategy was built using terms for AD, age/young onset, sex/gender, and incidence and prevalence. While terms for sex/gender were used to build the search strategy, these terms were left out of the final search in Pubmed as these terms did not add to the specificity of the search. The full search strategy is presented in Appendix Table A in Supporting Information S1.

2.2 | Study selection

The titles identified by the search strategy were screened by at least two reviewers (KK, ND, GP) on eligibility. The full texts of selected titles were then checked and included in the review if they met the following inclusion and exclusion criteria. Studies were included if (a) designed as a cross-sectional or prospective observational study; (b) the sample was drawn from the general or primary care population; (c) YOAD was defined as a diagnosis of AD before the age of 65 years confirmed by a medical doctor; and (d) sufficient data were presented to derive the prevalence and/or incidence of YOAD separately for women and men. Studies were excluded if (a) designed as a case-control study; (b) the diagnostic criteria for YOAD were not reported; (c) outcomes were reported for all-type dementia and the specific numbers for YOAD could not be derived; and (d) outcomes were reported for an age range including ages over 65 years and the specific numbers could not be derived for those under the age of 65. In case multiple papers reported results based on the same cohort, we selected only one paper to avoid double counting. In that case, we selected the paper that described results for the most recent outcomes and/or largest subsample of that cohort. Studies were included only if published in English.

2.3 | Data extraction

For each study, data were extracted by two reviewers (KK, YYC, MV) and checked by a third reviewer (ND, GP) using a custom-made form. The following data were extracted: title, first author, year of publication, country of data collection, study design, year of data collection, age range, diagnostic criteria for YOAD, total sample size, number of men, number of women, follow-up duration, and the outcome data. The outcome data were extracted for men and women

separately and included any of the following: number of cases with YOAD, prevalence, Incidence (percentage), incidence rate per 100.000 person-years, and mean age of onset. If the presented data were reported in different unit, for example, incidence rate per 1000 person-years, if possible they were converted into one of the units described above. Authors were contacted to complete missing data.

2.4 | Quality assessment

The quality of each study was assessed by two reviewers (KK, GP) using the Newcastle–Ottawa Scale (NOS).[23] The NOS was originally developed for cohort studies. An adapted version was used for the cross-sectional studies.[24] The quality assessment was performed independently by reviewers and disagreements were solved after discussion.

2.5 | Data synthesis

Few studies reported confidence intervals (CI) for prevalence and incidence. We therefore calculated these CIs for all studies using Wilson's formula to account for the low prevalence and incidence (CI_W).[25] Findings were synthesized on a narrative level. If three or more studies of the same study design were available that presented outcomes in the same units, pooled prevalence and incidence were estimated and a meta-analysis was conducted for that design and outcome. Meta-analyses were conducted using the package "metafor"[26] in R-studio v1.3[27] running with R v.4.0.2.[28] Random-effects meta-analyses were conducted to derive a pooled effect size. To test the hypothesis that women have higher prevalence and incidence of YOAD than men, men were taken as the reference group. Presented are the relative risk (RR) and 95% CI. The heterogeneity across the pooled studies was tested using the I^2-statistic. Publication bias was tested using Funnel plots and Egger's test.

3 | RESULTS

The search strategy identified 2529 and 2155 titles via Pubmed and Embase, respectively (Figure 1). After removal of duplicates, 3252 titles were screened on title and abstract and 75 studies remained for full-text screening. Eleven studies met the inclusion criteria. For two additional studies, authors were contacted to provide missing data[29,30]; sufficient information was received for one of these studies which could then also be included.[30] Thus, 12 studies were finally included in this systematic review: 6 cross-sectional studies and 6 prospective studies.

3.1 | Cross-sectional studies

The six cross-sectional studies were all conducted in different countries (Table 1). Three studies used door-to-door surveys,[22,31,32] one study matched registry data with census data,[33] one study used cross-sectional data from a cohort study,[34] and one study used cross-

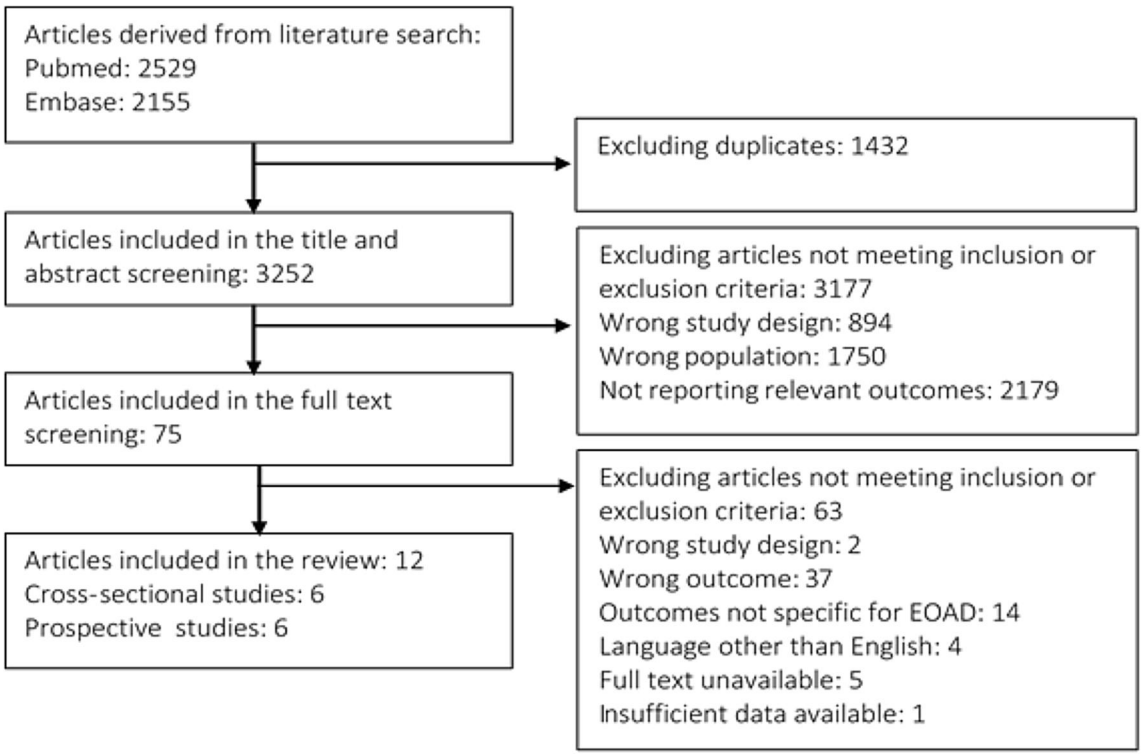

FIGURE 1 Flowchart presents the study selection

TABLE 1 Characteristics of the included studies

First author (year)	Country	Study design	Year of data collection	Diagnostic criteria	N	Age range (years)	Women (%)
Cross-sectional studies							
Borroni (2011)	Italy	Dementia registry matched with census data of the Brescia County	2001–2009	McKhann criteria	317,107	45–65	49.4
Bowirrat (2001)	Israel	Door-to-door survey among residents of three Arab villages (Umm-El-Fahm, Ara-Arára, Kafar-Qara)	1995	DSM-IV	186	60–64	79.6
El Tallawy (2019)	Egypt	Door-to-door screening in the Al Kharga district and Al Qusier city	2006–2012	DSM-IV-R	6458	50–60	47.3
Molero (2007)	Venezuela	Door-to-door survey of residents of downtown Maracaibo	1998–2000	DSM-IV	1074	55–64	63.6
Yamada (1999)	Japan	Adult Health Study, cohort study with bi-annual health examinations	1992–1996	DSM-3R	380	60–64	57.6
Zhou (2006)	China	Follow-up survey 8 years post-completion of the Nutrition Intervention Trial	1999–2000	DSM-IV + NINCDS-ADRDA	9294	50–65	61.3
Prospective studies							
Edland (2002)	United States (MN)	Medical records of the Rochester Epidemiology Project matched with census data for Rochester	1985–1989	DSM-IV	37,339	50–64	52.5
Garre-Olmo (2010)	Spain	Dementia registry matched with census data for that region	2007–2009	DSM-IV-TR	1,071,059	30–64	47.8
Kawas (2000)	United States (MD)	Baltimore Longitudinal Study of Aging, cohort study with 2-years follow-ups	1985–1998	DSM-3-R	494	55–64	34.4
Lobo (2011)	Spain	ZARADEMP cohort with baseline initiated in 1994, and follow-up in 1997 and 1999.	1994–1999	DSM-IV	4057	55+	57.7[a]
Mercy (2008)	United Kingdom	Addenbrook hospital's medical records matched with population census data for Cambridgeshire	2000-2006	NINCDS-ADRDA	75,600	45-64	approx. 50[a]
Schoenberg (1987)	United States (MN)	Mayo Clinic's medical records matched with population census data for Rochester	1960-1964	Decision rule based on diagnostic criteria[b]	18,991	29+	NR

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; NINCDS-ADRDA, Criteria proposed for the diagnosis of Alzheimer's disease in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke—the Alzheimer's disease and Related Disorders Association; NR, not reported.

[a]Exact number and/or percentage of women in the sample could not be derived for the specific age-range of interest.

[b]Decision rule: documented evidence of (1) previously normal intellectual and social function, (2) decline in intellectual and social function not caused by psychosis (including depression), (3) dementia as a predominant symptom, with definite evidence of memory impairment; (4) at least two of the following: disorientation, decline in personality and/or behavior, dyscalculia, apraxia and/or agnosia, problems with language, and impairment in judgment and/or abstract thinking; and (5) neurofibrillary tangles and/or senile plaques in the hippocampus and extratemporal cortical areas.

sectional data from a follow-up of a large-scale randomized controlled trial.[18] The most frequently used criterion for YOAD diagnosis was the DSM-IV. Sample sizes ranged markedly from 186 to 317,107.

The quality of the studies was mixed (Appendix Table B in Supporting Information S1). All studies used appropriate methods to assess the outcome (i.e., medical diagnosis using established criteria for YOAD); however, this was also an inclusion criterion. Adequate representativeness of the samples was likely for five studies, of which three presented data for the full population of their study region.[22,32,33] Of note, the population from one study region has been described to have a high prevalence of familial history of AD as well as a high frequency of consanguineous marriages, which may explain the higher prevalence of AD observed in this study.[32] Only one study had an adequate sample size (>100,000) to report reliable prevalence estimates given the low prevalence of YOAD.[33] Although none of the studies reported how sex was measured, variations in measurement are unlikely to have resulted in substantial misclassification to alter

TABLE 2 Prevalence and incidence of YOAD in women and men in each of the studies

First author (year)	Age range	*n*		*n* YOAD cases		Prevalence (% (CI_W))[a]		Incidence (% (CI_W))[a]		Incidence rate (CI)[b]	
		Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
Cross-sectional studies											
Borroni (2011)	45–65	156,751	160,356	41	40	0.03 (0.02–0.04)	0.02 (0.02–0.03)				
Bowirrat (2001)	60–64	148	38	10	0	6.76 (0.04–11.99)	0 (0–9.18)				
El Tallawy (2019)	50–60	3054	3404	5	2	0.16 (0.07–0.38)	0.06 (0.02–0.21)				
Molero (2007)	55–64	683	391	3	3	0.44 (0.15–1.28)	0.77 [0.26–2.23]				
Yamada (1999)	60–64	219	161	0	0	0 (0–1.72)	0 (0–2.33)				
Zhou (2006)	55–65	5697	3597	33	8	0.58 (0.41–0.81)	0.22 (0.01–0.44)				
Prospective studies											
Edland (2002)	50–54	7238	6821	1	2			0.01 (0–0.08)	0.03 (0.09–0.11)	13.8	29.3
	55–59	6403	6043	1	1			0.02 (0–0.09)	0.02 (0–0.09)	15.6	16.5
	60–64	5965	4869	2	2			0.03 (0.01–0.12)	0.04 (0.01–0.15)	33.5	41.1
Garre-Olmo (2010)	30–64	511,498	559,562	38	23			0.007 (0.005–0.010)	0.004 (0.003–0.006)	7.4 (5.3–10.2)	4.1 (0.8–6.1)
Kawas (2000)	55–64	170	324	1	0			0.59 (0.10–3.26)	0 (0–1.17)	132.0	0
Lobo (2011)	55–59	NR	NR	0	0					0 (0–1022)	0 (0–1182)
	60–64	NR	NR	0	0					0 (0–196)	0 (0–214)
Mercy (2008)[c]	45–64	37,800	37,800	10	9			0.03 (0.01–0.05)	0.02 (0.01–0.05)	4.41	3.97
Schoenberg (1987)	30–59	NR	NR	2	1					5.6 (0.7–20.2)	3.1 (0.1–17.2)

Abbreviations: CI, confidence interval; NR, not reported; YOAD, young-onset Alzheimer's disease.

[a]Prevalences and incidences were calculated based on reported number of participants and YOAD cases in women and men. To account for the low prevalences and incidences, confidence intervals were calculated using Wilson's formula for proportions (CI_W).[25]

[b]Incidence rates (cases per 100,000 person-years) could not be calculated from the derived data and were copied from the original studies.

[c]Mercy (2008) did not present exact numbers of women and men in the region. Presented numbers are based on the information that there were 75,600 citizens aged 45–64 years, with balanced distribution of women and men.[21]

the findings. None of the studies accounted in their analyses for differences between women and men in potential confounding factors, such as level of education and lifestyle.

Across the six studies, 92 out of 166,552 women and 63 out of 167,947 men were classified as having YOAD (Table 2). The pooled prevalence was 0.4% (95% CI = 0.1–2.1, I^2 = 98%) in women and 0.2% (95% CI = 0–1.2, I^2 = 92%) in men (Figure 2). The relative risk for YOAD was not statistically significant higher in women than in men (pooled RR = 1.54, 95% CI = 0.69–3.44, I^2 = 38%) (Figure 3). One study reported the average age of onset, but for the total group only (mean age = 60.9, SD = 3.8).[33] The Egger's test did not suggest funnel plot asymmetry suggesting absence of publication bias (Appendix Figure A in Supporting Information S1).

3.2 | Prospective studies

The six prospective studies were conducted in three different countries (Table 1). Four studies used registry or medical records data matched with census data[20,21,30,35] and two studies used

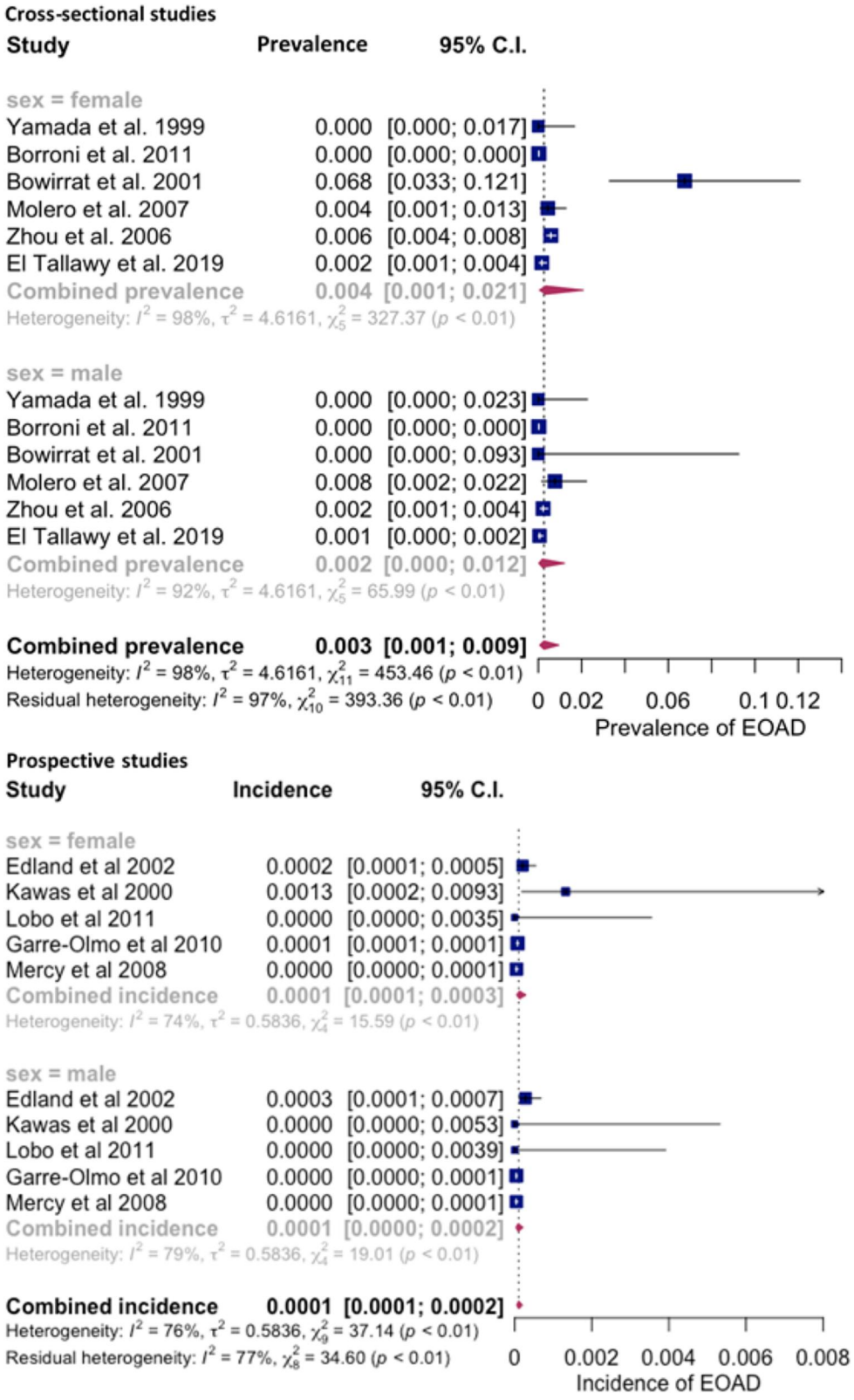

FIGURE 2 Pooled proportions for the prevalence (top) and incidence (bottom) of young-onset Alzheimer's disease in women and men

cohort designs.[36,37] The most frequently used criteria for diagnosis were the DSM criteria. Sample sizes ranged markedly from 494 to 1,071,059.

The quality of the studies was good for five of the six studies (Appendix Table B in Supporting Information S1). In line with our inclusion criteria, all studies used appropriate methods to assess the

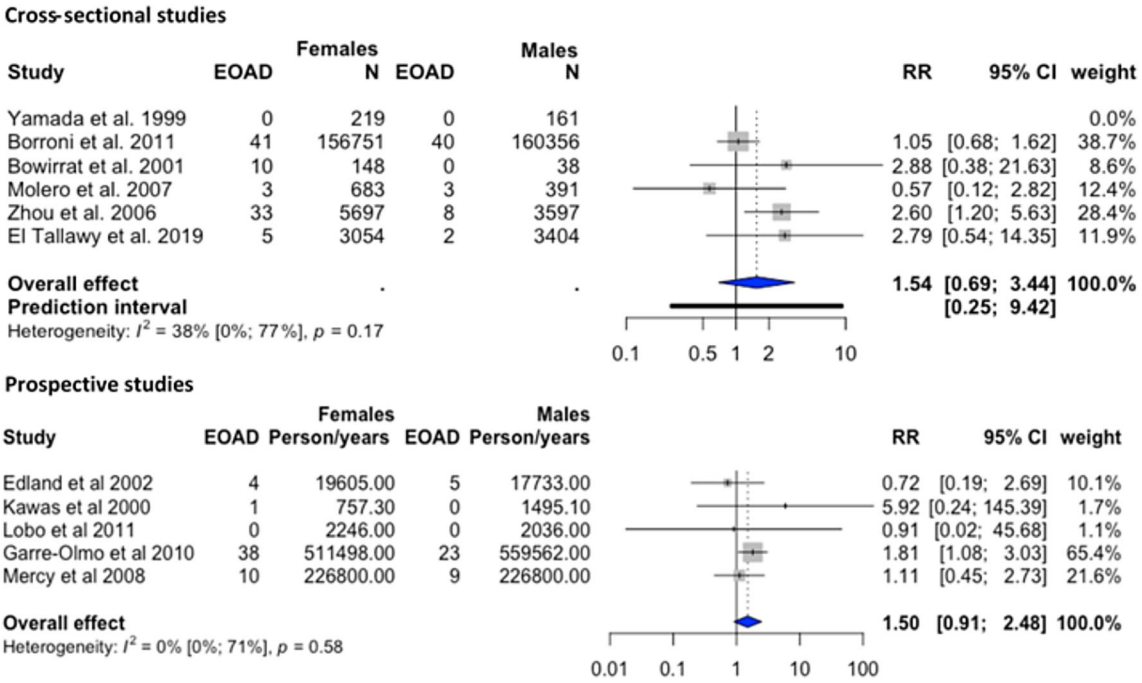

FIGURE 3 Meta-analysis of the incidence of young-onset Alzheimer's disease in women and men in cross-sectional studies (top) and prospective studies (bottom). Note that for the prospective studies, the incidence is based on the number of cases per person-years. Hence these numbers differ from the numbers presented in Table 2

outcome (i.e., medical diagnosis using established criteria for YOAD). All studies used long enough follow-up duration for the outcome to occur (i.e., 4+ years). The four studies that used census data had adequate follow-up,[20,21,30,35] but in the two cohort studies, the drop-out was selective and greater than 20%.[36,37] Adequate representativeness of the samples was likely for five studies, of which four presented data for the full population of their study region.[20,21,30,35] Although none of the studies reported how sex was measured, variations in measurement is unlikely to have resulted in substantial misclassification to alter the findings. None of the studies accounted in their analyses for differences between women and men in potential confounding factors, such as level of education and lifestyle.

Across the five studies that reported sufficient data to calculate incidence, 53 out of 569,074 women and 37 out of 615,419 men were classified as having YOAD (Table 2). Pooled across these studies, the incidence was 0.02% (95% CI = 0.01–0.08, I^2 = 74%) in women and 0.01% (95%CI = 0-0.05, I^2 = 83%) in men (Figure 2). Sex-specific Incidence rates were reported in five studies and ranged from 0 to 132 per 100,000 person-years in women and from 0 to 41 per 100,000 person-years in men (Table 2). The relative risk for YOAD was not statistically significant higher in women than in men (pooled RR = 1.50, 95% CI = 0.91–2.48, I^2 = 0%) (Figure 3). One study could not be included in the meta-analyses: that study reported higher incidence rates in women (5.6 per 100,000 person-years, 95% CI = 0.7–20.2) than men (3.1 per 100,000 person-years, 95% CI = 0.1–17.2).[35] One study reported the average age of onset, but for the total group only and including all types of dementia (mean age = 58.1, SD = 7.3).[30] The Egger's test did not suggest funnel plot asymmetry suggesting absence of publication bias (Appendix Figure A in Supporting Information S1).

4 | DISCUSSION

The findings of this systematic review show that the pooled point estimates for prevalence and incidence of YOAD are higher in women than men, but with wide, overlapping CIs. The differences in prevalence and incidence of YOAD between women and men were not statistically significant. However, the magnitude of the relative risks suggests a higher risk in women than in men. The low overall prevalence and incidence (<1%) mean that very large samples are required to reliably detect a statistically significant difference. In 10 of the 12 studies, the samples were relatively small. Subsequently, even the meta-analyses including pooled data of 334,499 (cross-sectional) and 1,184,493 (prospective) persons may have been underpowered to detect a statistically significant difference. Larger, purposely designed studies would be ideal but too expensive. Country-wide registry data or GP-records linked with census data may be a cost-efficient design to verify the current findings.

The relative risks of 1.50 (95% CI = 0.91–2.48) for the incidence in women versus men is in the same range as that found in a systematic review that examined sex differences in AD in older adults (meta-analysis of seven studies with participants aged 60+ years, odds ratio = 1.56, 95% CI = 1.16–2.10).[2] A more recent review on the prevalence and incidence of AD in older adults (aged 60+ years)

noted that all 22 studies that examined sex differences found higher prevalence and incidence in women than in men, but these differences were not statistically significant in any of the studies.[38] No meta-analysis was done. A study that was excluded from the current review based on its case–control design included a large sample of 732,853 participants with and without diabetes. Within the non-diabetic sample (n = 366,427), the incidence for YOAD was significantly higher in women (0.22, 95% CI = 0.21–0.22) than men (0.15, 95% CI = 0.15–0.16).[19] Also, in the total sample including participants with and without diabetes and all ages, being female was associated with a greater risk of AD (hazard ratio = 1.3, 95% CI = 1.25–1.37).[19] Thus, while statistically significant differences cannot always be detected, the finding that women have greater risks of developing AD than men appears consistent across studies and age groups. The similar relative risk in women compared with men for YOAD and LOAD makes it less likely that the higher lifetime incidence of AD is solely explained by longer life expectancy in women. Biological, socio-economic and lifestyle factors likely contribute to sex and gender differences in the prevalence and incidence of AD. Whether these factors also play a role in sex and gender differences in YOAD is less clear. There is evidence for genetic risk factors of YOAD,[39] but studies examining associations between social and lifestyle factors and YOAD are sparse.

Only two studies reported the average age of onset of YOAD, which was 60.9 (SD = 3.8) years in a cross-sectional study[33] and 58.1 (SD = 7.3) years in a prospective study.[30] As these studies reported the average age of onset for the total sample only, we were unable to compare the average age of onset between women and men. Given that the young age of onset is a key feature of YOAD, it would be of interest to explore sex differences in this characteristic of the pathology. Further, it is worth noting that the age ranges also varied significantly between studies. While some samples included adults from the age of 30, others restricted their age range to 60–64 years. If there are sex differences in the age of onset, we cannot disregard the possibility that a restrictive age category may be biased toward cases in one sex over the other.

Strengths of this review include the thorough screening and inclusion of studies that presented relevant data even if the women–men comparison was not a primary focus of that study. Also, authors were contacted for studies that provided insufficient data. This approach meant that we were able to include a relatively large number of studies for this specific research aim and understudied population. When interpreting the current findings, the following limitations need to be considered. First, as explained above, the sample sizes of many of the included studies was too small to provide reliable estimates given the low prevalence and incidence of YOAD in the population. One study with a reasonably large sample size (n = 75,600) did not present the total numbers of men and women.[21] To maximize the number of studies to be included in the meta-analyses, we approximated these numbers based on the information in that paper that the ratio of women and men was balanced. Sensitivity analyses in which we repeated the meta-analyses leaving out this study showed similar results (RR = 1.63, 95% CI = 0.83–3.21). Second, the heterogeneity across studies was high for the pooled prevalence and incidence. Post-hoc sensitivity analyses leaving out each of the studies one-by-one did not substantially lower the heterogeneity (prevalence: I^2 > 90%, incidence: I^2 > 66%). Hence it remains unclear what may explain the high heterogeneity and the pooled prevalence and incidence should be interpreted with caution. Third, the quality of the studies varied and two quality criteria were met by none of the studies. None of the studies defined how sex was measured, although variation in methods is unlikely to have an impact on the current findings. None of the studies adjusted for potential confounding factors of the association between sex and YOAD. The women-men comparison was often not the main focus in the analysis and studies that used registry or medical records data may not have information on potential confounders, such as education and lifestyle. Hence, the pooled estimates and relative risks presented in this review are based on crude, unadjusted data. Finally, the Eggers' test did not indicate the presence of funnel plot asymmetry and thus publication bias (Appendix Figure A in Supporting Information S1). But, as there were fewer than 10 studies for each meta-analysis, Egger's test may lack the statistical power to detect publication bias. No strong conclusions can, therefore, be drawn regarding potential publication bias.

In conclusion, given the low prevalence and incidence, wide confidence intervals and lack of statistical significance, no firm conclusions can be drawn on the existence of sex differences in YOAD. However, the obtained pooled relative risks cautiously suggest that women are more likely than men to develop YOAD. These findings make it less likely that the higher lifetime risk of AD is fully explained by the greater life expectancy in women than men. Further research using large databases are required to verify these findings.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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