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FEATURED ARTICLE

Global incidence of young-onset dementia: A systematic review and meta-analysis

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Abstract

Introduction: Reliable data on the incidence rates for young-onset dementia (YOD) are lacking, but are necessary for research on disease etiology and to raise awareness among health care professionals.

Methods: We performed a systematic review and meta-analysis on population-based studies on the incidence of YOD, published between January 1, 1990 and February 1, 2022, according to Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines. Data were analyzed using random-effects meta-analyses. Results were age-standardized, and heterogeneity was assessed by subgroup analyses and meta-regression.

Results: Sixty-one articles were included. Global age-standardized incidence rates increased from 0.17/100,000 in age 30 to 34 years, to 5.14/100,000 in age 60 to 64 years, giving a global total age-standardized incidence rate of 11 per 100,000 in age 30 to 64. This corresponds to 370,000 new YOD cases annually worldwide. Heterogeneity was high and meta-regression showed geographic location significantly influenced this heterogeneity.

Discussion: This meta-analysis shows the current best estimate of YOD incidence. New prospective cohort studies are needed.

KEYWORDS
incidence, meta-analysis, worldwide, young-onset dementia

1 | INTRODUCTION

Dementia is usually seen as a disease of older adults, but it also occurs in people younger than the age of 65 years, which is referred to as young-onset dementia (YOD).[1] YOD has a large impact on both the persons with dementia and their caregivers.[2] A diagnosis of YOD can be notoriously difficult, as patients present with different signs and symptoms, and health care professionals may not initially think of a neurodegenerative cause. First symptoms of YOD more often include difficulties in the behavioral, language, visual, or motor domains.[3,4] This is reflected by an average time between symptom onset and a diagnosis of YOD of 4.4 years, compared to 2.8 years for late-onset dementia (LOD).[5]

Information on the epidemiology in general, and the incidence of YOD in particular, is imprecise and scarce.[6] The few previous reviews on the epidemiology of YOD have focused mainly on the prevalence,

with one review also including incidence studies.[6] In a recent meta-analysis, we estimated the global age-standardized prevalence of YOD to be 119.0 per 100,000 persons, corresponding to 3.9 million people 30 to 64 years of age living with YOD.[7] No meta-analysis on the incidence of YOD has been conducted so far, which could yield more precise estimates or point toward important sources of variation therein. This is important for studying the etiology and risk factors of YOD, as well as for initiating prevention strategies. Incidence is also important for the planning of diagnostic services of YOD and improving the awareness in health care professionals.

Two widely cited incidence studies on YOD, both based on individual cohorts, found that the incidence doubles every 5 years of age[8] and no differences were observed between men and women.[9] Both studies showed that the incidence was highest for Alzheimer's disease (AD), but they differed in incidence rates for vascular dementia (VaD), frontotemporal dementia (FTD), and secondary dementias. A recent study from Kvello-Alme et al.[10] on the incidence of YOD in Norway reported higher incidence rates than previous studies, especially in the lower age ranges.

Our aim was to assess the current incidence of YOD through a systematic review and meta-analysis of all available data worldwide in order to obtain reliable estimates of the global incidence of YOD, and to investigate differences in incidence between sex and age groups and study designs.

RESEARCH IN CONTEXT

1. **Systematic review**: We performed a literature search in PubMed, Embase, CINAHL and PsychINFO on population-based studies on the incidence of dementia in people under the age of 65 years. We found no previous meta-analyses on the incidence of young-onset dementia.
2. **Interpretation**: We included 61 articles in this review. Meta-analyses showed age-standardized incidence rates increased from 0.17/100,000 person-years in age 30-34 years, to 5.14/100,000 person-years in age 60-64 years, resulting in a total incidence rate of 11/100,000 person-years in age 30-64 years. This corresponds to an annuals incidence of 370,000 new cases every year. Subgroup analyses showed similar incidence rates between men and women, and incidence rates were highest for Alzheimer's disease, followed by vascular dementia and frontotemporal dementia. Meta-regression showed geographical location significantly influenced the heterogeneity between studies.
3. **Future directions**: Annually, 370,000 people are newly diagnosed with young-onset dementia. This shows the public health impact is high, and it should raise awareness in healthcare professionals. Future studies should be aimed at the current knowledge gaps on subtypes of dementia, and difference in incidence between different ethnic groups.

2 | METHODS

2.1 | Search strategy and selection criteria

This systematic review and meta-analysis was conducted according to the MOOSE (Meta-analyses of Observational Studies in Epidemiology) guidelines.[11] PubMed, Embase, CINAHL, and PsychINFO were searched for articles that have been published between January 1, 1990 and March 31, 2020. An update of the search strategy was performed to include new articles published between March 31, 2020 and February 1, 2022. Population-based studies on the prevalence and incidence of YOD were eligible for inclusion (eMethods A). This review reports only on the incidence studies. A systematic review on the prevalence studies has been published published.[7] No language restrictions were applied, and, if necessary, studies were translated. Authors were contacted at least twice if articles were not available, or if additional data were needed. Reference lists of included studies and previous systematic reviews were checked manually for additional references. The study is registered with The International Prospective Register of Systematic Reviews (PROSPERO), number CRD42019119288. It is part of the larger PRECODE (Prevalence Recognition and Care pathways in young Onset Dementia) project on the prevalence, incidence, definition, and care pathways of YOD.

Articles were independently screened by two researchers (SH and KP) on title and abstract, and next on full texts. Cohen's kappa for interrater agreement was substantial (0.67).[12] Disagreements were resolved with the help of a third researcher (SK). When multiple articles reported on the same cohort, the article with the most elaborate data (e.g., largest sample size, most relevant age range) was included in this review.

To be eligible for inclusion, studies had to be population based. Symptom onset of dementia had to be before the age of 65 years. However, all studies in this review used 65 at age of diagnosis rather than age at symptom onset as inclusion criteria. The diagnosis had to be according to acceptable criteria (e.g., ICD, DSM, NINCDS-ADRDA), or by a clinician when these criteria were not described.

Studies conducted in specific patient groups (e.g., HIV patients) or care homes, or used mortality data were excluded for this review. Studies were included when they used registers from either hospital, primary care, or insurance companies, or were conducted in specific demographic subpopulations (e.g., women only, certain age ranges), since these could be included in subgroup meta-analyses. Studies were eligible for inclusion when they were published from 1990 onward. Studies with a study period before 1990 but publication after 1990 were included.

2.2 | Data analysis

Data extraction was performed by one researcher (SH) and checked by a second researcher (KP), using a standard data collection form.

Quality assessment was performed independently by the two researchers using the Risk of Bias Tool.[13] This tool was adjusted slightly to check the quality of incidence studies (eMethods B). Items were defined as "high risk" when information about this item was not described clearly in the article.

Meta-analyses were performed using R version 3.6.6, where incidence rates were pooled with random-effect meta-analysis using the Poisson distribution. A continuity correction was applied to studies with zero cases of YOD, by adding a constant of 0.5 to the denominator of the incidence rate.[14] Meta-analyses were performed on 5-year age bands beginning at age 30, since pooling all ages together would give biased results, due to the overrepresentation of higher age ranges. Subgroup analyses based on sex, subtypes of dementia, and study designs were conducted. The study designs were categorized as "cohort studies using register linkage to identify people with YOD," "cohort studies using active screening to identify people with YOD," and "retrospective register-based studies." When possible, analyses were age-standardized for the World Standard Population (WSP),[15] the European Standard Population (ESP),[16] and the United Stated Standard Population (USP)[17] using direct standardization. Studies were excluded from the meta-analysis when they reported incidence rates only in specific subpopulations, or when number of cases and person-years both were not reported.

Heterogeneity between studies was assessed with I^2, indicating what amount of the total variance is explained by between-study differences. Meta-regression was performed to analyze which aspects significantly influenced the heterogeneity between studies. Parameters investigated in the meta-regression were age range, size of the study, diagnostic criteria used, study design, and geographic location (i.e., the different world regions).

Funnel plots were visually assessed for symmetry to identify potential small study bias (see eMethods C).

Due to the nature of the study, no informed consent was necessary.

3 | RESULTS

A total of 22,191 articles were found from the original and updated search, and after removal of duplicates, 14,451 remained for screening. After screening titles and abstracts, 1022 articles remained for full-text screening. Of these, 61 articles reported on the incidence of YOD and were included in this systematic review (eFigure A).[9,10,18–76]

The quality of all studies was sufficient (Table 1 and eTable A), with lower ratings for register-based studies because of their passive case-finding methods. Studies differed with regard to several methodological aspects, with wide variations in included age ranges, diagnostic criteria, and study design.

Studies were conducted in different world regions, with the majority coming from Europe (34 studies), followed by North America (10 studies) and Asia (10 studies), and Oceania (2 studies) and South America (5 studies). No incidence studies on YOD were found for Africa. Figure 1 shows the world map of included studies. Due to insufficient data from studies outside Europe, no subgroup analysis on ethnicity could be performed.

3.1 | All-type dementia

Forty-seven articles reported incidence rates on all-type YOD (Table 1). Of these, five articles[9,21,30,31,48] could not be included in the meta-analysis, since they did not provide number of cases and person-years, and one article[29] reported incidence rates only for a specific ethnic subpopulation (see eTable B for an overview of included articles by analysis).

Table 2 shows the age-standardized incidence rates per 5-year age band, together with the crude incidence rates. The global age-standardized incidence rate of people aged 30 to 64 was 11 per 100,000 person-years worldwide (see Table 2), corresponding to ≈370,000 (95% confidence interval [CI] corresponding to 230,000 to 660,000) new cases each year worldwide. In Europe the age-standardized incidence rate was 14 per 100,000 person-years, whereas in the United States the incidence rate was 11 per 100,000 person years.

The crude annual incidence rate of YOD in the lowest age group 30 to 34 was 0.9 per 100,000 person-years (95% CI 0.1–4.6) and in the highest age group 60 to 64 56.6 per 100,000 person-years (95% CI 39.7–80.7) (see Table 2). On average, incidence rates doubled every 5 years of age, starting from the age of 40 (see Figure 2).

A meta-regression was performed on the crude incidence rates, with age range, study size, diagnostic criteria, study design, and geographic location as potential moderators of between study differences in separate univariable analyses. Geographic location, study size, and study design significantly influenced the heterogeneity between studies. Studies from North America, South America, and Oceania reported significantly higher incidence rates than studies from Europe (see Table 3). Prospective register studies reported significantly lower incidence rates compared to studies with active screening and studies with >100,000 person-years reported significantly lower incidence rates compared to studies with <5000 person-years. In multivariable regression only geographic location remained significant, with an R^2 of 84.2% (data of multivariable regression not shown).

Stratified meta-analysis for men and women showed that incidence rates were generally similar and the CIs overlapped greatly (see Figure 3 and eTable C). For men, the crude incidence rate was 38.3 per 100,000 person-years (95% CI 3.9–377.0), 0.3 per 100,000 person-years (95% CI 0.0–1.9) in the lowest age group 30 to 34 and 60.8 per 100,000 person-years (95% CI 15.9–231.5) in the highest age group 60 to 64. For women, the overall crude incidence rate was 35.9 per 100,000 person-years (95% CI 5.7–226.6), 0.6 per 100,000 person-years (95% CI 0.1–2.4) in the lowest age group 30 to 34 and 51.1 per 100,000 person-years (95% 12.1–215.6) in the highest age group 60 to 64. After the age of 60 the incidence rate for men increased visually more steeply than for women; however, this has not been statistically tested.

TABLE 1 Study characteristics of the included incidence studies

Study characteristics	Dementia type[a]			
	All-type YOD (N = 47)	Alzheimer's disease (N = 15)	Vascular dementia (N = 9)	Frontotemporal dementia (N = 8)
Study period				
<1990	2	3	2	0
1990-1999	3	5	2	1
2000-2009	7	1	0	2
2010-2019	29	4	4	5
unknown	5	2	1	0
Age ranges				
<30-64	6	1	1	0
30-64	6	3	2	2
35-64	1	0	0	0
40-59	0	1	1	1
40-64	6	2	1	1
45-64	6	2	0	2
50-59	2	0	1	0
50-64	7	1	3	2
55-64	3	5	0	0
60-64	10	0	0	0
Sample size				
<5000	6	6	1	0
5000-50,000	10	1	4	1
50,000-100,000	4	0	0	0
>100,000	17	4	3	6
Unknown	10	4	1	1
Diagnostic criteria				
ICD[b]	22	1	1	2
DSM[c]	16	8	4	3
Combination of criteria[d]	4	4	2	1
Other	5	2	2	2
Design				
Prospective studies				
Active screening	11	7	4	0
Register linkage	13	1	2	2
Retrospective studies				
Register-based	23	7	3	6
Mean quality assessment score (range)	7.45 (5–10)	7.56 (6–10)	7.38 (6–10)	7.57 (6–9)
World region				
Europe	28	10	6	6
North America	6	1	0	1
Asia	7	3	1	1
South America	3	1	1	0

(Continues)

TABLE 1 (Continued)

Study characteristics	Dementia type[a]			
	All-type YOD (N = 47)	Alzheimer's disease (N = 15)	Vascular dementia (N = 9)	Frontotemporal dementia (N = 8)
Oceania	2	0	0	0
Africa	0	0	1	0

Data shown is number of studies.
[a]Studies may be reported multiple times if they are included in multiple meta-analyses (all-type, Alzheimer's disease, vascular dementia, frontotemporal dementia)
[b]ICD = International Classification of Diseases
[c]DSM = Diagnostic and Statistical Manual of Mental Disorders
[d]Other criteria were NINCDS-ADRDA (National Institute of Neurological and Communicative Diseasess and Stroke - Alzheimer's Disease and Related Disorders Association), NINDS-AIREN (National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherché et l'Enseignement en Neurosciences) or other register codes

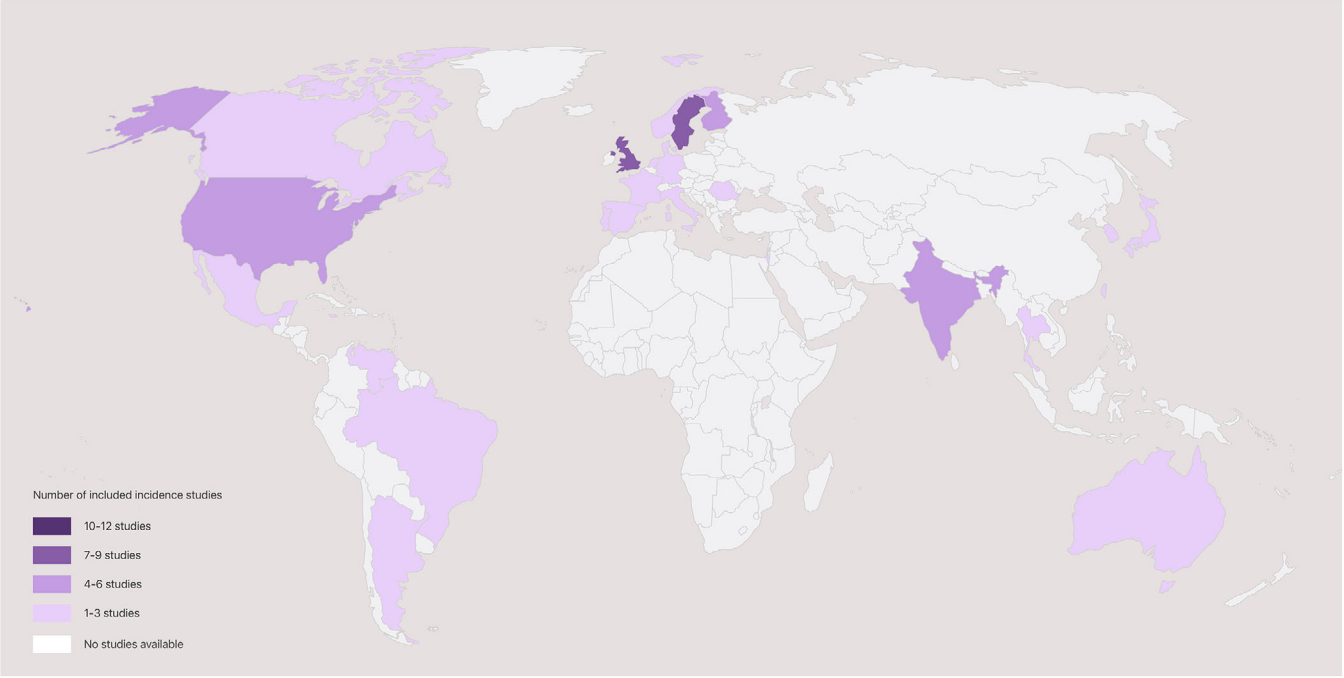


FIGURE 1 World map of included studies

TABLE 2 Crude rates and age-standardized incidence rates per 100,000 person-years for 5-year age bands

Age range	All-type dementia				
	Number of articles	Crude rate	Global[a]	Europe[a]	United States[a]
30-34	5	0.9 (0.1 – 7.2)	0.17 (0.02-1.33)	0.13 (0.01-1.01)	0.14 (0.02-1.12)
35-39	6	1.0 (0.2 – 4.8)	0.17 (0.03-0.84)	0.15 (0.03-0.70)	0.18 (0.04-0.85)
40-44	9	3.2 (1.0 – 9.9)	0.51 (0.16-1.59)	0.47 (0.15-1.47)	0.57 (0.18-1.78)
45-49	10	5.2 (2.0 – 13.8)	0.77 (0.29-2.03)	0.77 (0.30-2.04)	0.82 (0.32-2.18)
50-54	12	13.6 (7.8 – 23.7)	1.78 (1.02-3.10)	1.97 (1.13-3.44)	1.87 (1.07-3.26)
55-59	15	24.7 (17.4 – 35.1)	2.74 (1.93-3.89)	3.46 (2.43-4.91)	2.63 (1.85-3.73)
60-64	25	56.6 (39.7 – 80.7)	5.14 (3.60-7.32)	7.46 (5.23-10.63)	4.82 (3.38-6.87)
Total (30–64)	41	35.3 (24.0 – 51.7)	11.28 (7.06-20.11)	14.40 (9.28-24.20)	11.03 (6.85-19.80)

[a]Age-standardized incidence rates were calculated by means of direct standardization against the World Standard Population (global), European Standard Population (Europe) and United States Standard Population (United States). For each age band, we multiplied the crude incidence rate with the number of people in that age group in the standard population, and divided this by the total number of people aged 30 to 65 years in the standard population.

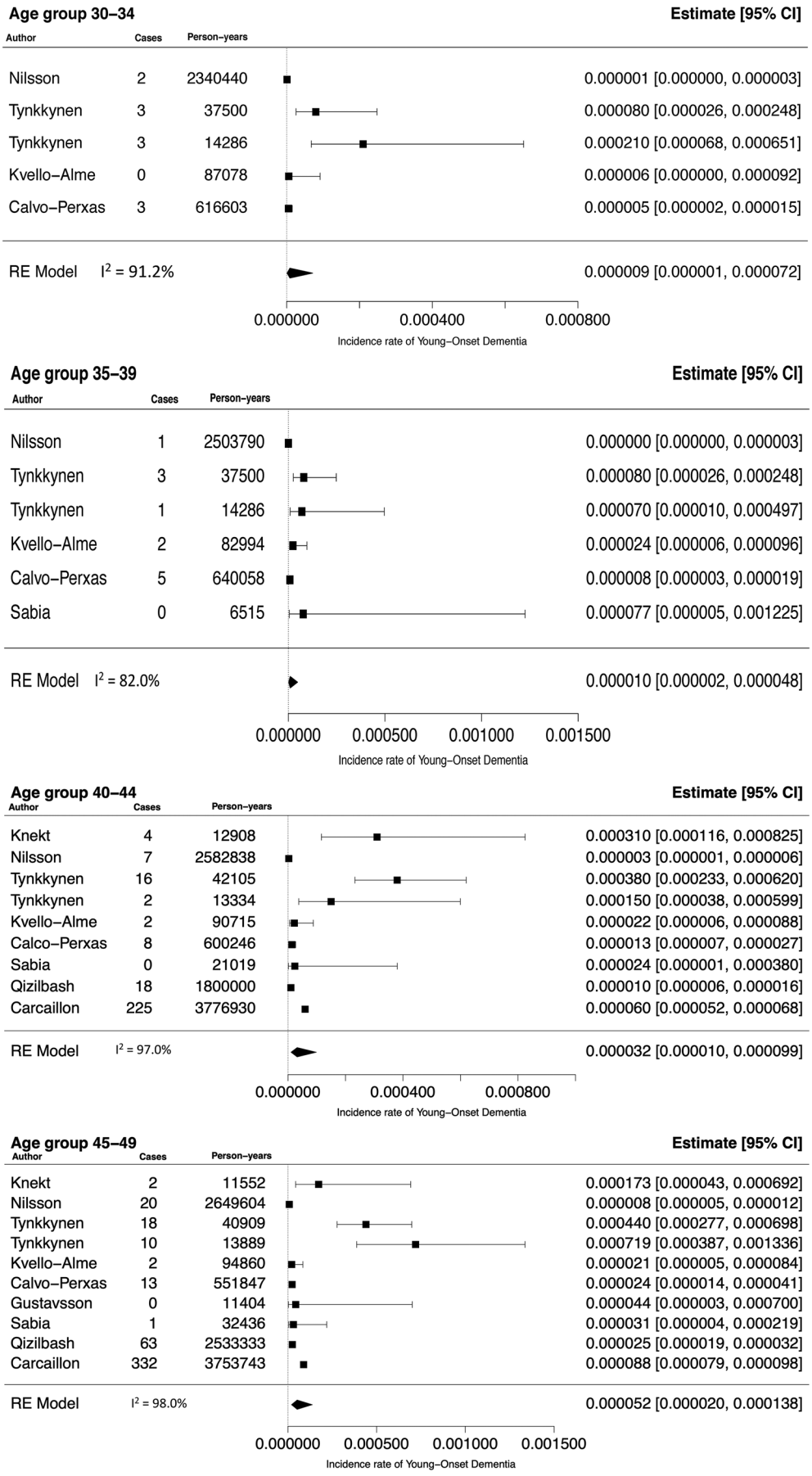
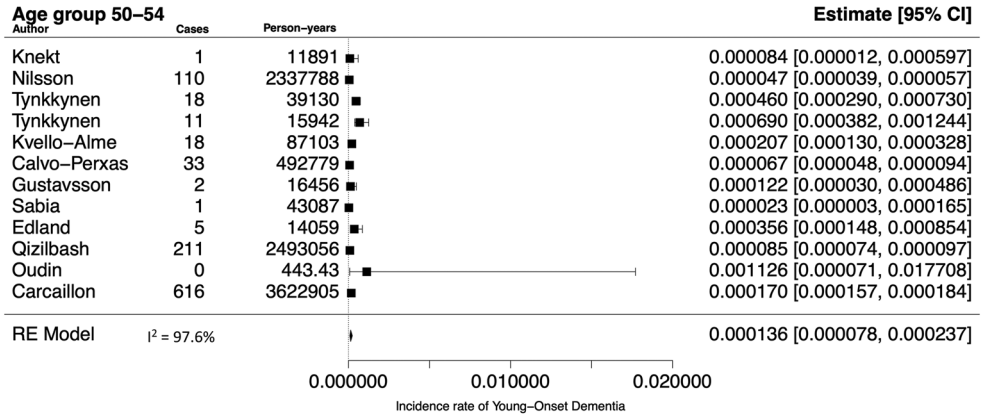
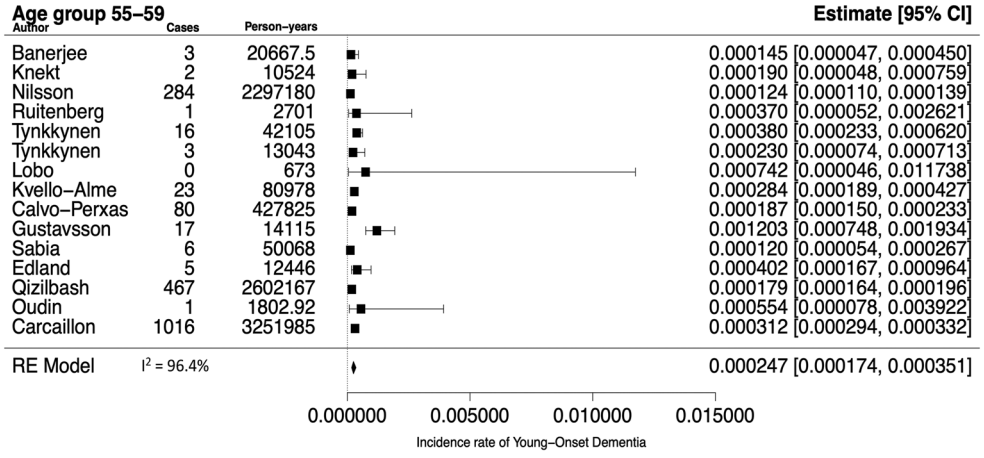


FIGURE 2 Forest plots 5-year age bands for all-type young-onset dementia (YOD)





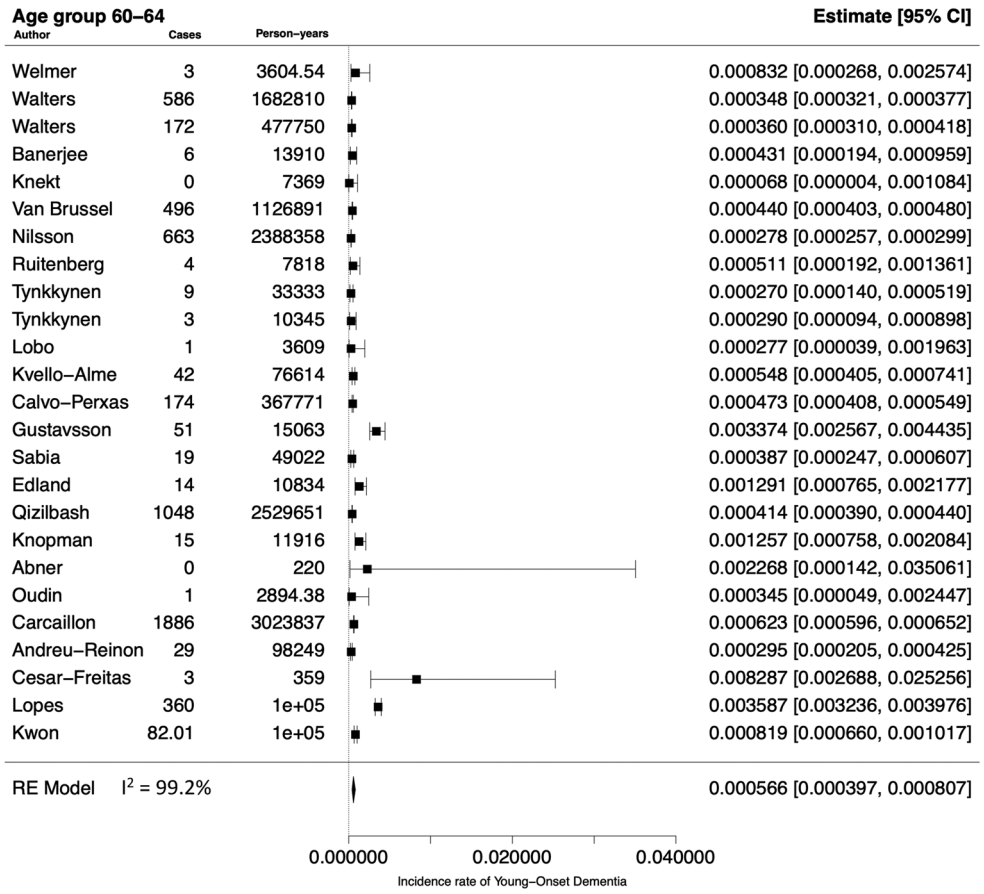


FIGURE 2 Continued

TABLE 3 Univariable random-effect analysis of the meta-regression

	Category	Coefficient	*P*-value
Age range	0-64	Reference	
	30-64	−0.8 (-2.3 to 0.6)	0.2737
	35-64	−0.6 (-3.4 to 2.1)	0.6525
	40-64	−0.2 (-1.8 to 1.5)	0.8551
	45-64	1.6 (0.0 to 3.1)	0.0495
	50-64	1.2 (-0.5 to 3.0)	0.1669
	55-64	−0.1 (-1.9 to 1.7)	0.9164
	60-64	1.4 (-0.1 to 2.9)	0.0669
Study size	<5000	Reference	
	5000-50,000	−1.3 (-3.0 to 0.5)	0.1472
	50,000-100,000	−1.1 (-3.1 to 0.9)	0.2938
	>100,000	−1.9 (3.4 to -0.3)	**0.0199**
Diagnostic criteria	DSM	Reference	
	ICD	0.2 (-0.8 to 1.1)	0.7018
	Other	0.6 (-1.0 to 2.2)	0.4840
Study design	Active screening	Reference	
	Prospective register study	−1.9 (-3.1 to -0.7)	**0.0018**
	Retrospective register study	−1.0 (-2.1 to 0.1)	0.0614
World region[a]	Europe	Reference	
	Asia	0.5 (-0.3 to 1.3)	0.1771
	North America	1.3 (0.5 to 2.1)	**0.0013**
	South America	2.5 (1.5 to 3.4)	**<0.0001**
	Oceania	2.6 (1.4 to 3.8)	**<0.0001**

Data are shown as coefficient (95% CI) *P*-value. The coefficients represent the difference in incidence rate between that group and the reference group.

[a]Africa was not included in the meta-regression since no data was available for this continent

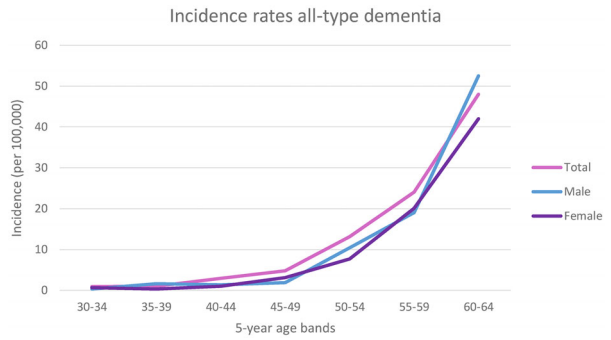


FIGURE 3 Pooled incidence rates of 5-year age bands for the total incidence (male and female), incidence rate for males and incidence rate for females.

Register-based retrospective studies were performed across all age ranges. Prospective cohort studies using register linkage to identify YOD cases were conducted in 35 years of age and older, whereas prospective cohort studies using active screening were conducted only in groups 55 years of age and older. Consequently, differences by study design could be explored in the later age groups only. In the age bands 55 years and older, 5-year incidence rates were highest for prospective cohort studies using active screening, followed by prospective cohort studies using register linkage, and finally retrospective register-based studies (eTable C).

3.2 | Dementia subtypes

Separate meta-analyses were performed for the dementia subtypes AD, VaD, and FTD.

A total of 15 articles reported on the incidence of AD. Of these, 10 could be included in the meta-analysis. Four articles did not report number of cases and person-years. Information on AD incidence was available only for the total incidence (age 30 to 64 years), and for 5-year age bands starting from age 50 onward. As a result, it was not possible to age-standardize rates. Crude incidence rates were 2.5 per 100,000 person-years (95% CI 0.6-9.3) in the age band 50 to 54 years, 8.2 per 100,000 person-years (95% CI 6.0–11.1) in the age band 55 to 59 years, and 35.8 per 100,000 person-years (95% CI 9.8–131.0) in the age band 60 to 64 years. The total crude incidence rate of AD was 9.8 per 100,000 person-years (95% CI 2.8-33.5) (eTable C). Differences in incidence rates by sex could be assessed, showing a higher incidence rate in women (12.7/100,000) than in men (5.4/100,000).

Nine articles reported on the incidence of VaD, one of which did not report both number of cases and person-years and was therefore excluded from meta-analysis. Incidence rates were pooled for the total incidence, and 5-year age bands starting from the age of 55. In the latter, incidence rates were 2.8 per 100,000 person-years (95% CI 1.6–4.9) for the age band 55 to 59 years and 7.2 per 100,000 person-years (95% CI 4.9–10.5) for the age band 60 to 64 years. When analyzing the crude incidence rate for VaD, the incidence rate was 4.0 per 100,000 person-years (95% CI 0.8–19.4). Incidence rates differed only slightly between women (6.0/100,000) and men (8.9/100,000).

Eight articles reported on the incidence of FTD, one of which did not report both number of cases and person-years and was therefore excluded from meta-analysis. Incidence rates were pooled only for the total incidence. The crude incidence rate was 1.1 per 100,000 person-years (95% CI 0.4-2.9) (eTable C). No information on sex differences was available.

4 | DISCUSSION

Based on this systematic review and meta-analysis with 61 population-based studies, the overall age-standardized annual incidence rate in 30- to 64-year-olds was 11 per 100,000 worldwide, corresponding to an annual incidence of 370,000 new cases worldwide using the world population of 2019 of people 30 to 64 years of age according to the United Nations (UN).[77] Incidence rates globally were higher, with increasing age from 0.17 per 100,000 person-years in people 30 to 34 years of age to 5.14 per 100,000 person-years in the age range 60 to 64

years. This difference was also seen in the United States, and in Europe the difference was slightly steeper.

Incidence rates were highest for dementia due to AD, followed by VaD and FTD. Incidence rates increased more steeply for men compared to women. Other subgroup analyses showed that incidence rates were highest in prospective cohort studies that used active screening, followed by prospective cohort studies that used record linkage, and lowest for retrospective register-based studies. Although heterogeneity was high, only geographic location was significant in the meta-regression on heterogeneity, with studies conducted outside Europe reporting significantly higher incidence rates than studies conducted in Europe.

To our knowledge, no previous meta-analysis on the incidence of YOD has been performed, but most cited incidence studies on YOD from Garre-Olmo et al. and Mercy et al. reported annual incidence rates of 13.4 per 100,000 person-years in the 30- to 64-year age range, and 11.5 per 100,000 person-years in the 45- to 64-year age range, respectively.[8,9] These are crude incidence rates rather than age-standardized rates and are lower than the crude rates of this meta-analysis (35.3/100,000 person-years in the age range from 30 to 64). Our crude incidence rates were also higher compared to a recent study by Kvello-Alme et al.[10] conducted in Norway, which reported an annual incidence rate of 14.8 per 100,000 person-years in the age range 30 to 64 years, and 25.0 per 100,000 person-years in the age range 45 to 64 years. It is important to note that these studies were retrospective register-based studies, which generally report lower incidence rates compared to prospective cohort studies with either active screening or register linkage. In addition, none of the studies age-standardized their results, so comparison of incidence rates can only be made based on the crude results.

A report from the World Health Organization (WHO) from 2012 studied incidence of dementia starting from age 60. They found an incidence of 310 per 100,000 person-years in the age group 60 to 64 years,[78] which is higher than the incidence of 56.6 per 100,000 person-years found in this review. However, their analysis was based on 3 studies of the age range 60 to 64 years, whereas our meta-analysis was based on 21 studies of the age range 60 to 64 years. Our lower incidence rates might be due to the inclusion of more studies, leading to a more nuanced result, since our 21 studies also included more register-based studies. Another review from Wolters et al. on the incidence of dementia from the age of 65 showed that for the age group 65 to 69 years, incidence was between 160 per 100,000 and 860 per 100,000 person-years,[79] which is also much higher than the rates we found for age 60 to 64. The studies included in the review of Wolters et al.[79] had smaller sample sizes and person-years than the studies included in our meta-analysis. The large sample sizes and person-years in our review come from studies with register-based case finding. Underestimation of incidence in these large studies is likely, because they rely on all people with YOD being registered in the databases used for the study. This could partly explain the difference in incidence rates found in this meta-analysis and the review from Wolters et al.[79] The World Alzheimer Report 2015[80] showed that the annual incidence of dementia in people 65 years of age and older was 8.6 million new cases per year. In comparison, we found 370,000 new cases of YOD per year, indicating that the incidence of YOD is substantially lower; however, due to the longer survival time of people with YOD the public health issue is still profound.

Our finding of a similar incidence rate between men and women for all-type dementia was in line with previous findings from Garre-Olmo et al.[8] and Kvello-Alme et al.[10] For AD, the overall incidence rates were similar, but the 5-year incidence rates starting from age 55 were higher for women compared to men. Although the difference between men and women was minimal, except for AD, there might be underlying causes for this difference, like a difference in diagnosis or care seeking. However, the information in this study was not sufficient to elaborate on this topic.

A previous meta-analysis on the prevalence of YOD showed prevalence increased with age, and was highest for AD, followed by VaD and FTD.[7] These observations also seem to hold for incidence rates. The relatively high prevalence estimates found in the previous review, combined with the incidence rates found in this review, show that YOD is a rare disease with a relatively long survival time. This is in line with previous research, showing that people with YOD have an average survival time after diagnosis of 7.9 years.[81] A recent study found an even longer survival time of over 10 years.[82] This emphasizes the need for accurate epidemiological data on the global burden of YOD, planning of diagnostic services, and provision of better health care.

Of interest, our meta-regression showed that crude incidence estimates were significantly higher in studies conducted in North America, South America, and Oceania compared to Europe. However, due to the small number of studies conducted outside Europe, these results should be interpreted with caution. The lower crude incidence in European studies is not reflected in the age-standardized incidence rates. The difference in the age-standardized incidence rates between the WSP, USP, and ESP are due to a difference in their population age structure, rather than a higher risk or incidence of YOD in the ESP. Because the ESP has a higher percentage of elderly people, the age-standardized incidence rates are higher than the WSP and USP. This explains the discrepancy between the lower crude incidence rates in European studies, but the higher age-standardized incidence rates in Europe. Case definitions of studies between world regions did not differ substantially, although methodology on cognitive assessment most likely differed between studies.

We tried to assess this risk of bias by using the Risk of Bias Tool. However, this tool is general, and studies using registers usually did not report in-depth information on the policies used. Different referral guidelines, assessment tools, and individual knowledge of the specialist can all influence the quality of the register. This was not incorporated in the Risk of Bias Tool and might explain part of the large heterogeneity we found between the studies that could not be assessed in our meta-regression.

In this review, most studies were conducted in Europe, and within Europe, several studies were conducted in Sweden. This may have led to an underrepresentation of incidence rates in other continents. This could influence the interpretation of the incidence rates for con-

tinents other than Europe, indicating more research in other regions is necessary.

Moreover, in regions where the probability of case finding is lower due to cultural values or a lack of resources for both care seeking and care access, information bias toward a lower incidence rate is possible. Although the meta regression showed higher incidence rates in all continents compared to Europe, information in continents with low-income countries was scarce, leading to probable information bias in these continents.

4.1 | Strengths

This systematic review is based on a comprehensive literature search incorporating a large number of studies in order to be as inclusive as possible. In addition, we contacted many authors if information on incidence rates were unclear or missing. With this approach, we were able to include several population-based cohort studies, the primary aim of which was not to investigate the incidence of YOD. However, because these cohort studies are drawn from representative populations and have a long follow-up, they provide important information and were considered for inclusion in this review. To compare estimates across populations with different age structures, we used age-standardized rates. Finally, we performed meta-analyses, including subgroup analyses and meta-regression, allowing us to pool estimates and explore between-study differences.

Because the incidence rate was sometimes 0, the data were transformed with GLMM based on the logit transformation, as this eliminates misleading results, which can occur when using other popular methods such as Freeman-Tukey double arcsine or normal logit transformation.

4.2 | Limitations

Most studies in this review used registers to identify people with YOD. Our meta-analysis showed these studies reported lower incidence rates than studies with active screening. Hence, the pooled incidence rates are likely to be an underestimation of the true population incidence. Studies using registers include persons that had been diagnosed with YOD by a health care professional. According to the World Alzheimer Report, only one third to one half of the people with dementia receive a routine clinical diagnosis.[83] However, research has shown passive case finding to be a more cost-effective way of measuring prevalence or incidence than active case finding, especially for rare diseases. In addition, although under-ascertainment of YOD is highly likely when using registers to identify cases, previous research showed registers play a valid role in dementia case ascertainment, and can be used for studying incidence if these registers meet high enough standards.[84] A systematic review on undetected dementia in health care claimed that the detection rate is even lower for people with YOD compared to LOD.[85] If this is true, incidence rates in this meta-analysis might be an underestimation of the truth, even more so than incidence rates for LOD.

Furthermore, we found significant heterogeneity between the studies. This heterogeneity is due to differences in several aspects of the study methodology. However, the meta-regression showed only significant variability due to geographic location. Other sources of heterogeneity probably exist, but these could not be inferred from the available data. In addition, previous research has shown that studies with big sample sizes/person-years increase I^2, due to more precise estimates and therefore smaller CIs. Because I^2 depends on the CIs, which are very small in the studies from this meta-analysis, this could explain part of the heterogeneity in our meta-analysis.[86]

4.3 | Future research

There is a need for more and better data. First, most data were from Europe, followed by North America, whereas no information was available for Africa. No subgroup analyses on ethnicity or continent could be performed and differences in incidence rates between different ethnic subgroups could not be investigated. Studies on the epidemiology of dementia are scarce in most continents; one explanation may be the difficulty in investigating incidence rates reliably using big cohort studies, which are expensive and time consuming. Given the meta-regression showing significant heterogeneity between geographic locations, more research in the continents of Asia, Oceania, South America, and Africa is warranted. Second, studies mostly assessed only the total incidence of YOD, or specifically assessed major etiologies. Although we found several studies including other important subtypes of dementia such as Parkinson's dementia or alcohol-related dementia, there was not enough information on these subtypes for the meta-analysis. Scarcity of incidence rates of subtypes of YOD is probably due to the very low incidence rates of several etiologies. However, because YOD has more diverse underlying causes than LOD,[87] data on these other subtypes are very important. Therefore, future research should focus on the incidence of different subtypes of YOD. Third, some studies provided insufficient information for meta-analysis. Therefore, future research should aim to standardize procedures and reporting of incidence studies, to make the separate studies more comparable and future meta-analyses even more reliable. To the best of our knowledge, no standardized procedures for incidence studies exist. Fourth, we were unable to analyze changes in incidence over time due to the low number of studies in each age band, despite the long timeframe we researched. This should be addressed in future research so that the influence of the changes of diagnosing dementia can be studied.

Finally, although this meta-analysis showed cohort studies that were using active screening reported higher incidence rates compared to cohort studies using registries, conducting very large cohort studies to investigate the incidence of YOD with active screening, especially in the younger age range, might not be feasible. Instead, more effort should go to implementing population-based disease registries. When these registries are extensive and complete, they represent a valid, cost-effective alternative for identifying incidence rates of YOD and other rare diseases in cohort studies.[88]

In conclusion, this systematic review and meta-analysis found a global age-standardized incidence rate of YOD of 11 per 100,000, which translates into 370,000 new cases per year worldwide. These numbers can still be considered an underestimation and should encourage more research into incidence, risk factors, and etiology. Findings should already raise awareness for policy makers to organize sufficient diagnostic services specialized in YOD and make health care professionals more open to consider a diagnosis of YOD, thereby increasing the recognition of the disease in young people. To address the knowledge gaps in future research, new prospective cohort studies or collaborative individual-participant meta-analysis of existing cohorts should assess different dementia subtypes, and report rates by sex and ethnicity.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

SH and KP acquired the data. SH and SK analyzed and interpreted the data. SH drafted the manuscript. KP, CB, RK, WvdF, JMP, FV, MdV, and SK critically revised the manuscript for important intellectual content. SK, KP, MdV, and FV supervised the study. The Young-Onset Dementia Epidemiology Study Group provided data and critically revised the manuscript.

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SUPPORTING INFORMATION

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

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