Global Prevalence of Young-Onset Dementia

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Global Prevalence of Young-Onset Dementia
A Systematic Review and Meta-analysis

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IMPORTANCE Reliable prevalence estimates are lacking for young-onset dementia (YOD), in which symptoms of dementia start before the age of 65 years. Such estimates are needed for policy makers to organize appropriate health care.

OBJECTIVE To determine the global prevalence of YOD.

DATA SOURCES The PubMed, Embase, CINAHL, and PsycInfo databases were systematically searched for population-based studies on the prevalence of YOD published between January 1, 1990, and March 31, 2020.

STUDY SELECTION Studies containing data on the prevalence of dementia in individuals younger than 65 years were screened by 2 researchers for inclusion in a systematic review and meta-analysis.

DATA EXTRACTION AND SYNTHESIS Prevalence estimates on 5-year age bands, from 30 to 34 years to 60 to 64 years, were extracted. Random-effects meta-analyses were conducted to pool prevalence estimates. Results were age standardized for the World Standard Population. Heterogeneity was assessed by subgroup analyses for sex, dementia subtype, study design, and economic status based on the World Bank classification and by meta-regression.

MAIN OUTCOMES AND MEASURES Prevalence estimates of YOD for 5-year age bands.

RESULTS A total of 95 unique studies were included in this systematic review, of which 74 with 2 760 379 unique patients were also included in 5-year age band meta-analyses. Studies were mostly conducted in Europe and in older groups in Asia, North America, and Oceania. Age-standardized prevalence estimates increased from 1.1 per 100 000 population in the group aged 30 to 34 years to 77.4 per 100 000 population in the group aged 60 to 64 years. This gives an overall global age-standardized prevalence of 119.0 per 100 000 population in the age range of 30 to 64 years, corresponding to 3.9 million people aged 30 to 64 years living with YOD in the world. Subgroup analyses showed prevalence between men and women to be similar (crude estimates for men, 216.5 per 100 000 population; for women, 293.1 per 100 000 population), whereas prevalence was lower in high-income countries (crude estimate, 663.9 per 100 000 population) compared with upper–middle-income (crude estimate, 1873.6 per 100 000 population) and lower–middle-income (crude estimate, 764.2 per 100 000 population) countries. Meta-regression showed that age range ($P < .001$), sample size ($P < .001$), and study methodology ($P = .02$) significantly influenced heterogeneity between studies.

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis found an age-standardized prevalence of YOD of 119.0 per 100 000 population, although estimates of the prevalence in low-income countries and younger age ranges remain scarce. These results should help policy makers organize sufficient health care for this subgroup of individuals with dementia.

STUDY REGISTRATION PROSPERO CRD42019119288

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Supplemental content

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Young-onset dementia (YOD) refers to onset of dementia before the age of 65 years.[1] Young-onset dementia affects partnerships, parenthood, social life, and occupational functioning[2] and causes considerable caregiver burden and delayed access to appropriate care owing to misdiagnosis.[3-6]

Dementia is generally perceived as a condition that affects older adults, with prevalence estimates of late-onset dementia (LOD) increasing exponentially with age.[7] Approximately 45 million people live with LOD worldwide.[8] The focus on LOD may marginalize the importance of dementia in younger people.[9] Exact figures on the burden of YOD are needed to determine the necessary budget and set priorities by policy makers.

Harvey et al[10] and Ikejima et al[11] have authored the most referenced studies on the prevalence of YOD, reporting estimates from 42.3 to 54.0 per 100 000 population. People with YOD were identified retrospectively with a register-based approach, so underreporting was likely. Three systematic reviews exist on the prevalence of YOD[12-14]; however, each included only a limited number of studies, concentrated on a specific diagnosis, or reviewed non-population-based studies.

Our primary goal was to assess the global prevalence of YOD using all available data on the prevalence of YOD. We also compared prevalence estimates between different subgroups of sex, age, causes, study design, and countries' economic status.

Key Points

Question What is the global prevalence of young-onset dementia?

Findings In this systematic review, a total of 95 studies were included, of which 74 studies with 2 760 379 unique patients were included in the meta-analysis; the global age-standardized prevalence of young-onset dementia was 119.0 per 100 000 population aged 30 to 64 years. Estimates increased from 1.1 per 100 000 population aged 30 to 34 years to 77.4 per 100 000 population aged 60 to 64 years.

Meaning These prevalence estimates show the importance of young-onset dementia worldwide; policy makers could use this information to organize sufficient health care for young people living with dementia.

Methods

Search Strategy and Selection Criteria

This systematic review and meta-analysis followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[15] We searched literature in PubMed, Embase, CINAHL, and PsycInfo for observational population-based prospective, retrospective, or cross-sectional studies on the prevalence or incidence of YOD (eMethods 1 in the Supplement). Studies were searched from January 1, 1990, to March 31, 2020, without language restrictions. The study is part of the larger PRECODE (Prevalence Recognition and Care Pathways in Young Onset Dementia) project.

Studies were eligible for inclusion in the prevalence report if they included individuals younger than 65 years. Cohort studies on demographic subpopulations (eg, certain age ranges, women only, ethnic minority populations) and population-based hospital, primary care, and insurance registry studies were included. Cohort studies restricted to specific patient groups at risk for developing YOD (eg, patients with Down syndrome or HIV) or to residents of care homes were excluded. Dementia diagnosis had to be set according to accepted criteria (ie, *International Classifications of Diseases* and *Diagnostic and Statistical Manual of Mental Disorders* [Third Edition] to *Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) or its subtypes (ie, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA], National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neuroscience [NINDS-AIREN]) or, in case criteria were not specified, studies had to report a diagnosis by a clinician. Studies relying on mortality data or death certificates were excluded because of expected misclassification bias due to underreporting.

Two researchers (S.H. and K.P.) independently screened both abstracts and eligible full texts. Disagreements were resolved by discussion, if needed, with a third researcher (S.K.). The Cohen κ for interrater agreement was substantial (0.67).[16] For cohorts with multiple publications, we chose the most complete data set (ie, largest sample, most relevant age range). Reference lists of included articles and reviews were checked for additional studies. Authors were contacted at least twice in case of missing data or to verify eligibility for inclusion.

Statistical Analysis

One researcher (S.H.) extracted study characteristics and outcome estimates using a uniform data extraction sheet (eMethods 2 in the Supplement) with cross-checking by a second researcher (K.P.). We used the risk of bias tool for quality assessments (eMethods 3 in the Supplement).[17] When checklist items were not reported or unclear, they were qualified as high risk.

Whenever possible, prevalence estimates were meta-analyzed using a generalized linear mixed-model random-effects meta-analysis (Metafor package in R, version 3.3.6 [R Program for Statistical Computing]).[18] Studies that did not report both the number of cases and sample size or studies investigating specific subpopulations only (eg, ethnic minorities) were not included in the meta-analysis.

First, crude meta-analyses were performed for all types of dementia and the subtypes Alzheimer disease (AD), vascular dementia (VaD), and frontotemporal dementia (FTD). A study was considered as covering all types of dementia if it reported 1 overall prevalence estimate for all causes and subtypes of dementia.

Because studies included different age ranges, we estimated age-specific prevalence by 5-year age bands. Next, because pooling into a single estimate would apply the same weight to each age group, we age-standardized estimates by

the World Standard Population of 2000 to 2025,[19] the United States Standard Population of 2000,[20] and the European Standard Population of 2011 to 2020[21] using direct standardization.

Subgroup analyses were performed based on sex, study methodology (cohort vs register-based studies), and economic status of countries. The latter was based on a country's gross national income per capita following the World Bank classification[22] (eTable 1 in the Supplement).

Meta-regression according to DerSimonian and Laird[23] assessed the mitigation of between-study differences in sample size, age ranges, diagnostic criteria, economic status, and study methodology. Analyses were run for each covariate separately, followed by multivariable analyses of significant covariates.

Heterogeneity was assessed using the I^2 statistic, showing the proportion of the total variance in pooled estimates that is explained by variation between studies. Funnel plots were visually inspected to account for small studies. P <.05 from 2-sided hypothesis testing was considered statistically significant in all analyses.

Results

We found 11 422 articles after removing duplicates, and 95 studies were eligible for inclusion (eFigure 1 in the Supplement),[10,11,24-116] for a total of 2 760 379 participants in the 5-year age band meta-analyses. The study characteristics are described in **Table 1** and eTable 2 in the Supplement. The quality of the studies was adequate (Table 1 and eTable 2 in the Supplement), but studies differed on methodology and data reporting. External validity was deemed problematic in some studies in which the study population did not represent the target population or in which nonparticipation was high. Incomplete reporting also lowered quality assessments.

The **Figure** shows where the included studies were conducted. Although studies from many countries were included, information on ethnicity was insufficient. Studies in the age range of 30 to 59 years were mainly performed among White populations and only 5 were performed in Asian populations (1 in a population aged 30-49 years[11] and 4 in populations aged 50-59 years[46,59,65,108]). Hence, no subgroup analyses on ethnicity could be performed.

Of the studies excluded from the meta-analysis, several investigated specific ethnic subpopulations. Smith et al,[60] Radford et al,[97] and Li et al[87] investigated Australian Indigenous people, in whom prevalence was higher compared with the non-Indigenous population. Raina et al,[58,69] Parlevliet et al,[103] and Nielsen et al[74] investigated ethnic minority groups in different countries and found higher prevalence compared with the general population. Liu et al,[31] Bartoloni et al,[83] and Phanthumchinda et al[26] reported a higher prevalence in people with a low socioeconomic status or poor housing conditions.

Overall Prevalence of YOD

Eighty-one studies[10,11,24-29,31-40,42,43,45-47,50,52,54-71,74-76,78,80-95,97-100,102-116] reported prevalence estimates on all types of YOD (Table 1). Of these, 21 studies were excluded from meta-analyses: 11 studies[26,31,58,60,69,74,83,84,87,97,103] reported solely on specific ethnic subpopulations, and 10 studies[35,45,54,88,91,104,105,107,116] lacked numerator or denominator data. The number of eligible studies ranged from 4 in the age band 30 to 34 years[10,11,93,113] to 45 in the age band 60 to 64 years.[10,11,24,25,27,33,34,37,39,42,43,46,50,56,57,59,62,63,65-67,70,71,75,78,80,82,85,92-95,98,99,106,108-111,113,115] Pooled analyses within 5-year age bands showed an increased prevalence with age (eFigure 2 in the Supplement and **Table 2**). Age-standardized prevalence estimates increased from 1.1 per 100 000 population in the group aged 30 to 34 years to 77.4 per 100 000 population in the group aged 60 to 64 years. The global age-standardized prevalence was 119.0 per 100 000 population in the maximum age span of 30 to 64 years, 159.4 per 100 000 population in Europe, and 114.7 per 100 000 population in the US. This corresponds to an absolute number of 3.9 million people living with YOD worldwide, of whom 0.5 million live in Europe and 200 000 live in the US.

Heterogeneity between studies was substantial (I^2 > 90%). Subgroup analyses were performed by sex, World Bank classification, and study methodology (eTable 3 in the Supplement). For sex, data were available for 5-year age bands from 50 years onward, showing generally a similar prevalence for men and women (eg, for 50-54 years, 67.2 vs 81.2 per 100 000 population). For analyses based on World Bank classification, data from high-income countries were available for all age ranges, from upper-middle-income countries for 60 to 64 years of age, and from lower-middle-income countries for 50 to 64 years of age. No data were available for low-income countries. In the age band of 60 to 64 years, prevalence was highest in upper-middle-income countries (1873.6 per 100 000 population), followed by lower-middle-income countries (764.2 per 100 000 population) and high-income countries (663.9 per 100 000 population). Regarding study methodology, register-based studies were conducted across all age ranges, whereas cohort studies were only conducted for groups aged 50 to 64 years. Comparing the prevalence estimates in these later age bands, cohort studies reported higher prevalences (eg, 60-64 years, 1135.5 vs 302.1 per 100 000 population).

Both univariable and multivariable meta-regression were performed on crude estimates (**Table 3**). In multivariable meta-regression, age range, sample size, and study methodology significantly accounted for between-study differences in prevalence estimates, with an R^2 of 85.9%. Prevalence estimates increased for studies with a higher mean age and studies with a smaller sample size.

Alzheimer Disease

Twenty studies[10,11,30,33,37,41,44,47,51,53,55,72,73,81,85,93,95,101,108,113] reported on the prevalence of AD. The number of studies eligible for meta-analyses ranged from 3 (age group, 35-39 years)[11,93,113] to 14 (age group, 60-64 years)[10,11,25,30,37,44,53,73,85,93,95,101,108,113] (eTable 3 in the Supplement). The age-standardized prevalence was 41.1 per 100 000 population worldwide, 54.1 per 100 000 population in Europe, and 31.8 per 100 000 population in the US (Table 2).

Table 1. Characteristics of the Included Studies[a]

Characteristic	Dementia type			
	All (n = 81)	AD (n = 20)	VaD (n = 13)	FTD (n = 12)
Study period				
Before 1990	4	0	0	0
1990-1999	12	8	5	2
2000-2009	27	6	4	6
2010-2019	19	3	2	3
Unknown	19	3	2	1
Age range, y				
<30-64	7	2	1	2
30-64	3	3	3	4
40-59	1	1	0	0
40-64	6	1	1	1
45-64	3	0	0	0
50-59	7	3	1	5
50-64	6	1	1	0
55-64	9	4	3	0
60-64	39	5	3	0
Sample size				
<500	26	1	0	0
500-1000	9	3	2	0
1000-2000	8	2	2	0
>2000	27	14	9	12
Unknown[b]	11	0	0	0
Diagnostic criteria				
ICD	12	1	0	0
DSM-III to *DSM-5*	43	9	6	4
NINCDS-ARDRA	1	3	0	0
NINDS-AIREN	0	0	1	0
Combination of above	15	7	6	3
Other[c]	10	0	0	5
Design				
Cohort				
Cross-sectional	57	10	7	0
Prospective	3	0	0	0
Register-based	21	10	6	12
Mean quality assessment (range)[d]	8.1 (4-10)	8.4 (8-10)	8.0 (7-10)	7.9 (7-9)
World Bank classification				
High-income	46	10	7	12
Upper-middle-income	18	7	4	0
Lower-middle-income	16	3	2	0
Low-income	1	0	0	0
Continent				
Europe	27	8	5	9
Asia	33	9	5	2
North America	7	0	0	0
South America	6	1	1	0
Africa	4	1	1	0
Oceania	4	1	1	1

Abbreviations: AD, Alzheimer disease; *DSM-III*, *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition); *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition); FTD, frontotemporal dementia; *ICD*, *International Classification of Diseases*; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences; VaD, vascular dementia.

[a] Unless indicated otherwise, data are presented as number of studies. Studies may be reported multiple times if they are included in multiple meta-analyses (all types, AD, VaD, FTD).

[b] Studies with unknown sample size (and number of cases) were not eligible for meta-analyses.

[c] Other diagnostic criteria were subtype specific (eg, Neary and McKahnn criteria for FTD).

[d] Scores range from 4 to 10, with higher scores indicating higher-quality assessment of the studies.

eTable 3 and the eResults in the Supplement show results of subgroup analyses by sex, World Bank Classification, and study methodology.

Vascular Dementia

All 13 studies on the prevalence of VaD[10,11,33,37,40,47,51,55,85,93,95,108,113] were eligible for inclusion in the

Figure. World Map of Included Studies

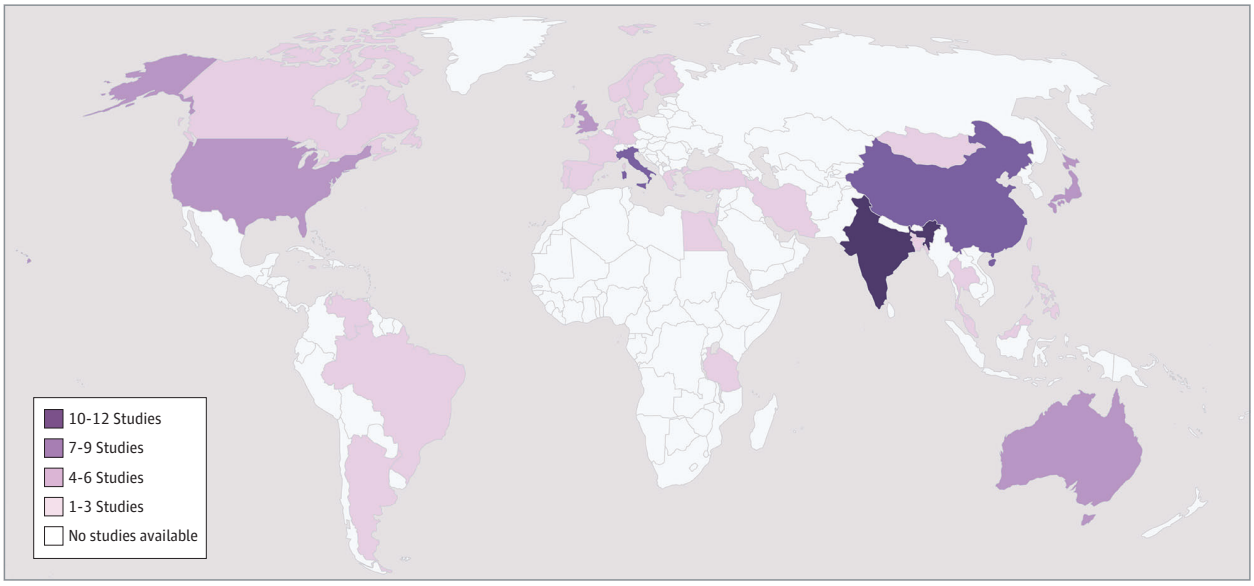

Table 2. Age-Standardized Prevalence Estimates for 5-Year Age Bands per 100 000 Population

Age range, y[a]	Dementia type											
	All			AD			VaD			FTD		
	WSP	ESP	USP	WSP	ESP	USP	WSP	ESP	USP	WSP	ESP	USP
30-34	1.1	0.8	0.9	NA	NA	NA	0.2	0.2	0.2	0.02	0.01	0.02
35-39	1.0	0.9	1.1	0.1	0.1	0.1	0.6	0.5	0.6	0.02	0.01	0.02
40-44	3.8	3.5	4.3	0.1	0.1	0.1	0.8	0.73	0.9	0.1	0.04	0.1
45-49	6.3	6.4	6.8	0.1	0.1	0.1	0.4	0.4	0.5	0.3	0.3	0.3
50-54	10.0	11.1	10.6	1.5	1.7	1.6	1.1	1.3	1.2	0.2	0.3	0.3
55-59	19.2	24.3	18.5	6.9	8.8	6.7	2.9	3.6	2.7	1.0	1.3	1.0
60-64	77.4	112.4	72.6	24.8	36.0	23.3	8.9	12.9	8.3	0.7	1.0	0.6
All	119.0	159.4	114.7	41.1	54.1	31.8	14.9	19.5	14.3	2.3	2.9	2.3

Abbreviations: AD, Alzheimer disease; ESP, European Standard Population; FTD, frontotemporal dementia; USP, United States Standard Population; VaD, vascular dementia; WSP, World Standard Population.

[a] For AD, the total is in the age range 35 to 64 years; for all other types of dementia, the total is in the age range 30 to 64 years.

meta-analysis. The number of studies eligible for meta-analyses ranged from 3 (age group, 30-34 years)[11,93,113] to 7 (age group, 60-64 years).[10,11,37,85,93,95,108,113] The age-standardized prevalence of VaD was 14.9 per 100 000 population worldwide, 19.5 per 100 000 population in Europe, and 14.3 per 100 000 population in the US (Table 2). The results of subgroup analyses are presented in eTable 3 and the eResults in the Supplement.

Frontotemporal Dementia

All 12 studies on the prevalence of FTD[10,11,40,47-49,72,77,79,93,96,113] were included in the meta-analysis. The number of studies eligible for meta-analyses ranged from 3 (age group, 30-34 years)[11,49,93] to 5 (age group, 60-64 years).[10,11,49,93,113] The age-standardized FTD prevalence for the group aged 30 to 64 years was 2.3 per 100 000 population worldwide, 2.9 per 100 000 population in Europe, and 2.3 per 100 000 population in the US (Table 2).

Other Types

Only 4 studies[11,33,47,106] reported data on dementia with Lewy bodies and Parkinson disease dementia, but these studies were too diverse for pooling in a meta-analysis (eTable 4 in the Supplement). Three studies on alcohol-related dementia[47,93,113] reported prevalence estimates from 4.9 to 16.3 per 100 000 for 30 to 64 years of age. All were conducted in high-income countries and used the register-based study design. No meta-analysis was conducted.

Discussion

Based on 95 population-based studies, the global age-standardized prevalence in individuals aged 30 to 64 years was 119.0 per 100 000 population. Using the United Nations world population of 2019,[117] this projects to 3.9 million people aged 30 to 64 years living with YOD worldwide. Age-standardized

Table 3. Meta-Regression Analysis of Study Characteristics in Univariable (Crude) and Multivariable Analyses and Interactions Between Characteristics

	Crude analysis		Multivariable analysis	
	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
Age range, y				
<30-64	1 [Reference]	NA	1 [Reference]	NA
30-64	0.3 (−0.5 to 1.1)	.43	0.2 (−0.5 to 0.8)	.63
40-64	1.6 (0.7 to 2.5)	<.001	1.3 (0.5 to 2.1)	.001
45-64	1.4 (0.7 to 2.1)	<.001	1.2 (0.7 to 1.8)	<.001
50-64	1.6 (0.7 to 2.4)	<.001	1.9 (1.1 to 2.8)	<.001
55-64	2.6 (1.9 to 3.2)	<.001	1.9 (1.1 to 2.7)	<.001
60-64	3.5 (2.9 to 4.1)	<.001	2.3 (1.6 to 3.0)	<.001
Sample size				
0-499	1 [Reference]	NA	1 [Reference]	NA
500-999	−0.3 (−1.4 to 0.7)	.56	−0.3 (−0.8 to 0.3)	.35
1000-1999	0.5 (−0.5 to 1.4)	.34	0.4 (−0.1 to 0.9)	.09
2000-4999	−1.6 (−2.7 to −0.6)	.002	−1.4 (−2.1 to −0.8)	<.001
≥5000	−2.4 (−3.2 to −1.6)	<.001	−2.0 (−2.8 to −1.2)	<.001
Study methodology				
Cohort	1 [Reference]	NA	1 [Reference]	NA
Register-based	−1.9 (−2.6 to −1.1)	<.001	0.9 (0.2 to 1.5)	.02
Diagnostic criteria				
Other	1 [Reference]	NA	NA	NA
ICD	−1.2 (−2.9 to 0.5)	.15	NA	NA

Abbreviations: *ICD*, *International Classification of Diseases*; NA, not applicable.

prevalence was lower in the US than in Europe, similar in women and men, highest in upper-middle-income countries, and highest for AD, followed by VaD and FTD. Register-based studies reported lower prevalence estimates than cohort studies.

The observed prevalence is higher than earlier estimates from Harvey et al[10] (54.0 per 100 000 population in 2003) and Ikejima et al[11] (42.3 per 100 000 population in 2009). Both of these studies were retrospective register-based studies that reported lower estimates compared with the cohort studies in our meta-analysis and are therefore likely to be underestimations.

Analysis of 5-year age bands showed a large increase in prevalence in the group aged 60 to 64 years, except for FTD. Estimates for this age band are comparable with another systematic review by Prince et al,[7] who reported on dementia prevalence for 60 years and older. They estimated 48.1 million people older than 60 years with dementia in 2020, when we estimated 3.9 million people had YOD. This neatly conceptualizes YOD prevalence in the overall dementia prevalence. Our findings fit the general observation that prevalence of dementia increases exponentially from 60 years of age onward. However, the sharp increase between groups aged 55 to 59 and 60 to 64 years could be partially explained by the scarcity of studies in younger bands and their reliance on register data. Therefore, the prevalence in the younger bands might be an underestimation. On the other hand, a clear definition of YOD is lacking, and our cutoff at 65 years of age remains arbitrary.[1] Given the profound delay in diagnosis, with a mean delay of 4.4 years between initial symptoms and diagnosis,[5,6] the true YOD prevalence is probably also higher in older bands. According to the World Alzheimer Report, only one-third to one-half of the people living with dementia receive a routine clinical diagnosis.[118] Hence, the reported estimates should be seen as a lower boundary of the true YOD prevalence.

The overall prevalence in this review was highest for AD, followed by VaD and FTD. However, in the lower age ranges, until 50 years of age, VaD prevalence is highest, and FTD prevalence is higher than AD prevalence. However, these analyses were based on few studies, so interpreting these prevalence estimates with caution is warranted. We found a relatively low overall prevalence for FTD compared with the total YOD prevalence. However, all studies on FTD were register based and were conducted in high-income countries. Furthermore, FTD is frequently underdiagnosed or misdiagnosed.[5,6] Because no pathological data were available, this is also most likely an underestimation. In addition, prevalence of FTD peaked at 55 to 59 years of age. Studies investigating FTD characteristics report the same peak at age of onset,[119] probably owing to the high genetic component in this subtype of dementia at this age.[120]

The higher AD prevalence is in line with the findings of Harvey et al,[10] although Ikejima et al[11] found a higher prevalence of VaD followed by AD. Clinical diagnoses of subtypes of dementia are subject to a lack of precision, and they might not always represent the pure AD or vascular pathology.[121] Furthermore, the included studies differed with regard to study protocols and diagnostic criteria for AD and VaD. Because diagnosing dementia subtypes depends on diagnostic criteria, available measurement tools, and clinician expertise, no certainty about the subtypes can be applied without pathological information.

For this review, only the subtypes AD, VaD, and FTD had sufficient data to be analyzed separately. However, to better understand the prevalence, health care needs, and underlying causes of YOD, research on all subtypes of YOD is needed.

Although there were interstudy differences in prevalence for men and women, we observed similar prevalence for both sexes. For dementia subtypes, we only had sufficient information on AD, again finding similar prevalence estimates. More research on putative sex differences in the prevalence of YOD subtypes is still necessary.

We age standardized for the World Standard Population, European Standard Population, and United States Standard Population. The reported difference in prevalence estimates among them is owing to a difference in the age structure of the populations, rather than a difference in the risk of YOD. Because the prevalence of YOD increases with age, prevalence of YOD is higher in the older European Standard Population than the younger World Standard Population and United States Standard Population. Unfortunately, we lacked data for age standardization for other parts of the world.

Heterogeneity between studies was high, with many subgroup analyses showing I^2 > 90%. Previous systematic reviews on prevalence studies found similar results.[122] In addition, research has shown an association between high sample sizes and increased I^2 heterogeneity, because study-specific confidence intervals become very narrow.[123] Hence, it should not be seen as an absolute measure of heterogeneity. Meta-regression showed heterogeneity in prevalence estimates was partly explained by variability in included age ranges, sample sizes, and study methodology. Several differences between study designs might explain this heterogeneity. Population-based cohort studies adopt an active case finding with standardized protocols, leading to more accurate case finding; however, such studies are expensive and time consuming. Therefore, sample sizes of these studies are often relatively small, making them less suitable for studying rare diseases, such as YOD. Register-based studies are a cost-effective alternative but use passive case finding and are prone to misclassification bias and underreporting by relying on routine data (eg, primary, secondary, or tertiary care, insurance claims, or death certificates).[124,125] However, the register-based studies in this review included young age bands and rarer causes of dementia. This can therefore be considered a strength of these register-based studies for prevalence estimates.[126] We found no cohort studies reporting prevalence of dementia younger than 50 years; therefore, evidence of YOD prevalence in lower age ranges is based solely on register-based studies.

Finally, studies from high-income countries reported a lower prevalence, but they were more often register-based studies compared with studies from upper-middle- and lower-middle-income countries. Because insufficient data on ethnicity were available, we were unable to study ethnic differences. Future research is therefore needed to focus on possible differences in YOD prevalence between ethnic groups.

Strengths and Limitations

There are considerable strengths to this study. First, our inclusive search strategy without language restrictions led to the inclusion of 95 eligible articles, resulting in the largest review in this field, to our knowledge. More than 100 researchers were contacted to provide data for the meta-analysis. Nevertheless, not all requested data were available to us. Furthermore, in the meta-analyses, we did not pool across all age ranges in a single step. This would lead to an overestimation, given the overrepresentation of the later age ranges, especially 60 to 64 years of age. Therefore, we used 5-year age bands and direct standardization, leading to overall prevalence estimates for 30 to 64 years of age.

This study has some limitations that should be addressed in future studies. Studies from Africa and low-income countries were underrepresented; therefore, their estimates are lacking. In addition, 41 of the 95 included studies only reported on the age band 60 to 64 years. Consequently, crude prevalence estimates are most likely biased upward. Estimates of the 5-year age bands resulted in more conservative estimates, but fewer articles could be included in these analyses owing to a lack of information. Ideally, future studies on the prevalence of dementia will cover the full adult age range. In addition, meta-regression was only possible on the crude estimates because not all studies reported age-specific prevalence estimates.

In the meta-analyses of 5-year age bands, some of the sample sizes were small. However, post hoc analyses restricted to larger studies showed only slight changes in prevalence estimates in the 60- to 64-year age band. All studies were included because the studies with smaller sample sizes were often cohort studies, which are more accurate than register-based studies when investigating prevalence.

Subgroup analyses based on the World Bank classification were performed because analyses on ethnicity were not possible. The classification was chosen because it correlated with a given country's quality of life measures, including educational level and mortality rates.[127]

Because YOD prevalence was not the main focus of most studies but was integrated into studies of total dementia prevalence, this led to reporting often being suboptimal for the purpose of this review (eg, no prevalence by sex and age ranges). Other between-study differences related to information sources (eg, primary care or hospital registers), methods for case ascertainment, and diagnostic criteria. Dementia diagnosis was sometimes poorly defined and not always reported properly.

In addition, the meta-analyses were performed on proportions. Because the prevalence was often near zero, data were transformed with generalized linear mixed models based on the logit transformation, because this eliminates misleading results that can occur when using other popular methods such as Freeman-Tukey double arcsine or normal logit transformation.[128]

Conclusions

In conclusion, monitoring the prevalence of YOD is essential to adequately plan and organize health services. Based on the available literature, this systematic review and meta-analysis estimated the age-standardized prevalence to be 119.0 per

100 000 population globally. Although this is higher than previously thought, it is probably an underestimation owing to lack of high-quality data. This should raise awareness for policy makers and health care professionals to organize more and better care for this subgroup of individuals with dementia. To yield more accurate and comparable prevalence estimates in the future, efforts should be made to conduct more cohort studies and to standardize procedures and reporting of prevalence studies. In addition, more data are needed from low-income countries as well as studies that include younger age ranges.

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