FEATURED ARTICLE

Global estimates on the number of persons across the Alzheimer's disease continuum

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Abstract

Introduction: Global estimates on numbers of persons in early stages of Alzheimer's disease (AD), including prodromal and preclinical, are lacking, yet are needed to inform policy decisions on preventive measures and planning for future therapies targeting AD pathology.

Methods: We synthesized the literature on prevalence across the AD continuum and derived a model estimating the number of persons, stratified by 5-year age groups, sex, and disease stage (AD dementia, prodromal AD, and preclinical AD).

Results: The global number of persons with AD dementia, prodromal AD, and preclinical AD were estimated at 32, 69, and 315 million, respectively. Together they constituted 416 million across the AD continuum, or 22% of all persons aged 50 and above.

Discussion: Considering predementia stages, the number of persons with AD is much larger than conveyed in available literature. Our estimates are uncertain, especially for predementia stages in low- and middle-income regions where biomarker studies are missing.

1 | INTRODUCTION

The extraordinary burden of Alzheimer's disease (AD) and dementia is widely accepted, and opinion leaders and policy makers worldwide call for action. The estimated global number of patients with dementia now exceeds 50 million, costing more than a trillion US dollars per year.[1–3] Dementia is the fifth leading cause of death globally[4] and AD the fourth leading cause of disability-adjusted life-years (DALYs) lost in persons aged 75 years and older.[5] In addition, most patients have one or more family caregivers who devote time and effort in unpaid care, resulting in psychological morbidity, social isolation, physical ill health, and financial hardship.[6] We see two important limitations to this narrative.

First, it only describes the end stage of a several decades long disease. Global estimates of the burden, both in terms of the number of people afflicted and societal costs (albeit likely small per person, at least in preclinical AD) for AD stages prior to dementia, are missing. AD starts with an asymptomatic phase with neuropathologic changes, including amyloid beta (Aβ) deposition and pathologic tau.[7,8] The presence of such brain pathology can be detected in vivo with Aβ and tau biomarkers[7] and this preclinical stage can last for 20 to 30 years without any symptoms.[9,10] Some may remain in the preclinical stage for the remainder of their lives,[11] whereas others (20% to 73% depending on stage[12]) develop measurable cognitive symptoms that meet criteria for mild cognitive impairment (MCI). In presence of a positive biomarker for AD pathology, this stage is called prodromal AD,[7,13] and lasts on average for 3 to 5 years[9] after which many but not all progress to AD dementia.[14] Whether an individual in any stage on the AD continuum will progress and develop AD-related symptoms is highly variable and dependent on both genetic and environment-related factors, and many with underlying AD pathology may indeed never develop symptoms at all.

Second, even within the dementia stage of AD, published estimates are generally based on populations with a clinical diagnosis, either of dementia irrespective of etiology (herein referred to as general dementia),[1,2] or a clinical diagnosis of probable or possible AD but without biomarker confirmation of AD pathology.[15] Biomarker evidence, needed to confirm the etiology of these populations, is missing from the majority of older research, largely because of changing diagnostic criteria over time.

After numerous failed trials in AD dementia,[16] it was suggested that we need to start treatment earlier and in biomarker-confirmed populations; that is, in the prodromal or even preclinical stages of AD, with the goal of delaying or stopping disease progression and to prolong the period of full autonomy in daily-life-activities.[17] Today, prodromal AD is together with mild AD dementia the most common focus for experimental therapies targeting AD pathology in ongoing clinical trials.[18] Moreover, the predementia stages of AD are important targets for preventive measures that have been shown to reduce the risk of cognitive decline and dementia.[19–21] The size of this population is an important starting point for policy making and health-care planning. The advent of an effective new therapy is expected to put high pressure on already strained health-care systems and recent studies suggest we are ill prepared.[22,23] Relevant estimates on the size of the potentially eligible patient population are central for better preparation.

The Project Alzheimer's Value Europe (PAVE) consortia sought to fill this data gap by conducting a review of currently available evidence on the prevalence of AD and suggesting best estimates on the total number of persons, worldwide and across the AD continuum.

2 | METHODS

2.1 | Literature review

We performed a targeted literature review on the prevalence of AD, with focus on meta-analyses based on systematic literature reviews (SLRs) published in the past 10 years, reporting prevalence estimates of any disease stage, with or without biomarker confirmation of AD pathology.

The review methods were predefined in a study protocol including eligibility criteria, search strategy, and methods for data extraction and synthesis. An initial search for SLRs was complemented with targeted searches for original studies to fill data gaps in the SLRs. A single reviewer conducted the selection process throughout, with a subset of their selections assessed by another reviewer. The review yielded a total of 55 records meeting the predefined criteria (Suppl 1, including flow diagram, in supporting information). Out of these records, we selected the best available sources for a global model on the prevalence of AD across the AD continuum, giving preference to meta-analyses reporting data from multiple cohorts and reporting prevalence estimates stratified by sex, age, and country/region, where available. The selection of papers was repeatedly discussed with the panel of advisors (steering group).

2.2 | Stages

We considered three stages across the AD continuum, all presuming underlying AD pathology: preclinical AD, prodromal AD, and AD dementia. The preclinical AD stage is inclusive of persons with normal cognition (NC), persons with subjective cognitive decline or impairment (SCD or SCI) having normal scores on cognitive

tests but experiencing subjective cognitive symptoms or expressing cognitive complaints, and persons at the end of the preclinical AD continuum with measurable symptoms but insufficient to meet MCI criteria.[12,24,25] This preclinical AD stage corresponds to stages 1 and 2 per the most recent National Institute on Aging–Alzheimer's Association (NIA-AA) research criteria.[7] Prodromal AD is inclusive of persons with MCI defined by objectively verified decline in memory or other cognitive domain, with no impairment or minimal impairment in activities of daily living (ADL),[26,27] and corresponds to stage 3 of the NIA-AA research criteria.[7] AD dementia is inclusive of persons meeting the criteria for a clinical diagnosis of dementia[28] or probable or possible AD[29] (NIA-AA stages 4, 5, 6).[7]

2.3 | Biomarkers

Relevant AD biomarkers included measures of Aβ and tau pathology assessed in cerebrospinal fluid (CSF) or with positron emission tomography (PET). All persons on the AD continuum are required to have evidence of Aβ deposition (herein referred to as Aβ-positive).[7,24] Of note, a diagnosis of Alzheimer's *disease* would require additional evidence of pathologic tau.[7,8] We opted for this inclusive approach, incorporating the full AD continuum in our prevalence estimates, to get an exhaustive picture of individuals with symptomatic AD or at elevated risk of developing symptomatic AD. This includes Aβ-positive persons without tau pathology as well as Aβ-positive persons with other neurocognitive disorders that may be the primary cause of their (eventual) symptoms. We believe this inclusive approach is a good starting point for deriving relevant prevalence estimates, in the light of the changing diagnostic criteria and definitions over time.

2.4 | Data analysis

Prevalence estimates of well-defined AD populations were extracted, and where available, stratified by geographic region and key determinants of AD including age, sex, and apolipoprotein E (*APOE*) ε4 status (Suppl 2 in supporting information).

We designed a model that combined data from different sources to achieve prevalence estimates for each disease stage including biomarker-confirmed AD pathology. We considered Aβ positivity to be sufficient for each stage in concordance with 2011 NIA-AA criteria,[24] while not considering data on tau biomarkers. This was motivated by the goal of being inclusive of all stages on the AD continuum, and because of limitations in the available data. The selected data and key assumptions for each stage are described below, and further details are available as supporting information (Suppl 3). The uncertainty in point estimates was considered by calculating uncertainty ranges based on the confidence intervals from the source publications, where available. Data for age groups from 50 years and upward were available for AD dementia and preclinical AD, whereas data for prodromal AD were available for age groups 60 years and upward.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature primarily using PubMed. While individual studies are available on the prevalence across all stages of the Alzheimer's disease (AD) continuum, estimates on the global burden of AD are typically limited to the dementia stage, and samples without biomarker confirmation of AD pathology.

2. **Interpretation**: The burden of AD is much larger than conveyed in the literature, and the majority of persons on the AD continuum are in predementia stages. The paucity of data on predementia AD and biomarker-confirmed populations, especially from low- and middle-income regions, make our estimates uncertain.

3. **Future Directions**: The size of the global burden of AD illustrates a huge window of opportunity for prevention strategies, including modifiable risk reduction and pharmacological interventions. Policy makers and health-care planners worldwide can use our data to inform their decisions, while more research on the prevalence of biomarker-confirmed AD is needed.

For AD dementia, we selected detailed data on general dementia prevalence by country, sex, and age,[1] complemented with data stratified by sex for age groups 50 to 54 and 55 to 59 years from a separate study.[30] Global but less detailed estimates available on clinical AD dementia[31] and more recent European data on general dementia[32] were considered in a sensitivity analysis. We assumed 70% of persons with general dementia have AD (60% to 80% in the uncertainty range)[33] and multiplied these estimates with prevalence estimates of Aβ positivity from a global meta-analysis on persons with clinical AD dementia.[34]

For prodromal AD, we multiplied prevalence estimates of clinical MCI[35] with prevalence estimates of Aβ positivity in persons with MCI,[10] both stratified by age as reported in two separate global meta-analyses.

For preclinical AD, we selected prevalence estimates of Aβ positivity from a global meta-analysis on persons with NC or SCI stratified by age,[10] and recalculated a weighted estimate for the NC+SCI population assuming 25% of the preclinical AD population are SCI.[36] Then, to get prevalence estimates for the general population, we multiplied our estimates by the ratio of the NC+SCI population to the general population, considering that NC+SCI equals the general population minus persons with MCI[35] or dementia.[1]

The resulting prevalence estimates were then multiplied by global population sizes for 2020, extracted from United Nations population statistics, stratified by country, 5-year age groups starting at 50 years, and sex (https://population.un.org/wpp/DataQuery/).

2.5 | Subgroups

In addition to the sex and age stratification detailed above, we estimated the number of persons in selected subgroups.

First, the combined group of persons with prodromal AD and mild AD dementia represents a common target population in clinical trials on therapies targeting AD pathology,[18] and the size of this group is therefore of particular interest. We assumed proportions of AD dementia patients with mild AD dementia starting at 60% up to age 75 declining to 45% at age 85,[37,38] (+/– 10% points in uncertainty range).

Second, we considered *APOE ε4* carriers in preclinical AD and prodromal AD, because they are at elevated risk of AD progression,[39] and therefore of particular interest for intervention. *APOE ε4* status shows significant variability across the world.[40] However, in absence of evidence on differing proportions of *APOE ε4* carriers across geographic regions in preclinical and prodromal AD, we assumed the same estimates for all countries. We used estimates of Aβ positivity for *APOE ε4* carriers and observed proportions of *APOE ε4* carriers in NC, SCI, and MCI populations from the same study.[10]

3 | RESULTS

3.1 | Literature review

Our searches yielded seven large global[1,10,12,30,31,34,35] and one European[32] meta-analyses on the prevalence of stages across the AD continuum, often stratified by age and sex. Studies on biomarker-confirmed populations were found for all stages, originating from Europe, the United States, Japan, South Korea, China, India, and Australia.[10,12,34] Studies on differences across countries or regions were only available for the dementia stage of AD.[1,31,32] Although sex differences have been found in original studies across all stages,[41] they are not fully considered in meta-analyses of the predementia stages of AD. Other determinants that were considered in individual studies included education, ethnicity, and genetic profile. Study details and their reported prevalence estimates are provided as supporting information (Suppl 2), while their main findings are described below.

The prevalence of clinical AD dementia increases with age and seems higher in women compared to men.[30,31,42] This female preponderance is not confirmed in all studies[43] and may be stronger in Europe and North America compared to Asia.[31] There is geographic variation in the prevalence of general dementia, also when controlling for age and sex.[1] However, the evidence in support for such geographic variation in persons with AD dementia is weak at best.[31,42] Also, in studies on the prevalence of general dementia the evidence suggests that the sex difference increases with age.[1,32] Other key risk factors for AD dementia include low education,[44,45] carrying one or two *APOE ε4* alleles,[39] and Black or Hispanic ethnicity.[46,47] The prevalence of Aβ positivity in clinical AD dementia populations is high, but decreases with age, while remaining high in *APOE ε4* carriers.[34] There does not seem to be an association between Aβ positivity and sex or education.[34]

The prevalence of clinical MCI increases with age and is higher for persons with lower levels of education.[35] There is conflicting evidence on whether there is a higher prevalence in men compared to women.[35] The prevalence of Aβ positivity in MCI increases with age and is higher in *APOE ε4* carriers, and those with higher level of education.[10]

Similarly, also in persons with normal cognition or SCD, the prevalence of Aβ positivity increases with age[10,12] and is higher for *APOE ε4* carriers, and those with higher level of education.[10] Neither of two recent comprehensive meta-analyses found a significant difference between men and women,[10,12] whereas the evidence for differences across ethnicities was considered insufficient for meta-analysis.[12]

3.2 | Model estimates of populations on the AD continuum

The available evidence on AD dementia was combined into prevalence estimates for persons aged 50 and above, stratified by 5-year age group, sex, and geographic region (Table 1). The weighted global mean increased with age and was higher for women. Estimates varied quite a lot across regions and were up to 85% higher and 61% lower than the weighted global mean in some regions and age groups. Applying these estimates to population sizes resulted in 32 million persons with Aβ-positive AD dementia globally (Tables S4.1 and S4.4 in supporting information). This constituted 1.7% of all persons aged 50 and above, and two thirds (65%) were women. Considering the uncertainty in prevalence estimates resulted in an uncertainty range between 26 and 39 million. In the sensitivity analysis, using alternative data from a meta-analysis on clinical AD dementia[31] combined with prevalence of Aβ positivity[34] resulted in 20% lower estimates for women and 5% higher for men (Table S4.2).

For prodromal AD, data were considered sufficient for deriving prevalence estimates stratified by age, starting at 2.7% at 60 years of age, increasing to 26.7% at age 90+ (Table 2). Data were insufficient for stratifying by sex or geographic region. Therefore, assuming these estimates are applicable to both sexes worldwide we estimated the number of persons with prodromal AD at 69 million, ranging between 42 and 110 million (Table 3). This constituted 3.7% of all persons aged 50 and above, 57% of which were women. Also, our results suggest persons with prodromal AD (i.e., MCI due to AD) constitute 55% of those with MCI (estimated at 126 million).

For preclinical AD, data were considered sufficient for deriving prevalence estimates stratified by age and sex, while data by geographic region were not sufficient for stratification (Table 2). The resulting estimates started at 12% at age 50 and diverged to 7.5% and 13.6% for women and men, respectively, at age 90+. Assuming these estimates are applicable worldwide we estimated the number of persons with preclinical AD at 315 million, ranging between 258 and 376 million (Table 3). This constituted 17% of all persons aged 50 and above, and 52% of those were women.

In total, these estimates provide an overall prevalence across the AD continuum of 22% of all persons aged 50 and above, increasing steeply with age (Figure 1). This corresponds to a total of 416 million

TABLE 1 Model prevalence estimates of Aβ-positive AD dementia, estimated by age, sex, and GBD region[1] (uncertainty range)

	Men							Women						
	60–64	65–69	70–74	75–79	80–84	85–89	90+	60–64	65–69	70–74	75–79	80–84	85–89	90+
Asia Pacific, high income	0.9% (0.8%-1.1%)	1.4% (1.2%-1.7%)	2.3% (1.9%-2.7%)	3.9% (3.2%-4.6%)	6.5% (5.3%-7.8%)	10.3% (8.3%-12.6%)	19.7% (15.6%-24.3%)	0.6% (0.5%-0.7%)	1.1% (0.9%-1.3%)	2.0% (1.7%-2.4%)	3.7% (3.1%-4.4%)	7.0% (5.7%-8.4%)	12.6% (10.1%-15.4%)	28.0% (22.2%-34.4%)
Asia, Central	0.6% (0.5%-0.7%)	0.8% (0.7%-0.9%)	1.9% (1.6%-2.3%)	3.5% (2.9%-4.1%)	7.0% (5.7%-8.4%)	13.9% (11.1%-16.9%)	13.7% (10.8%-16.8%)	0.6% (0.5%-0.7%)	0.8% (0.7%-0.9%)	1.9% (1.6%-2.3%)	3.5% (2.9%-4.1%)	7.0% (5.7%-8.4%)	13.9% (11.1%-16.9%)	13.7% (10.8%-16.8%)
Asia, East	0.8% (0.6%-0.9%)	1.2% (1.0%-1.4%)	1.8% (1.5%-2.1%)	3.0% (2.5%-3.6%)	5.0% (4.1%-6.0%)	8.0% (6.4%-9.7%)	15.0% (11.9%-18.5%)	0.9% (0.8%-1.1%)	1.6% (1.3%-1.8%)	2.6% (2.1%-3.0%)	4.3% (3.6%-5.1%)	7.4% (6.1%-8.9%)	12.1% (9.7%-14.8%)	23.8% (18.8%-29.2%)
Asia, South	0.8% (0.6%-0.9%)	1.2% (1.0%-1.4%)	1.8% (1.5%-2.1%)	3.0% (2.5%-3.6%)	4.9% (4.0%-5.9%)	7.8% (6.2%-9.4%)	14.5% (11.5%-17.8%)	1.0% (0.8%-1.2%)	1.6% (1.3%-1.8%)	2.4% (2.0%-2.9%)	4.0% (3.3%-4.7%)	6.5% (5.3%-7.8%)	10.2% (8.1%-12.4%)	19.0% (15.0%-23.3%)
Asia, Southeast	1.1% (1.0%-1.3%)	1.6% (1.4%-1.9%)	2.4% (2.0%-2.8%)	3.7% (3.1%-4.4%)	5.7% (4.6%-6.8%)	8.4% (6.8%-10.3%)	14.6% (11.6%-18.0%)	1.1% (1.0%-1.3%)	1.9% (1.6%-2.2%)	3.1% (2.6%-3.6%)	5.4% (4.4%-6.3%)	9.3% (7.6%-11.1%)	15.3% (12.2%-18.6%)	30.4% (24.0%-37.3%)
Australasia	1.1% (1.0%-1.3%)	1.7% (1.5%-2.0%)	2.7% (2.3%-3.2%)	4.5% (3.7%-5.3%)	7.2% (5.9%-8.7%)	11.4% (9.1%-13.9%)	21.2% (16.8%-26.0%)	1.1% (1.0%-1.3%)	1.7% (1.5%-2.0%)	2.7% (2.3%-3.2%)	4.5% (3.7%-5.3%)	7.2% (5.9%-8.7%)	11.4% (9.1%-13.9%)	21.2% (16.8%-26.0%)
Oceania	0.4% (0.3%-0.4%)	1.1% (0.9%-1.3%)	2.3% (1.9%-2.6%)	4.2% (3.5%-4.9%)	8.3% (6.8%-10.0%)	14.7% (11.8%-17.9%)	14.5% (11.5%-17.8%)	0.4% (0.3%-0.4%)	1.1% (0.9%-1.3%)	2.3% (1.9%-2.6%)	4.2% (3.5%-4.9%)	8.3% (6.8%-10.0%)	14.7% (11.8%-17.9%)	14.5% (11.5%-17.8%)
Europe, Central	1.0% (0.8%-1.2%)	1.4% (1.2%-1.7%)	2.0% (1.7%-2.4%)	2.9% (2.4%-3.4%)	4.2% (3.5%-5.1%)	6.0% (4.8%-7.3%)	9.6% (7.6%-11.8%)	1.1% (1.0%-1.3%)	1.6% (1.4%-1.9%)	2.4% (2.0%-2.9%)	3.7% (3.1%-4.4%)	5.8% (4.7%-6.9%)	8.7% (6.9%-10.5%)	15.0% (11.9%-18.4%)
Europe, Eastern	0.6% (0.5%-0.7%)	0.8% (0.7%-0.9%)	1.9% (1.6%-2.3%)	3.5% (2.9%-4.1%)	6.8% (5.6%-8.2%)	13.8% (11.0%-16.8%)	13.5% (10.7%-16.7%)	0.6% (0.5%-0.7%)	0.8% (0.7%-0.9%)	1.9% (1.6%-2.3%)	3.5% (2.9%-4.1%)	6.8% (5.6%-8.2%)	13.8% (11.0%-16.8%)	13.5% (10.7%-16.7%)
Europe, Western	0.7% (0.6%-0.8%)	1.1% (0.9%-1.3%)	1.7% (1.4%-2.0%)	2.8% (2.3%-3.3%)	4.5% (3.7%-5.4%)	7.1% (5.7%-8.6%)	13.1% (10.4%-16.1%)	1.3% (1.1%-1.5%)	2.0% (1.7%-2.3%)	3.2% (2.6%-3.7%)	5.2% (4.3%-6.1%)	8.5% (6.9%-10.1%)	13.3% (10.7%-16.2%)	24.9% (19.8%-30.7%)
North Africa/Middle East	1.4% (1.2%-1.6%)	2.2% (1.9%-2.6%)	3.7% (3.1%-4.3%)	5.8% (4.8%-6.8%)	9.5% (7.8%-11.3%)	16.5% (13.2%-20.1%)	16.3% (12.9%-20.0%)	1.4% (1.2%-1.6%)	2.2% (1.9%-2.6%)	3.7% (3.1%-4.3%)	5.8% (4.8%-6.8%)	9.5% (7.8%-11.3%)	16.5% (13.2%-20.1%)	16.3% (12.9%-20.0%)
Sub-Saharan Africa	0.6% (0.5%-0.7%)	0.9% (0.8%-1.1%)	1.4% (1.2%-1.6%)	2.3% (1.9%-2.7%)	3.3% (2.7%-3.9%)	5.2% (4.1%-6.3%)	9.7% (7.7%-11.9%)	1.3% (1.1%-1.5%)	1.9% (1.6%-2.2%)	2.8% (2.3%-3.3%)	4.5% (3.7%-5.3%)	6.7% (5.5%-8.0%)	10.4% (8.4%-12.7%)	19.8% (15.7%-24.3%)

(Continues)

TABLE 1 (Continued)

|	Men							Women						
	60-64	65-69	70-74	75-79	80-84	85-89	90+	60-64	65-69	70-74	75-79	80-84	85-89	90+
USA	0.8% (0.7%-1.0%)	1.3% (1.1%-1.5%)	2.3% (1.9%-2.6%)	4.0% (3.4%-4.8%)	7.1% (5.8%-8.5%)	12.1% (9.7%-14.8%)	25.0% (19.8%-30.7%)	0.6% (0.5%-0.7%)	1.1% (0.9%-1.3%)	2.0% (1.7%-2.4%)	3.8% (3.2%-4.5%)	7.2% (5.9%-8.7%)	13.0% (10.4%-15.9%)	29.1% (23.1%-35.8%)
Canada	0.8% (0.7%-1.0%)	1.3% (1.1%-1.5%)	2.3% (1.9%-2.6%)	4.0% (3.4%-4.8%)	7.1% (5.8%-8.5%)	12.1% (9.7%-14.8%)	25.0% (19.8%-30.7%)	0.6% (0.5%-0.7%)	1.1% (0.9%-1.3%)	2.0% (1.7%-2.4%)	3.8% (3.2%-4.5%)	7.2% (5.9%-8.7%)	13.0% (10.4%-15.9%)	29.1% (23.1%-35.8%)
Caribbean	1.0% (0.8%-1.2%)	1.8% (1.5%-2.1%)	2.7% (2.2%-3.1%)	5.1% (4.2%-6.0%)	8.3% (6.8%-9.9%)	17.2% (13.8%-21.0%)	17.0% (13.4%-20.9%)	1.0% (0.8%-1.2%)	1.8% (1.5%-2.1%)	2.7% (2.2%-3.1%)	5.1% (4.2%-6.0%)	8.3% (6.8%-9.9%)	17.2% (13.8%-21.0%)	17.0% (13.4%-20.9%)
Latin America	0.9% (0.7%-1.0%)	1.5% (1.2%-1.7%)	2.6% (2.2%-3.1%)	4.4% (3.7%-5.2%)	7.3% (6.0%-8.7%)	12.1% (9.7%-14.8%)	24.2% (19.1%-29.7%)	0.8% (0.7%-1.0%)	1.6% (1.3%-1.8%)	2.9% (2.4%-3.4%)	5.3% (4.4%-6.2%)	9.6% (7.8%-11.4%)	17.2% (13.8%-21.0%)	38.4% (30.4%-47.2%)
Global mean prevalence (weighted by population size)	0.8% (0.7%-1.0%)	1.3% (1.1%-1.5%)	2.1% (1.7%-2.4%)	3.4% (2.8%-4.0%)	5.7% (4.6%-6.8%)	9.3% (7.5%-11.4%)	17.2% (13.7%-21.2%)	1.0% (0.8%-1.1%)	1.6% (1.3%-1.8%)	2.6% (2.2%-3.1%)	4.5% (3.7%-5.3%)	7.7% (6.3%-9.1%)	13.0% (10.4%-15.9%)	25.4% (20.1%-31.2%)
% more in region with highest prevalence	67%	75%	78%	69%	67%	85%	45%	41%	42%	40%	29%	25%	32%	51%
% less in region with lowest prevalence	54%	37%	32%	34%	42%	45%	45%	61%	49%	26%	23%	24%	34%	47%

Notes: Data were derived from Alzheimer's Disease International[1] and Ossenkoppele et al.[34] assuming 70% of general dementia have a clinical AD diagnosis (60% to 80% in uncertainty range). No uncertainty data were available on general dementia prevalence from Alzheimer's Disease International.[1] Data for age groups 50 to 54 (0.0672% in men and 0.0812% in women) and 55 to 59 (0.169% in men and 0.212% in women) were drawn from a separate study, reporting estimates stratified by age and sex but not country;[30] see Table S2.2 in supporting information.

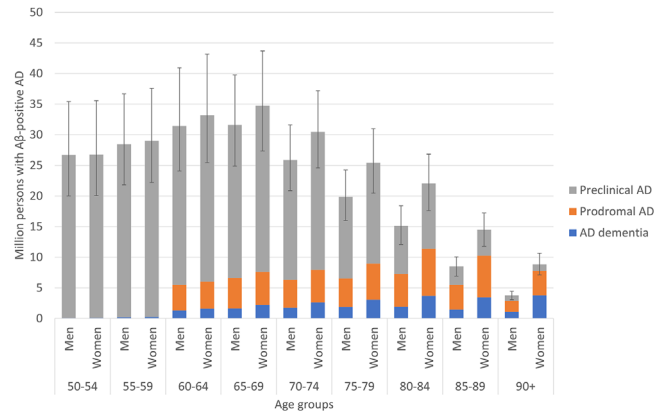Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; GBD, Global Burden of Disease.

TABLE 2 Model prevalence estimates of Aβ-positive preclinical and prodromal AD (uncertainty range)

	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90+
Prodromal AD			2.7%	3.8%	5.2%	8.5%	15.9%	25.8%	26.7%
			(1.2%–5.6%)	(2.2%–6.7%)	(3.6%–7.6%)	(5.3%–13.1%)	(9.6%–24.8%)	(17.7%–35.2%)	(18.5%–36.4%)
Preclinical AD (men)	12.0%	14.7%	16.5%	19.4%	22.4%	24.4%	23.4%	18.8%	13.6%
	(9.0%–15.8%)	(11.3%–18.9%)	(13.4%–19.4%)	(16.1%–22.6%)	(18.7%–26.3%)	(21.0%–27.2%)	(21.7%–23.2%)	(18.7%–17.3%)	(14.6%–10.8%)
Preclinical AD (women)	12.0%	14.7%	16.5%	19.3%	22.2%	23.9%	22.2%	16.1%	7.5%
	(9.0%–15.8%)	(11.3%–18.9%)	(13.4%–18.9%)	(16.0%–22.5%)	(18.5%–26.0%)	(20.6%–26.5%)	(20.7%–21.7%)	(16.4%–14.1%)	(9.2%–4.0%)

Notes: Data were unavailable for estimating the prevalence of prodromal AD in ages below 60, and insufficient for considering separate estimates for men and women. Data were derived from Jansen et al.[10] and Petersen et al.[35]

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease.
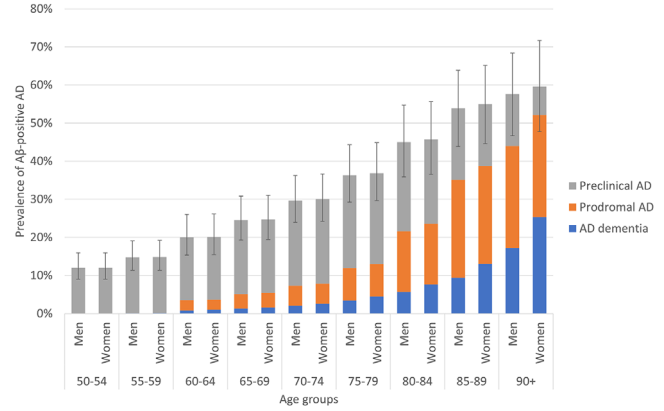
FIGURE 1 Prevalence of Aβ-positive AD across the Alzheimer's continuum, estimated by age, sex, and stage (whiskers indicate uncertainty ranges). Data were derived from various studies[1,10,30,34,35] assuming 70% of general dementia have a clinical AD diagnosis (60% to 80% in uncertainty range). Data were unavailable for estimating the prevalence of prodromal AD in ages below 60, and insufficient for considering separate estimates on the prevalence of prodromal AD for men and women. Aβ, amyloid beta; AD, Alzheimer's disease

FIGURE 2 Estimated number of persons with Aβ-positive AD across the AD continuum, estimated by age, sex, and stage (whiskers indicate uncertainty ranges). Derived from Figure 1 combined with world population sizes (https://population.un.org/wpp/DataQuery/). Aβ, amyloid beta; AD, Alzheimer's disease

persons worldwide, ranging between 327 and 525 million (Figure S5.1 and Table S4.5 in supporting information). Women are somewhat over-represented, especially in advanced ages and with advanced disease stages, constituting 54% overall (Figure 2).

3.3 | Subgroups

The number of persons with prodromal AD and mild AD dementia were estimated at 87 million, of which 59% were women (Table S4.3 in supporting information).

TABLE 3 Million persons on Alzheimer's disease (AD) continuum worldwide, estimated (uncertainty range)

	Men	Women	Both sexes
AD dementia	11.4	20.9	32.3
	(9.3–13.7)	(16.9–25.3)	(26.3–39.0)
Prodromal AD	29.5	39.5	69.0
	(17.9–47.5)	(24.4–62.1)	(42.3–109.6)
Preclinical AD	150.4	164.8	315.2
	(122.5–180.4)	(135.4–195.5)	(257.9–375.9)
Full AD continuum	191.4	225.1	416.4
	(149.8–241.6)	(176.7–282.9)	(326.5–524.5)

Note: Derived from Tables 1 and 2 combined with world population sizes (https://population.un.org/wpp/DataQuery/).

TABLE 4 Million persons on Alzheimer's disease (AD) continuum in Europe, estimated (uncertainty range)

	Men	Women	Both sexes
AD dementia	1.9	5.0	6.9
	(1.6–2.3)	(4.1–6.1)	(5.6–8.4)
Prodromal AD	5.9	9.4	15.2
	(3.6–9.2)	(5.9–14.4)	(9.5–23.6)
Preclinical AD	23.5	28.9	52.3
	(19.4–27.7)	(24.2–33.4)	(43.6—61.0)
Full AD continuum	31.3	43.3	74.5
	(24.6–39.2)	(34.2–53.8)	(58.8–93.0)

Note: Derived from Tables 1 and 2 combined with world population sizes (https://population.un.org/wpp/DataQuery/).

The number of *APOE ε*4 carriers with preclinical AD and prodromal AD were estimated at 175 million and 40 million, respectively, constituting 55% and 57% of all with preclinical AD and prodromal AD, respectively (Table S4.3).

European estimates provided 6.9 million persons with AD dementia, 15 million with prodromal AD, and 52 million with preclinical AD, together constituting 25% of all Europeans aged 50 and above (Table 4). Alternative data from a recent meta-analysis on general dementia in Western Europe[32] confirmed these estimates for men but resulted in 19% lower estimates for women (Table S4.2).

4 | DISCUSSION

4.1 | Main findings

Making use of the best available epidemiologic evidence, we derived a global estimate of 416 million persons in the AD continuum, a number far exceeding the commonly cited estimate of ≈50 million persons with dementia.[1,3] This constitutes 22% of the 1.9 billion people aged 50 and above across the world. This demonstrates that the majority of persons with AD pathology do not have dementia but are in the early stages of the disease. Indeed, most of the persons in our estimates are in the preclinical stage of AD, meaning that they do not have any overt

symptoms and may never develop symptoms. However, even when just counting persons with prodromal AD, a key target population for candidate AD therapies, our estimates (69 million) well exceed commonly cited estimates of AD burden. In addition to providing further illustration of the sheer size of the challenges posed by AD, our results show the window of opportunity for dementia prevention. Individuals with pre-dementia AD are highly relevant from a policy and health-care perspective because they are at risk of developing AD dementia. A better understanding of the size and features of this population can inform national dementia plans and prevention strategies including brain health campaigns geared toward modifiable risk factors.[20]

Our estimates can also be used by health-care planners to assess the potential number of persons eligible for new candidate therapies targeting AD pathology. Our subgroup consisting of persons with prodromal AD and mild AD dementia, estimated at 86 million, is a good example as this is a target population for several drug candidates. Not all will present to health care and some will be unwilling, or have contraindications, to treatment and diagnostic procedures. Furthermore, the health-care systems in different countries will have different constraints on the delivery of such treatment to their populations.[22,23] A previous European analysis assumed 13 and 38% of persons with MCI and dementia, respectively, presented to health care.[48] Applying these assumptions to our European estimates provides a potentially

treatable patient population of 3.4 million persons in Europe alone (1.3 million in the United States with the same assumptions), notwithstanding contraindications or other restrictions to treatment eligibility. The contraindications issue is itself an important aspect that is likely to be debated.[49] Also, our numbers above would increase if more people would present at memory clinics when new therapies become available.

Our estimate of the 32 million persons with AD dementia is comparable to previous and now dated estimates of 27 million persons with AD in 2006.[15] An increase is expected due to aging of the global population.[1] To our knowledge, global estimates of the number of persons with preclinical and prodromal AD have not been published previously. Our estimates for the United States differ from those estimated by an incidence-based approach by Brookmeyer et al.[50] They estimated the US number of persons with $A\beta$-positive preclinical AD, prodromal AD, and clinical AD at 38, 1.8, and 3.6 million, respectively, to be compared to our US estimates of 20, 5.6, and 2.8 million, respectively. The relatively large differences are likely explained by the methodological differences (i.e., incidence-based vs. prevalence-based model) and the selection of input data. The incidence-based approach has the advantage of enabling future projections on population sizes, while being sensitive to accurate data on incidence rates and mortality.[51] We considered the evidence on prevalence to be more robust for deriving global estimates, because the identified incidence studies did not have a global scope, did not report data stratified by age and sex, did not study AD dementia specifically, or did not include biomarker evidence of AD pathology. Our estimates are also comparable to the most recent updates on dementia prevalence from the World Health Organization's global status report on the public health response to dementia[52] (Suppl 6 in supporting information). We note that there are discrepancies in individual age and sex groups while the total estimates are almost identical. There may also be larger differences for individual countries and regions.

While our estimates are reported for populations aged 50+ across stages, the systematic reviews we drew our evidence from did not include age groups below 60 years for prodromal AD. Neither did we include ages below 50 years of age despite the availability of such data.[30] We considered the numbers in these low age groups to be comparatively negligible, but estimates for prodromal AD in lower ages constitute a data gap that should be filled in future research.

It should be noted that our estimates include both persons whose symptoms are actually due to their underlying AD, and persons who have underlying AD pathology but whose symptoms are (partially) due to other conditions (including mixed dementias). This implies that part of this population would still be expected to develop symptoms even if their AD pathology could be halted or reversed.

Higher age is the dominant determinant of higher prevalence in AD. With aging populations, this is the primary cause of the increasing numbers of persons with AD that have been seen over time, and which is expected to continue. The evidence is also clear for *APOE* status, where *APOE ε*4 carriers exhibit a higher risk of AD pathology and progression to more severe stages.[9] Persons with higher level of education have a lower risk of clinical manifestation of AD,[44,45] whereas highly educated cognitively normal persons and persons with MCI have a higher risk of $A\beta$ positivity compared to those with less education.[10] This is consistent with the cognitive reserve hypothesis, suggesting that education protects against clinical deterioration despite increasing AD pathology.[53] Thus, attention to factors related to the cognitive reserve may be particularly important in predementia AD. Alternative explanations include potential bias in those with higher education being more prone to seek medical care.

Sex differences are more complex as they depend on the disease stage. Women with normal cognition or MCI in fact perform better on verbal memory and fluency domains compared to men and might miss early diagnosis. On the other hand, they progress faster to more advanced stages, once symptoms manifest.[41,54] There is also evidence suggesting that women have higher tau pathology burden,[55] faster accumulation of tau,[56] and faster rates of brain atrophy, even controlling for AD pathology, compared to men.[41,57] Our results add to the existing body of literature by defining sex ratios in biomarker-confirmed cases.

It is well known that most individuals with AD dementia are women, which we also confirm with our estimates of two thirds of persons with $A\beta$-positive AD dementia being women. In Europe the estimated number of women is almost double that of men with AD, while differences in other regions such as in the United States are smaller; a better understanding of such regional effects is needed. It is often argued that higher frequency in women, when observed, is due to higher female longevity; however, we also demonstrated a relatively higher prevalence of $A\beta$-positive AD dementia in women compared to men when stratified by age. The increase of AD dementia prevalence with age in women might be related to the selective survival hypothesis, whereby women at older age have a cerebrovascular disadvantage compared to men, who tend to die earlier of cardiovascular events.[58] In prodromal AD, although several studies have indicated that MCI frequency is higher among men, the systematic review we found concluded that the evidence for such a difference was conflicting and thereby considered insufficient for our purpose. Considering the same prevalence for men and women, the overall number of estimated women with $A\beta$-positive prodromal AD was still higher than that of men. This finding would be in line with the natural history of the disease and the known female bias. More data are needed to clarify the sex ratio at prodromal stages of the disease. Interestingly, we found that also the estimated numbers of persons with preclinical AD was overall higher among women. Prevalence in each age bracket was similar across sexes, with the exception of the oldest old; here, a lower female estimated prevalence was observed, likely due to the fact that in this age a higher fraction of women have progressed to symptomatic stages of the pathology. Overall, our data support the notion that while men and women present with the preclinical form of AD at similar frequency, women may sustain their cognitive capacity for longer but then eventually decline faster (resulting together with higher survival rates in higher prevalence of dementia), while a larger proportion of $A\beta$-positive men remain in the prodromal stage. This could indicate a different form of cognitive reserve across the sexes, which should also be considered in the assessment of sex-specific response to interventions.

There is a complex of potential interactions with other risk factors that may explain these sex differences, including factors that are more or less prevalent in men or women (e.g., higher education), those that may be modified by sex (e.g., *APOE* status), and those that are sex-specific (e.g., menopause).[54] More research on this topic is called for.[54,59]

Several recent US studies report on differences in AD dementia prevalence and incidence across ethnicities,[46,47,60,61] including higher risks in Black, Hispanic, and Native Hawaiian ethnic groups and lower in Asian American groups, compared to White groups. The differences between ethnicities may be explained by both genetic factors (e.g., *APOE* status) and environmental factors including comorbidity, education, and socioeconomics.[60] The available data were unfortunately not considered sufficient for inclusion in our model, and again more research is needed.[60]

All determinants above, including demographics, genetics, and socioeconomic and lifestyle factors may in part explain differences across geographic regions. While controlling for age and sex, such differences were clearly demonstrated for general dementia[1] whereas the evidence was weaker for AD dementia.[31] It is uncertain to what extent additional risk factors can be identified explaining the remaining differences across countries. Education level, *APOE* status, and ethnicity are interesting candidates for further research, as they all vary across different regions and populations. Part of the reported differences may also be due to methodological differences across studies.

4.2 | Uncertainty

There are several sources of uncertainty in our estimates.

First, the diagnostic criteria and definitions of different stages of AD have changed over time[7] and have been applied differently in different studies over the last few decades. Still today, many studies on AD dementia rely on clinical diagnosis without biomarker confirmation[31] and many studies refer to AD while only including dementia stages of AD. Our approach to address this variation was to combine evidence from large meta-analyses including their uncertainty measures, and adjust estimates with explicit assumptions where needed. We specifically considered Aβ positivity as sufficient to be included in our estimates, including for preclinical AD, in concordance with the 2011 NIA-AA diagnostic criteria[24] and as considered in other studies.[12,50] However, based on recently suggested criteria, Aβ pathology is sufficient for "Alzheimer's pathologic change" whereas tau-pathology is also required for "Alzheimer's disease."[7] About 30% of the population herein defined as preclinical AD is expected to also have tau pathology.[43,62] Nevertheless, the presence of either should be considered an elevated risk for developing prodromal AD and AD dementia.[12,14]

Second, there is variation in the methods for measuring both biomarkers and clinical symptoms across studies, which may explain part of the variation in their reported prevalence estimates. Across studies, Aβ positivity has been measured with varying PET tracers (e.g., Pittsburg compound B, florbetapir, or florbetaben) with differing quantitative measure cutoffs or visual reads, and with varying CSF assays with different cutoffs for abnormal Aβ42 levels or Aβ42/Aβ40 ratios.[10,12] Varying measures of clinical symptoms include whether they consider memory/cognitive complaints, objectively measured memory/cognitive impairment (e.g., by varying Mini-Mental State Examination cutoffs), impairment in ADL, and combined cognitive and functional measures (e.g., global scores of the Clinical Dementia Rating scale).[35] Altogether, the "biomarker affair" is not yet entirely settled because harmonization studies providing normative data and cut-off limits with homogeneous technologies are still scant and urgently needed.[63,64]

Third, the subject recruitment strategy and related study design properties vary across studies and have been suggested to limit the generalizability of study findings.[10] Many studies on participants with normal cognition recruit subjects via advertisements, which may induce self-selection bias and restrict generalizability.[10] Conversely, MCI participants are commonly recruited from clinical settings, which may also limit their generalizability to the general population.[10] Two-phase study designs are common, where participants are first assessed by simple standardized screening tests, and only screen-positives advance to thorough diagnostic assessment. A review suggested that about two thirds of dementia studies are limited by the failure to adjust for false screen-negatives in such studies.[1]

In practice, it is unclear how large an effect these discrepancies have on the final prevalence estimates. Indeed, Jansen et al. concluded that neither biomarker modality nor recruitment strategy for cognitively normal persons were associated with the prevalence of Aβ positivity.[10] For the purpose of our study, we used the reported confidence intervals to explore the overall uncertainty in published point estimates.

4.3 | Limitations

Our estimates are limited by the uncertainty in the original studies and meta-analyses from which we have drawn our model inputs, and the paucity of data on predementia AD stages and biomarker-confirmed populations, especially from low- and middle-income regions of the world. We have tried to minimize this uncertainty by drawing from large meta-analyses rather than individual original studies. This may have resulted in neglecting some important differences across specific populations or countries, but is supported by the lack of consistent data on potential differences across countries in predementia stages of AD. Moreover, we extrapolated the published evidence to countries where data are missing. This is another important limitation and we strongly point out the need for future studies on the prevalence of predementia stages of AD across countries to test our extrapolations. Not least, biomarker data are limited to high-income regions of the world. More studies elsewhere are warranted. As with any epidemiological study using statistical inference we do not know how far off our prevalence estimates are, and cannot confirm our uncertainty ranges include the true prevalence of AD in the global population. This needs to be tested in future studies. However, our data can offer a relevant starting point from which better estimates can be developed over time.

Also, a more comprehensive model that takes differences in education, *APOE* status, and ethnicity into account may provide more accurate estimates. Our subgroup analysis stratifying by *APOE* status was simplistic in assuming the same proportions of *APOE ε*4 carriers across all geographic regions. Finally, our literature search may have missed relevant articles due to its targeted approach (including single review and use of bibliographic filters) as well as limitations in publication languages (English, French, German, and Spanish) and publication time (2010–2020).

4.4 | Conclusions

In conclusion, when taking into account predementia stages, the number of persons with AD is much larger than what is conveyed in available literature and the public discourse, which typically focuses on the prevalence of dementia. The vast majority of persons on the AD continuum do not have dementia but are in the predementia stages of disease, providing a window of opportunity for prevention. Policy makers worldwide can use our estimates to inform national dementia plans, brain health campaigns, and other efforts in preventing symptomatic stages of AD. Health-care planners can use our estimates to assess the number of eligible patients for treatment, should a new therapy be approved for early stages of AD. In parallel, we see the scientific need for more research on the prevalence across the AD continuum, specifically in low- and middle-income regions, and preferably including biomarker confirmation of AD pathology. Such studies should, in addition to geography, specifically consider the effects of sex, genetics (including *APOE* status), education, and ethnicity. They should also consider other aforementioned factors that determine prevalence estimates of AD, including its diagnostic criteria, stage definitions, methods for the assessment of biomarkers and symptoms, subject recruitment strategies, and related study design properties. This research would help to test our estimates, which are uncertain especially for predementia stages in low- and middle-income regions where biomarker studies are missing.

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SUPPORTING INFORMATION

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