Received: 11 October 2020 | Revised: 29 March 2021 | Accepted: 5 April 2021

DOI: 10.1002/alz.12362

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Population estimate of people with clinical Alzheimer's disease and mild cognitive impairment in the United States (2020–2060)

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Abstract

Introduction: The estimate of people with clinical Alzheimer's disease (AD) and mild cognitive impairment provides an understanding of the disease burden.

Methods: We estimated people with cognitive impairment using a quasibinomial regression model in 10,342 participants with cognitive test scores.

Results: The 2020 US Census–adjusted prevalence of clinical AD was 11.3% (95% confidence interval [CI] = 10.7–11.9): 10.0% among non-Hispanic Whites, 14.0% among Hispanics, and 18.6% among non-Hispanic Blacks. We estimate that in 2020, 6.07 (95% CI = 5.75–6.38) million people were living with clinical AD, which increases to 13.85 (95% CI = 12.98–14.74) million in 2060, 423% higher among Hispanics, 192% higher among Blacks, and 63% higher among Whites. However, there are predicted to be more significant increases in later years among those over 85 and women compared to men.

Discussion: The number of people with clinical AD will increase as the "baby boom" generation reaches older ages, exerting a strong upward influence on disease burden.

KEYWORDS
2020 US prevalence, clinical Alzheimer's disease, forecasting, mild cognitive impairment

1 | INTRODUCTION

Disease forecasting has been an area of intense interest to the scientific community for more than seven decades.[1] The forecasting developments include failures of success[2] and the pandemic of chronic disease.[3] The US demographic characteristics have been changing with the "baby boom" generation reaching older ages,[4,5] resulting in a larger number of older adults[6,7] and growth in diverse populations,[8,9] which significantly impacts individuals, families, and society.[10–11] A lack of effective therapeutic agents has exacerbated the expected increase in health-care and caregiving costs,[12–14] as the number of people with Alzheimer's disease (AD) increases. Therefore, the demographic-specific number of people with clinical AD and mild cognitive impairment (MCI) from 2020 through 2060 provides the opportunity to understand the national-level resources and policies needed to fight AD in minority and vulnerable populations.

Previous estimates of the prevalence of clinical AD and MCI were based on detailed clinical evaluation using a comprehensive battery of cognitive tests.[15–18] Several research studies and meta-analyses have used the clinical diagnosis to estimate prevalence and forecast disease.[19–20] However, performing clinical evaluations can be time-consuming and expensive in population studies, and medical records could increase classification errors. In our earlier work, we developed likelihood scores to estimate the 2010 US Census–adjusted prevalence of clinical AD and MCI. We characterized the secular trend in the prevalence of clinical AD from 1993 to 2012,[21] and those scores can also forecast disease.

This article aims to extend the likelihood score approach to estimate the number of people with clinical AD and MCI in the United States from 2020 through 2060. Using the Chicago Health and Aging Project (CHAP), we will estimate the 2020 US Census–adjusted prevalence of clinical AD and MCI by age and race/ethnicity (Blacks, Whites, and Hispanics).

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed, Google, and ResearchGate. The focus of the search was previous research on estimates of clinical Alzheimer's disease (AD) and mild cognitive impairment (MCI) in the United States. The 2020 US Census–adjusted estimates are not generally available. The relevant citations for people with clinical AD and MCI are appropriately cited.
2. **Interpretation**: Using a large community-based population study in 10,342 individuals representing three racial/ethnic groups, we report the 2020 adjusted US prevalence and the number of people with clinical AD and MCI in the United States. The number of people with clinical AD increases from 6.07 million in 2020 to 13.85 million in 2060. The percent increase in clinical AD cases among Hispanics and Blacks is more significant than non-Hispanic whites.
3. **Future directions**: Our findings suggest continued monitoring of clinical AD and MCI in the US population, especially with the current COVID-19 outbreak impacting the cognitive health of older adults.

2 | METHODS

The CHAP study enrolled participants based on a door-to-door census in four Chicago neighborhoods where residents were non-Hispanic White, Hispanic, and non-Hispanic Black.[22] The inclusion criteria required the study participants to live on the South Side of Chicago and be 65 years and older. The first cycle of data collection started in 1993 and ended in 1996 when we enrolled 78.7% of residents over 65, with a follow-up between 1997 and 1999. Between 2000 and 2012, four successive cohorts of participants reaching the age of 65 enrolled, joining the original cohort. Of the 10,801 total participants, 10,342 (95.8%) participants performed at least one neuropsychological test and provided demographic covariates. During the study, 5583 (54.0%) participants died, and 1349 (13.0%) were lost to follow-up (Appendix Figure A1).

The Institutional Review Board of the Rush University Medical Center approved the study protocols, and all participants provided written informed consent for in-home cognitive assessments for clinical AD.

2.1 | Clinical AD and MCI likelihood scores

The likelihood scores used results from the four short cognitive tests administered during in-home population interviews. The cognitive tests consisted of two tests of episodic memory based on immediate and delayed story recall of the East Boston Memory Test (scores ranging from 0 to 12),[23] one test for executive function based on the Symbol Digit Modalities Test (SDMT; scores ranging from 0 to 75),[24] and the Mini-Mental State Examination (MMSE; scores ranging from 0 to 30).[25] In general, higher cognitive test scores indicated better cognitive performance and a lower risk of clinical AD and MCI according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[26]

We estimated the person-specific likelihood of clinical AD and MCI using a sample weight–adjusted generalized logistic regression model of clinically diagnosed clinical AD and MCI, as predicted by the short-battery cognitive test scores.[21] This regression model is also included as independent variables age at clinical evaluation, female sex, formal education (in years), and Black race/ethnicity. The likelihood scores provide the probability of clinical disease based on neuropsychological test scores, ranging from 0 to 1, rather than cutoffs that introduce misclassification errors. The likelihood scores used the short-battery test scores and demographic characteristics in 10,342 participants with 36,408 cognitive assessments between 1993 and 2012. Hence, a participant can contribute to the age-specific prevalence of clinical AD and MCI throughout the study.

2.2 | US Census demographics from 2020 through 2060

We used the projected demographic-specific characteristics of the US population, available through the Centers for Disease Control (CDC) WONDER application for US Census projections from 2020 through 2060.[27] The census data consisted of estimates of US population and consisted of age (65–69, 70–74, 75–79, 80–84, 85 and over), ethnicity (Hispanic vs. non-Hispanic), and racial groups (White, Black, Asian, Native American, and others). The population sizes also consisted of men and women. We combined 5-year age groups to create three 10-year age intervals: 65 to 74, 75 to 84, and over 85 years for the three racial/ethnic groups—non-Hispanic White, Black, and Hispanics for men and women. The prevalence and number of people were estimated for the 5-year age groups and combined at the final step. A single group for Hispanic ethnicity, and the remaining Whites and Blacks classified on their non-Hispanic ethnicity. The study participants identified their ethnicity as White, Black, Asian, Pacific Islanders, or others, and their ethnicity of Hispanic or non-Hispanic origin. The study sample consisted of a small number of participants who reported multiple races and were classified as minorities, non-Hispanic Blacks or Hispanic, if the multiple race consisted of one of them.

2.3 | Statistical analysis

Baseline descriptive statistics for 10,342 participants, stratified by the three race/ethnicity groups for demographic characteristics, such as age, the number of formal years of education completed, the sex of the participant, and the crude prevalence based on the likelihood scores. Descriptive statistics included means and standard deviations for continuous characteristics and percentages for categorical characteristics for baseline population interviews.

To estimate the number of older adults in our study population with clinical AD and MCI, we used a generalized additive quasibinomial regression model with the likelihood scores as the outcome variable and four participant characteristics: age (65–74, 75–84, and 85 and older), race/ethnicity (White, Black, Hispanic), sex, and education (standardized for the CHAP study sample).[28] The sandwich variance estimator accounted for repeated observations and overdispersed likelihood scores (see the Methods section in the Appendix for more details). The model also included years since the first cognitive assessment and an additional person-specific random effect for baseline probability of clinical AD. We estimated the 2020 US Census–adjusted prevalence of clinical AD by standardizing the yearly age–sex–race estimates with each group-specific prevalence weighted to the US Census using the corresponding group sizes. We estimated the number of people with clinical AD by weighing the group-specific prevalence with the number of people in each age, race/ethnicity, and sex group. We estimated their confidence interval using the model sandwich estimator for demographic groups. This process was repeated for each year to forecast people with the disease. We used a similar modeling approach for forecasting all-cause MCI in the United States. We used marginal totals of sex and race/ethnicity within each age group. We followed a similar process for estimates specific to race/ethnicity and sex groups. The likelihood scores also used a conservative last observation carried forward imputation when they had died or due to non-participation. Therefore, the extrapolation for count estimates also adjusted for truncation due to mortality and missing data. Statistical analyses used several packages and graphical representations provided using the R program.[29]

3 | RESULTS

Of the 10,342 participants in our study, 36.2% identified as non-Hispanic White, 1.3% as Hispanic, and 62.5% as non-Hispanic Black (Table 1). The mean baseline age was 71.0 years. Among participants aged 65 to 74 years old, more were Black than were White (77% vs. 55%); among participants 85 years and older, fewer were Black (5% vs. 13%). Participants attained a mean of 12 years of formal education. More than 60% of participants were women. The crude baseline prevalence of clinical AD using the likelihood score was 15.0% in the study population overall, 18.1% among Black participants, 14.1% among Hispanic participants, and 9.7% among Hispanic participants. The MCI prevalence was 27.3% (overall), with Blacks also having a higher prevalence of MCI compared to Whites (32.6% vs. 20.3%), while the Hispanic prevalence of MCI (26.8%) was between that of Blacks and Whites.

TABLE 1 Sample characteristics of 10,342 participants by race/ethnicity

	Non-Hispanic White N = 3742	Hispanic N = 132	Black N = 6458
Age, y, N (%)			
65–74	2053, 55%	88, 66%	5006, 77%
75–84	1190, 32%	34, 26%	1144, 18%
85 and older	499, 13%	10, 8%	308, 5%
Sex, N (%)			
Males	1452, 39%	44, 33%	3955, 39%
Females	2503, 61%	88, 67%	2503, 61%
Education, y, mean (SD)	13.8, 3.2	12.1, 4.4	11.4, 3.4
Prevalence, %			
Clinical AD	9.7%	14.2%	18.1%
MCI	20.3%	26.8%	32.6%

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; SD, standard deviation; y, years.

3.1 | 2020 US Census–adjusted prevalence of clinical AD and MCI

The overall 2020 US Census–adjusted prevalence of clinical AD was 11.3% (95% confidence interval [CI] = 10.7–11.9), with Blacks having nearly twice the prevalence as Whites (18.6% vs. 10.0%), and the prevalence was 14.0% among Hispanics (Table 2). The age-specific prevalence of clinical AD was 5.3% (95% CI = 4.9–5.7) among adults 65 to 74 years old, 13.8% among adults 75 to 84 years old (95% CI = 13.1–14.5), which increased to 34.6% among adults 85 years and older (95% CI = 33.3–35.8).

The overall patterns in age- and race/ethnicity-specific prevalence of clinical AD carried over to groups jointly defined by age and race/ethnicity. In each race/ethnicity, the prevalence of AD was higher with the progressively older age category. In each of the three age categories, the prevalence of AD was highest among Blacks, lowest among Whites, and intermediate among Hispanics.

The 2020 US Census–adjusted prevalence of all-cause MCI was 22.7% (95% CI = 22.3–23.2), which was more than twice the prevalence of clinical AD (Table 2). The overall prevalence of MCI was higher among Blacks than Whites (32.0% vs. 21.1%), and 25.9% among Hispanics was between Blacks and Whites. The prevalence of MCI also showed variability by age and race/ethnicity, with higher rates among Blacks than Whites in each age group (Table 2).

3.2 | Number of people with clinical AD and MCI from 2020 through 2060

We estimated that 6.07 (95% CI = 5.75–6.38) million older adults in the United States had clinical AD in 2020 (Table 3). This number will increase by 18% to 7.16 million in 2025 and 128% to 13.85 million

TABLE 2 2020 US Census–adjusted prevalence, cases per 100 persons, (95% CI) of clinical AD and MCI, by age and race/ethnicity using 10,342 participants from the Chicago Health and Aging Population Sample

	Clinical AD prevalence, cases per 100 (95% CI)	MCI prevalence, cases per 100 (95% CI)
All participants		
Non-Hispanic White	10.0 (9.6–10.4)	21.1 (20.8–21.5)
Hispanic	14.0 (12.0–16.1)	25.9 (24.5–27.3)
Black	18.6 (18.0–19.1)	32.0 (31.7–32.4)
Overall prevalence	11.3 (10.7–11.9)	22.7 (22.3–23.2)
65–74 years		
Non-Hispanic White	4.3 (4.1–4.6)	20.2 (19.9–20.6)
Hispanic	7.0 (5.8–8.3)	24.9 (23.5–26.3)
Black	10.1 (9.6–10.6)	30.9 (30.6–31.3)
Age-specific prevalence	5.3 (4.9–5.7)	21.9 (21.5–22.4)
75–84 years		
Non-Hispanic White	11.9 (11.3–12.4)	23.1 (22.7–23.4)
Hispanic	18.7 (15.8–21.5)	28.2 (26.7–29.7)
Black	25.2 (24.5–25.9)	34.7 (34.3–35.1)
Age-specific prevalence	13.8 (13.1–14.5)	24.6 (24.2–25.1)
Over 85 years		
Non-Hispanic White	31.6 (30.7–32.5)	20.7 (20.3–21.0)
Hispanic	44.0 (39.3–48.7)	25.5 (24.1–26.9)
Black	54.0 (53.0–55.0)	31.6 (31.2–32.1)
Age-specific prevalence	34.6 (33.3–35.8)	22.1 (21.6–22.5)

Note: Prevalence estimates derived from a quasibinomial regression model for likelihood of probable clinical AD and MCI adjusting for age, race/ethnicity, sex, and education.
Abbreviations: AD, Alzheimer's disease; CI, confidence interval; MCI, mild cognitive impairment.

in 2060. In 2020, of all people with clinical AD, estimated prevalence was 70.8% White, 17.5% Black, and 11.7% Hispanic. By 2060, the proportions of persons with AD who are Black and Hispanic will increase to 24.5% and 26.8%, respectively, while it will decrease to 50.8% of Whites.

The number of people in the United States with MCI increased from 12.23 (95% CI = 11.99–12.47) million in 2020 to 21.55 (95% CI = 21.00–22.10) million in 2060 (Table 3), an increase of 9.32 million (76.2%) from 2020 to 2060. The number of Whites with MCI increased from 9.10 million in 2020 to 11.46 million in 2060, increasing by 2.36 million (25.9%) over the years. In comparison, Hispanics increased from 1.30 million to 5.64 million, an increase of 4.34 million (333.8%) from 2020 to 2060. The number of Blacks with MCI increased from 1.84 million in 2020 to 4.45 million in 2060, increasing by 2.61 million (141.8%).

3.3 | Age-specific number of people with clinical AD from 2020 through 2060

The number of those 65 to 74 years old with clinical AD increases from 1.65 (95% CI = 1.36–1.94) million in 2020 to 2.51 million in 2060 (Figure 1), an increase of 0.86 million (52.1%) from 2020 to 2060. The number of those 75 to 84 years old with clinical AD increased from 2.18 (95% CI = 1.90–2.46) million in 2020 to 4.66 million in 2060, increasing 2.48 million (113.8%) in four decades. Finally, the number of people aged over 85 with clinical AD increased from 2.24 million in 2020 to 6.67 million in 2060, increasing 4.43 million (197.8%) over 40 years.

The number of people over 85 years old with clinical AD was higher than those in the 65 to 74 and 75 to 84 age groups in 2020. However, the number of people with clinical AD between 75 and 84 years old and over 85 years old was identical in 2021 (2.25 vs. 2.27 million). Between 2022 and 2030, the number of those 75 to 84 years old with clinical AD becomes higher than the number of people with clinical AD over 85 years old. The number of those over 85 years old continued to increase between 2040 and 2060 than among those 75 and 84 years old. These findings suggest the strong influence of significant changes in age demographics on the number of people with clinical AD.

3.4 | Sex-specific number of people with clinical AD from 2020 through 2060

The number of women with clinical AD increased from 3.74 (95% CI = 3.51–3.97) million in 2020 to 8.22 (95% CI = 7.99–8.43) million in

TABLE 3 Projected number of people in the United States (in millions) with clinical AD (in millions) 2020 to 2060, by race/ethnicity and year

Year	Non-Hispanic White	Hispanic	Black	Total
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Number of people with clinical AD (millions)				
2020	4.30 (4.12–4.48)	0.71 (0.61–0.81)	1.06 (1.03–1.09)	6.07 (5.75–6.38)
2021	4.40 (4.21–4.58)	0.76 (0.64–0.85)	1.10 (1.07–1.14)	6.25 (5.92–6.58)
2022	4.53 (4.30–4.68)	0.79 (0.67–0.90)	1.15 (1.11–1.19)	6.46 (6.12–6.80)
2023	4.67 (4.47–4.86)	0.83 (0.71–0.95)	1.20 (1.17–1.24)	6.70 (6.34–7.05)
2024	4.80 (4.59–5.00)	0.87 (0.74–1.00)	1.26 (1.22–1.30)	6.93 (6.56–7.29)
2025	4.93 (4.72–5.13)	0.92 (0.79–1.06)	1.31 (1.27–1.36)	7.16 (6.78–7.55)
2030	5.72 (5.48–5.95)	1.19 (1.02–1.37)	1.61 (1.57–1.67)	8.53 (8.07–8.99)
2040	7.03 (6.76–7.30)	1.90 (1.63–2.18)	2.23 (2.17–2.29)	11.16 (10.55–11.77)
2050	7.29 (7.02–7.56)	2.77 (2.38–3.16)	2.66 (2.58–2.73)	12.73 (11.99–13.46)
2060	7.03 (6.77–7.30)	3.72 (3.20–4.23)	3.10 (3.01–3.19)	13.85 (12.98–14.71)
Number of people with MCI (millions)				
2020	9.10 (8.95–9.24)	1.30 (1.22–1.37)	1.84 (1.81–1.86)	12.23 (11.99–12.47)
2021	9.34 (9.19–9.49)	1.37 (1.30–1.45)	1.92 (1.90–1.94)	12.64 (12.39–12.89)
2022	9.61 (9.46–9.77)	1.45 (1.37–1.53)	2.01 (1.99–2.03)	13.08 (12.82–13.33)
2023	9.88 (9.72–10.03)	1.53 (1.45–1.62)	2.10 (2.07–2.12)	13.51 (13.24–13.77)
2024	10.12 (9.96–10.28)	1.62 (1.53–1.71)	2.19 (2.16–2.21)	13.93 (13.65–14.20)
2025	10.38 (10.20–10.54)	1.71 (1.62–1.81)	2.28 (2.25–2.31)	14.37 (14.08–14.65)
2030	11.36 (11.18–11.54)	2.19 (2.08–2.32)	2.70 (2.67–2.73)	16.26 (15.92–16.59)
2040	11.67 (11.49–11.86)	3.26 (3.08–3.44)	3.23 (3.19–3.26)	18.16 (17.76–18.57)
2050	11.24 (11.06–11.42)	4.40 (4.16–4.64)	3.64 (3.60–3.68)	19.29 (18.82–19.75)
2060	11.46 (11.27–11.64)	5.64 (5.33–5.60)	4.45 (4.40–4.50)	21.55 (21.00–22.10)

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; MCI, mild cognitive impairment.

2060 (Figure 2), increasing by 4.48 million (119.7%) women with clinical AD over the next four decades. On the other hand, the number of men with clinical AD increased from 2.34 (95% CI = 2.08–2.60) million in 2020 to 5.64 (95% CI = 5.36–5.92) million in 2060, an increase of 3.30 million (141.0%) men with clinical AD between 2020 and 2060. In 2020, 1.40 million more women have clinical AD than men, with this difference increasing to 2.58 million in 2060. Hence, the sex gap in the number of people with clinical AD is expected to continue to widen in the United States over the next four decades.

4 | DISCUSSION

In the United States, an estimated 6.07 million adults ages 65 and older had clinical AD in 2020, which will increase to 13.85 million in 2060. The age-specific number of people with clinical AD will also increase, as the post-World War II "baby boom" generation will become increasingly older. In 2020, the number of people living with clinical AD was higher among those over 85 years old than among younger age groups. However, based on our projections for prevalence, starting in 2022, the number of those 75 to 84 years old with clinical AD will exceed 85 years and older with clinical AD. The change in age demography shows a shift in the population burden of clinical AD, with more younger individuals having the disease than in the oldest age groups.

As the US population shifts with increases in the number of minorities, we can expect the number of minorities with clinical AD to increase in the coming years, highlighting the vital need to include underrepresented populations in research studies. Also of public health significance is that more women had clinical AD in 2020 than men. This gap will continue to widen over the next 5 years and will have a higher burden on women.[30] The significant increases in the overall and demographic-specific number of people with clinical AD will require more significant resources over the coming years.

The 2020 adjusted prevalence of clinical AD was lower than the 2010 adjusted prevalence of clinical AD from the same study population.[17,21] The difference in prevalence over the 10 years is primarily due to change in population demographics, specifically the significant increase in the number of those 65 to 74 years old and 75 to 84 years old. The expansion in these age groups is much more significant than the change in those more than 85 years old. The change in population demographics makes the prevalence estimates adjusted for the 2020 US Census smaller than the 2010 US Census prevalence estimates. However, the 2010 US Census–adjusted prevalence of clinical AD using our approach was similar to the 2010 US

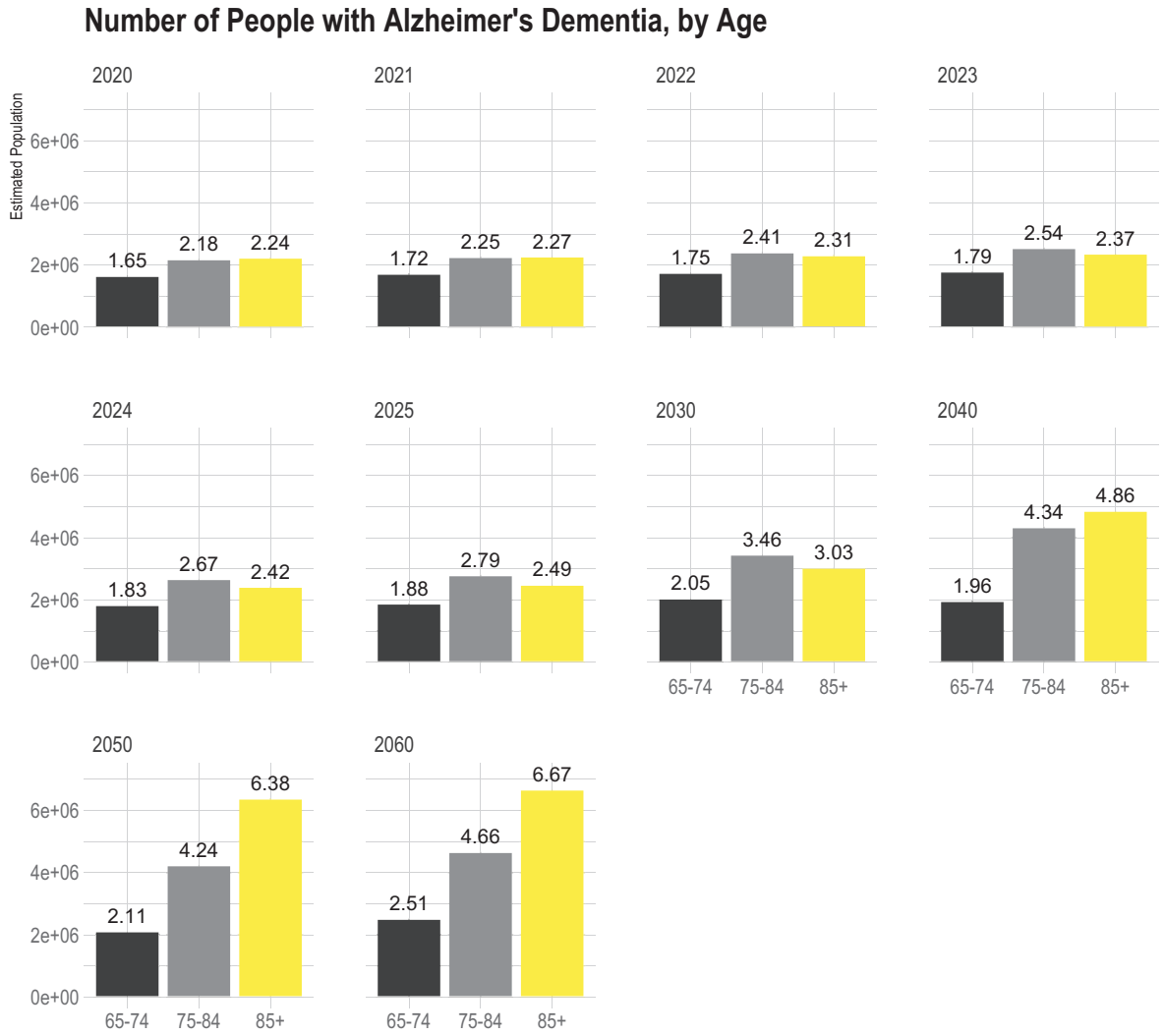

FIGURE 1 Age distribution of projected number of people in the United States (in millions) with clinical Alzheimer's disease (AD) from 2020 to 2060. The blue bar shows the estimated US population between 65 and 74 years old with clinical AD, the gray bar for ages 75 to 84, and yellow for over 85 years. The six panels show the estimated US population for the projected population from 2020 to 2060. The estimated number of people above bars are in millions

Census–adjusted prevalence estimates in other epidemiological studies and meta-analyses.[19]

Several studies have reported a decrease in AD and dementia incidence over the last few decades,[31–33] and some were suggesting no recent changes in prevalence and incidence.[21,34–35] The projections use prevalence in our study sample, and these might change depending on the future changes in disease occurrence. Similar forecasts can be made with the Global Burden of Disease Institute for Health Metrics data visualization software tools for the United States in future years based on International Classification of Disease conditions.[36] Future work comparing the different approaches might provide better estimates of AD and dementia in the population.

The age-specific prevalence of clinical AD was 2- to 3-fold higher over each of the 10-year age intervals. The 2020 age-specific prevalence of clinical AD was similar to previous estimates.[37] The race-specific prevalence of clinical AD is also noteworthy; it was highest among Blacks, followed by Hispanics and non-Hispanic Whites. This finding is consistent with previous findings that Blacks have a much larger prevalence than other racial/ethnic groups.[17,18]

The number of people with clinical AD in the United States is estimated to be 6.07 million, slightly higher than the previously reported 5.8 million.[38] However, considering the statistical uncertainty in the two estimates, the two approaches generated estimates that are consistent with each other. The estimate presented here uses the dementia likelihood score based on a short-battery cognitive test in 10,342 participants. In contrast, the previous estimate used the clinical diagnosis of clinical AD in 1954 people, nearly one eighth of the CHAP study population with clinically diagnosed clinical AD. Second, the likelihood scores use the population sample, but the previous estimates use a more complex stratified random sampling scheme. However, our population sample used all participants and included no sampling weights in the estimation model.

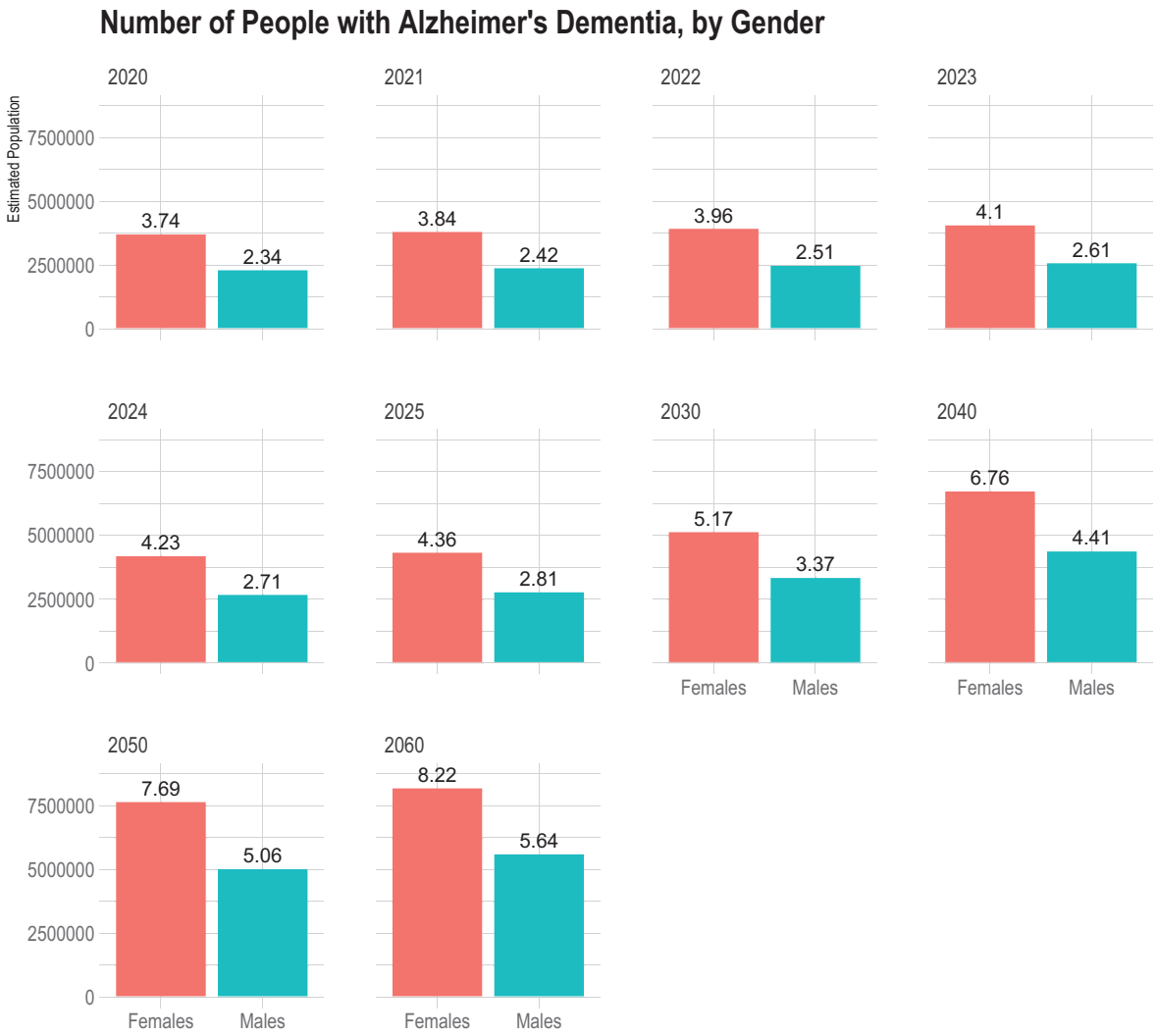

FIGURE 2 Sex distribution of projected number of people in the United States (in millions) with clinical Alzheimer's disease (AD) from 2020 to 2060. The red bar shows the estimated number of females with clinical AD, and the green bar shows the estimated number of men in the US with clinical AD. The six panels show the estimated females and males in the US with clinical AD from 2020 to 2060. The estimated number of people above bars are in millions

We also provided the number of people with MCI in the United States from 2020 through 2060. The number of people with MCI in the United States is twice the number of people living with clinical AD. We estimate that 12.23 million people had MCI due to all causes in 2020, which will increase to 21.55 million in 2060. This increase in the number of people living with MCI will have implications for AD as people with MCI progress to dementia with high transition probabilities leading to increased clinical AD.[39] The increase in the number of those with MCI translates to health-care costs and caregiving needs of families depending on the level of cognitive impairment.[40]

This study has important strengths. First, we used likelihood scores rather than clinical diagnoses to estimate the number of people with clinical AD and MCI from 2020 through 2060, decreasing the estimates' variability and increasing precision with large sample size. We provide the number of people living with clinical AD and MCI from 2020 through 2060, covering a broad spectrum of cognitive impairment. Importantly, we establish the impact of population demographics on the number of people with clinical AD regarding age, race/ethnicity, and sex—the population demographic changes between 2020 and 2060. The likelihood scores also accounted for mortality and missing data. Hence, the influence of attrition on our findings on the estimated number of people with these conditions is minimal.

The study has several limitations. The study was active until 2012, which increases the variability in the projections on the number of people living with cognitive impairment. The 2020 US Census adjusted the prevalence of clinical AD and MCI and the number of people with these conditions carried forward to 2020 through 2060 using linear extrapolation. We derived the likelihood scores from a short-battery test. Although the classification accuracy for clinical AD was 0.92, and MCI was 0.89, these scores might not fully capture AD's clinical diagnosis. Although the estimates for the number of people with clinical AD adjusted for demographic characteristics and weighted the

estimates for the projected 2020 US Census, there may be some residual confounding in the regression models and the effect of extrapolation on our estimates. Also, the clinical AD scores in these analyses are based on the 1984 NINCDS-ADRDA criteria for AD;[41] it is possible that estimates based on the 2011 National Institute on Aging—Alzheimer's Association criteria for AD dementia[42] may differ slightly.

The estimates for the number of people with clinical AD and MCI did not include the 5% of the US population that is not part of the three major racial/ethnic groups. Hence, the number of people living with these conditions is a conservative estimate. Suppose we used clinical AD prevalence in this racial/ethnic group to be the same as combined estimates. In that case, we expect the number of people with clinical AD to be 6.38 million in 2020, reaching 14.68 million in 2060. Our sample size for the Hispanic population was relatively small compared to the non-Hispanic White and Black sample sizes. The CHAP study is a population-based study of people residing in urban Chicago communities. Although the study population has population risk factors comparable to national estimates, the generalizability to the US population requires careful justification. The primary advantages of our study have been very rigorously conducted compared to most studies of AD, including being strictly population-based, of large sample size, of long duration with care to maintain constant methodology, biracial (the largest US racial/ethnic groups—Non-Hispanic White and Black). For these reasons and the lack of evidence of systematic regional variation within the United States, in contrast to strong evidence of racial/ethnic variation, it has enjoyed wide use by others to form US estimates. However, the Hispanic racial/ethnic group is exceedingly small; we plan to address this limitation in future studies. The education adjustment in regression models used an average of 12 years of education. If the population education levels were lower than 12 years, our estimate is likely conservative because higher education reduces cognitive impairment. However, factorial invariance of education on cognitive test scores can be a potential issue to be addressed in future research.

In summary, the 2020 US Census–adjusted prevalence and estimate of the number of people living with clinical AD and MCI provides the population-level impact of mild and severe cognitive impairment on individuals-at-risk and their families. Although the US Census–adjusted prevalence of clinical AD might be lower in 2020 than 2010, the number of people living with clinical AD increases dramatically. We expect further changes in these counts as the US population continues to age, with an increasing number of minorities at risk over the next four decades. More people fall in the over 65 age group, placing higher social, individual, and economic stress on families and society.

ACKNOWLEDGMENTS

This work was supported by grants from the National Institute of Health (NIH)—R01AG057532, R01AG051635, and R01AG058679.

AUTHOR CONTRIBUTIONS

Dr. Rajan designed and conceptualized the study, conducted data analysis, interpreted the findings, and drafted and revised the manuscript for intellectual content. Drs. Weuve, Barnes, Wilson, and McAninch reviewed and revised the manuscript and provided intellectual content. Dr. Evans designed and conceptualized the study, reviewed and revised the manuscript, and supervised the study and data collection.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

De-identified data are available on request for qualified investigators from www.riha.rush.edu/dataportal.html.

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How to cite this article: Rajan KB, Weuve J, Barnes LL, et al. Population estimate of people with clinical Alzheimer's disease and mild cognitive impairment in the United States (2020–2060). *Alzheimer's Dement*. 2021;17:1966–1975.

APPENDIX

Methods: The regression models for forecasting the number of people with clinical AD and MCI used likelihood scores for 10,342 participants from the CHAP spanning 36,058 short-battery cognitive assessments of two tests of episodic memory, one test of perceptual speed, and the MMSE. Person-specific cognitive test scores were used to estimate the likelihood score at each given time of assessment. A quasibinomial regression model was used to examine the population average of clinical AD and MCI disease prevalence of the study sample. An unstructured working correlation matrix and a sandwich variance estimate were used to capture the study's repeated design and the working correlation matrix. The model included a time variable to capture annual changes in likelihood scores for the study. The regression model also adjusted for the participant's age, sex, race and ethnicity, and education.

The study estimates were standardized to the 2020 US population estimates for each 5-year age category for each race/ethnicity and sex categories. After the age-specific, race and ethnic-specific, and sex-specific estimates were derived, marginal sums and their associated confidence intervals were derived for interest categories. For age-specific estimates, we summarized the population totals over race/ethnic groups and sex. For race-specific estimates, we summarized the population totals over age groups and sex. For sex-specific estimates, we summarized the population totals over age groups and race/ethnicity. The confidence intervals used the sandwich variance estimate and derived the corresponding confidence intervals for population totals.

The likelihood scores were based on a polychotomous regression model with probabilities close to 1, indicating a high likelihood of clinical AD and probability close to 0 showing no cognitive impairment. The second set of probabilities for MCI with higher values indicated a higher likelihood of MCI, and probabilities close to zero indicated a lower likelihood of MCI. The regression models used the continuum of probabilities rather than cutoffs because cutoffs introduce misclassification errors. Simplistically, prevalence can be thought of as the number of people with the disease divided by the number of people at risk of having the disease. If ND were the people with the disease and N were the people at risk of having the disease, then the prevalence can

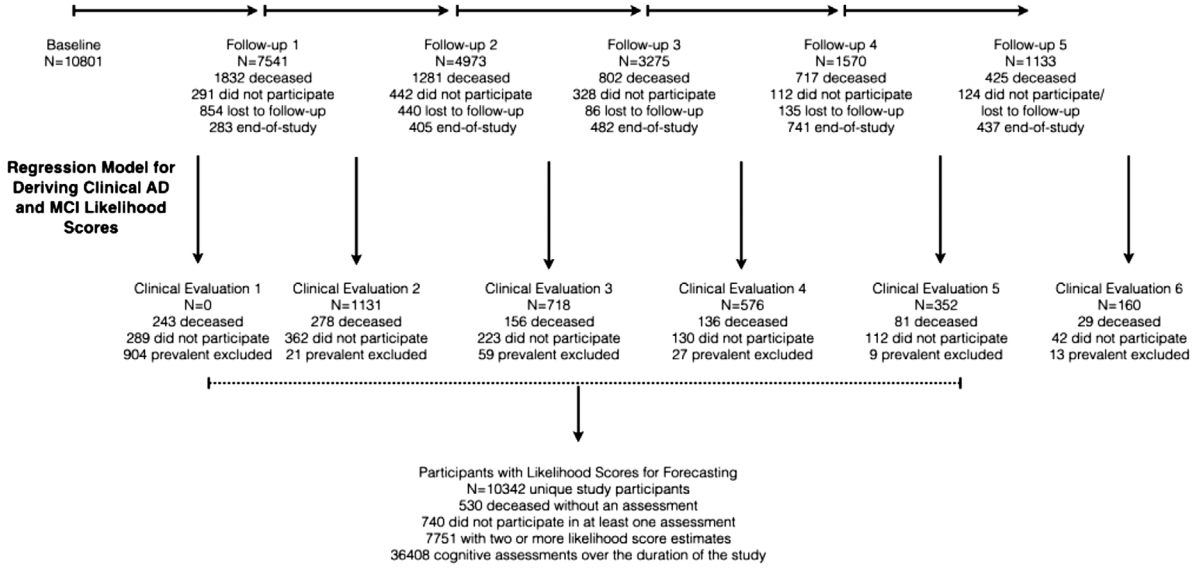

FIGURE A1 Flow Chart of Study Sample for Derivation of Likelihood Scores and Implementation of Likelihood Scores for the 10,342 Study Participants. AD, Alzheimer's disease; MCI, mild cognitive impairment

be written as:

$$p = \frac{N_D}{N} \quad (1)$$

In terms of the person-specific estimate,

$$p = \frac{\sum_{i=1}^{N} Y_{Di}}{N} \quad (2)$$

where Y_{Di} is the person-specific Bernoulli variable of whether they have the disease. $Y_{Di} \sim B(1, P_{Di})$, and the sum of the Bernoulli $Y_{Di} \sim$ Binomial(N, P_{Di}). Hence, the population average of Y_{Di} provides an estimate of the overall population prevalence. After careful standardization of the population demographics, we can estimate the population prevalence of the clinical AD and MCI for a given year. We also compared the sandwich variance estimate from our quasibinomial model to bootstrap variance and found the confidence interval to largely overlap. The resampling variance estimates took a substantially longer time to estimate yet did not provide substantial improvements in the variance estimate. Hence, we used the sandwich variance estimate. We will include the details on our website and develop a visualization based on our prediction algorithm.