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A Comparison of an Australian Observational Longitudinal Alzheimer's Disease Cohort to Community-Based Australian Data

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Abstract.
Background: Observational Alzheimer's disease (AD) cohorts including the Australian, Biomarkers, Imaging and Lifestyle (AIBL) Study have enhanced our understanding of AD. The generalizability of findings from AIBL to the general population has yet to be studied.
Objective: We aimed to compare characteristics of people with AD dementia in AIBL to 1) the general population of older Australians using pharmacological treatment for AD dementia, and to 2) the general population of older Australians who self-reported a diagnosis of dementia.
Methods: Descriptive study comparing people aged 65 years of over (1) in AIBL that had a diagnosis of AD dementia, (2) dispensed with pharmacological treatment for AD in Australia in 2021 linked to the Australian census in 2021 (refer to as PBS/census), (3) self-reported a diagnosis of dementia in the 2021 Australian census (refer to as dementia/census). Baseline characteristics included age, sex, highest education attainment, primary language, and medical co-morbidities.
Results: Participants in AIBL were younger, had more years of education, and had a lower culturally and linguistically diverse (CALD) population compared to the PBS/census cohort and dementia/census cohort (mean age ± standard deviation – AIBL 79 ± 7 years, PBS/census 81 ± 7, $p < 0.001$, dementia/census 83 ± 8, $p < 0.001$; greater than 12 years of education AIBL 40%, PBS/census 35%, $p = 0.020$, dementia/census 29%, $p < 0.001$; CALD – AIBL 3%, PBS/census 20%, $p < 0.001$, dementia/census 22%, $p < 0.001$).
Conclusions: Our findings suggest that care should be taken regarding the generalizability of AIBL in CALD populations and the interpretation of results on the natural history of AD.

Keywords: Alzheimer's disease, Australian Biomarkers Imaging and Lifestyle study, Australian census, culturally and linguistically diverse, dementia, generalizability

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INTRODUCTION

Our understanding of the clinical progression of Alzheimer's disease (AD) including amyloid-β (Aβ) aggregation, tau hyperphosphorylation, neuroinflammation and cognitive decline have been improved through longitudinal observational studies of AD cohorts over the last two decades.[1] These have been via routine clinical assessments, cognitive ratings, lifestyle questionnaires, genetic testing and monitoring of biomarkers including blood, cerebrospinal fluid (CSF) and neuroimaging (brain magnetic resonance imaging [MRI], amyloid and tau positron emission tomography [PET] scans). These clinical cohorts have enriched the understanding of the natural history of AD, the risk factors for AD, and helped guide the development of AD clinical trials.[2–4]

However, there have been concerns regarding the generalizability of findings derived from longitudinal observational AD cohorts. Participants in these cohort studies tend to be predominately Caucasians that are well educated and of higher socioeconomic status, require less visits to see their doctors, have fewer medical co-morbidities, and consume fewer medications compared to the general population.[5] A comparison of the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort in the United States (US) to a community-based cohort from the Atherosclerosis Risk In Communities (ARIC) study, a prospective observational cohort investigating the etiology of atherosclerosis and cardiovascular disease in the US, by Gianattasio et al. showed significant differences in education attainment (completed high school – ADNI 85% versus ARIC 52%), gender (male – ADNI 55% versus ARIC 41%), ethnicity (black – ADNI 4% versus ARIC 24%), hypertension (ADNI 48% versus ARIC 77%), and apolipoprotein E (*APOE*) status (*APOE* ε4 allele carrier – ANDI 85% versus ARIC 52%).[6] Compared to the US census in 2019 for people aged over 60 years old, the ADNI cohort had a lower participation of people who identified as either ethnoculturally underrepresented populations such as Blacks or Latinx (ADNI 11% versus US census 2019 25%) or completed less than 12 years education (ADNI 16% versus US census 2019 44%).[7] These raise concerns regarding the generalizability of the ADNI cohort to culturally diverse and low education populations and could potentially lead to biased estimates of associations with AD and our understanding on the progression of AD in this population.

To our knowledge, there have not been any studies comparing an Australian observational AD cohort to the community. The Australian Imaging, Biomarkers and Lifestyle (AIBL) Study is an ongoing longitudinal cohort study in Australia that began in late 2006 whose overall goal is to determine the extent that demographics, baseline cognitive profile, biomarkers (blood, CSF, MRI, and PET scans), genetic and lifestyle factors can predict a person's development of AD.[8]

Our aim was to determine if the characteristics of participants with a diagnosis of AD dementia in the AIBL study are representative of the general population of older Australians (aged 65 years old or over) with a diagnosis of AD dementia. We specifically chose AD dementia for comparison between the two groups of AIBL study and the community Australian population due to there being a population denominator in the community that could be used as a comparator. The comparators were older Australians who were under Therapeutic Goods Administration-approved pharmacological treatment (i.e., donepezil, rivastigmine, galantamine, and memantine) for AD as per the Australian Pharmaceutical Benefits Scheme (PBS) linked with the Australian Census performed in 2021 and older Australians who self-reported dementia in the 2021 Australian Census. The PBS is the Australian Government's subsidized drug prescription program. Since people undergoing pharmacological treatment for AD under the PBS are required to have a confirmed diagnosis of AD by a specialist/consultant physician,[9–12] we therefore have an appropriate population denominator for comparison. We also compared the AIBL cohort to older Australians who self-reported dementia, which was not AD specific but would include people in the community with AD dementia that were not on PBS-listed pharmacological treatment for AD, in the 2021 Australian Census. Thus, our goal was to identify if the findings from the AIBL study on the natural history of AD are generalizable to community-based cohorts.

METHODS

Study design and ethics approval

Descriptive analyses of baseline characteristics of participants enroled into the AIBL study from late 2006 to early 2023 with AD dementia who were aged 65 and over were performed. These characteristics were compared to (1) a community-based population of older Australians aged 65 and over under pharmacological treatment for AD as per the PBS in 2021 that have been linked with the Australian census

performed in 2021 (referred to as PBS/census), and to (2) a community-based population of older Australians aged 65 and over who self-reported dementia in the Australian census 2021 (referred to as dementia/census). Ethics has been approved for the AIBL study by St Vincent's Health Melbourne Human Research Ethics Committee (HREC Reference number: 028/06). Use of the PBS and Australian census data was approved by the Australian Bureau of Statistics and the University of Sydney.

Sampling

AIBL

Prior to enroling in the AIBL study, individuals were recruited via a media campaign for volunteers or from their treating physician. Potential participants were subsequently screened over the phone for their demographics (age, sex), medical history, and concerns regarding cognition.[13] Individuals were excluded from the study if they had a history of non-Alzheimer's dementia, schizophrenia, bipolar disorder, significant current depression (defined as a geriatric depression scale > 5/15), Parkinson's disease, cancer (other than basal cell skin carcinoma) within the last two years, symptomatic stroke, current uncontrolled or life-threatening medical illness, diagnosed obstructive sleep apnea, past head injury with over one hour of post-traumatic amnesia, or current regular alcohol consumption exceeding two standard drinks per day for females or four per day for males. Eligible individuals then proceeded for an in-person review at sites in Melbourne, Victoria and Perth, Western Australia, where after giving written informed consent, they underwent clinical, cognitive and mood assessments, blood sample collection, lumbar puncture for CSF collection, brain imaging and completed a questionnaire on health including medical history and medication use, and lifestyle every 18 months. The questionnaire asked participants to self-report 28 conditions including date of diagnosis, kind, severity, treatment and is provided in Supplementary Figure 1. A diagnosis of AD dementia was made by a panel of clinicians and neuropsychologists. Data was collected at the first time point when a diagnosis of AD dementia was made.

Pharmaceutical Benefits Scheme (PBS)/Australian Census 2021

We reviewed all people in Australia aged 65 and over who were dispensed medications via the PBS from 1 January 2021 to 31 December 2021. The data on people dispensed with medications was stored on the Australian Bureau of Statistics' Datalab platform via the Multi-Agency Data Integration Project. Only unique deidentified identifications (IDs) of people using medications in Australia in 2021 were used in this study. The deidentified IDs were then matched via data linkage to their Australian Census 2021 IDs via a person linkage spine ID on Datalab. From this dataset, we then reviewed all people dispensed pharmacological treatment for AD (donepezil, rivastigmine, galantamine and memantine), either for commencement or continuation of treatment.

Cholinesterase inhibitors under the PBS are indicated for the treatment of mild to moderately severe AD. The criteria for initial commencement of cholinesterase inhibitors is a baseline Mini-Mental State Examination (MMSE) or Standardized Mini-Mental State Examination (SMMSE) score of 10 or more, a diagnosis of AD confirmed by or in consultation with a specialist/consultant physician (including a psychiatrist) and the treatment must be the sole PBS-subsidized therapy for the condition.[10–12] If the MMSE/SMMSE was between 25 to 30, the result of a baseline Alzheimer Disease Assessment Scale, cognitive sub-scale may also be specified to the PBS. Continuation of cholinesterase inhibitors via the PBS is if a person had demonstrated a meaningful response to the initial treatment as per the treating physician after six months.[10–12] Memantine can be accessed via the PBS for people with moderately severe AD. Initial commencement of memantine is a baseline MMSE or SMMSE score of 10 to 14, the diagnosis of AD is confirmed by or in consultation with a specialist/consultant physician (including a psychiatrist) and the treatment must be the sole PBS-subsidized therapy for the condition.[9] Continuation of memantine via the PBS is if a patient has demonstrated a meaningful response to the initial treatment as per the treating physician after six months.[9]

The Australian Census performed on 10 August 2021 collected further demographics than PBS data. Since the census was performed in 2021, the PBS data from 2021 was collected to ensure accuracy regarding demographics. People were asked in the census if they had been told by a doctor or a nurse if they had any of the following long-term health conditions and if it had lasted or was expected to last for six months or more: arthritis, asthma, cancer (including remission), dementia (including AD), diabetes (excluding gestational diabetes), heart disease (including heart attack or angina), kidney disease, lung condition (includ-

Table 1
Harmonization of medical co-morbidities between AIBL and 2021 census

2021 census	AIBL
Arthritis	Arthritis
Cancer (including remission)	Cancer
Diabetes (excluding gestational diabetes)	Diabetes
Heart disease (including heart attack or angina)	Heart attack
	Angina
	Atrial fibrillation
Kidney disease	Kidney disease
Mental health (including depression or anxiety)	Anxiety
	Depression
	Psychiatric disorders
Stroke	Stroke

ing chronic obstructive lung disease or emphysema), mental health condition (including depression or anxiety) and stroke (Supplementary Figure 2, Question 28). The 2021 census had people who self-reported dementia that was not specific to AD. Therefore, our analysis reviewed older Australians dispensed pharmacological treatment for AD via the PBS either for commencement or continuation of treatment. We also reviewed older Australians who self-reported dementia in the 2021 census separately as a comparator. Although self-reported dementia is not AD specific, it would include people in the community who were not on PBS listed medications for AD dementia. In addition, a history of lung conditions including chronic obstructive pulmonary disease, emphysema and asthma was not collected in the AIBL data and was also excluded in the census data collection as a comparison could not be performed.

Data collection

Data collected in both groups included age in years, gender, highest education attainment, primary language, country of birth, and self-reported medical co-morbidities including arthritis, cancer, diabetes, heart disease, kidney disease, mental health and stroke. The AIBL data was at the time of the AIBL visit of diagnosis of AD dementia, while census data was in 2021. Harmonization of medical co-morbidities obtained from the AIBL questionnaire to the 2021 census is shown in Table 1.

Subgroup analyses of AIBL 2021 data

As cumulative AIBL data will not offer a meaningful comparison for the average age of people living with AD between AIBL AD cohort and the census, the age of AIBL participants with a diagnosis of AD dementia who were assessed in 2021 was collected.

Statistical analyses

Any duplicate IDs on the PBS database, and PBS IDs which were not able to be linked with the census 2021 IDs via the spine ID were excluded from analyses. All missing data was assumed to be missing at random and excluded from analyses. Descriptive analyses were performed to look at between-group differences. All baseline characteristics were tabulated showing frequencies and percentages for categorical variables and mean/standard deviation or median/interquartile range for continuous data where appropriate. The two groups were compared using a two-sample *t*-test for normally distributed continuous data, and chi-square χ^2 test was employed for categorical data. Data was presented as mean $\pm$ standard deviation (SD), unless otherwise stated. A p value of less than 0.05 was considered as statistically significant. Analyses was performed using Stata/IC Version 16.1 (StataCorp LLC, College Station, TX) and R Version 4.3.0 (R Foundation for Statistical Computing).

RESULTS

There have been 3,667 participants enroled in the AIBL study as of April 2023. Of these, 591 (16%) participants aged 65 years and older have had a diagnosis of AD dementia (referred to as AIBL AD cohort). In 2021, there were 54,346 people aged 65 or older in Australia who were dispensed with one of the four medications for the treatment of AD that were linked to the Australian census in 2021 (referred to as PBS/census AD cohort). There were 164,425 people aged 65 or older in Australia who self-reported dementia (referred to as dementia/census cohort).

Table 2
Medications used in the treatment of AD dementia for people aged 65 and above in Australia and have linked 2021 census and PBS data

Medication (%)	PBS/Census(*n = 54,346*)
Acetylcholinesterase inhibitors (AChEIs)*	49,070 (90)
Donepezil	36,891 (68)
Rivastigmine	7,589 (14)
Galantamine	5,589 (10)
Memantine	7,331 (13)
Dual AChEI/Memantine	2,055 (4)

*The sum of people using each AChEI is greater than 90% due to people switching between AChEIs.

For the PBS/census AD cohort, the most commonly dispensed medication drug class for AD (Table 2) were acetyl-cholinesterase inhibitors (AChEIs; 49,070 people [90%]), of which donepezil was predominant (36,891 people [68%]), followed by rivastigmine (7,589 people [14%]) and galantamine (5,589 people [10%]). Non-AChEI drug memantine was used by 7,331 people (13%). A small portion of the cohort (2,055 people [4%]) used dual therapy of AChEIs and memantine for AD. Medication dispensing records have not been collected in the AIBL study, and therefore no AIBL data is available for this comparison.

A comparison of the baseline characteristics including medical co-morbidities for all cohorts is presented in Table 3 and stratified by sex in Table 4. The AIBL AD cohort was younger compared to the PBS/census and dementia/census cohorts (mean age $\pm$ SD, AIBL 79 ± 7 years, PBS/census 81 ± 7 years, $p < 0.001$, dementia/census 83 ± 8 years, $p < 0.001$). A subgroup analyses of AIBL 2021 data demonstrated that the mean age of AIBL participants with a diagnosis of AD dementia who were assessed in 2021 was similar to the overall AIBL AD cohort (mean age $\pm$ SD, AIBL 2021 78 ± 6 years versus AIBL 79 ± 7 years, $p = 0.409$), and was younger than both the PBS/census cohort ($p = 0.011$) and the dementia/census cohort ($p < 0.001$). All cohorts had a slightly higher portion of females than males (AIBL 306 people [52%] versus PBS/census 31,088 people [57%], $p = 0.011$; versus dementia/census 97,579 [59%], $p < 0.001$). A quarter of the PBS/census AD and dementia/census cohort did not report their highest education attainment (PBS/census 11,479 people [22%], dementia/census 41,671 [25%]). 60% (332 people) of the AIBL AD cohort had less than 12 years of education, compared to 65% (27,317 people) in the PBS/census AD cohort ($p < 0.001$) and 71% (87,281 people) in the dementia/census dementia cohort. 40% (217 people) in the AIBL AD cohort had greater than 12 years education, with 21% (117 people) reporting post-graduate education (15 + years education). This was much higher than the PBS/census and dementia/census cohorts (>12 years education PBS/census 14,618 [35%] dementia/census 35,473 [29%], 15 + years education PBS/census 1,214 people [2%] dementia/census 2,278 [2%]). There was a higher proportion of females who reported having less than 12 years education compared to males in all cohorts (female < 12 years education AIBL 188 people [66%], PBS/census 17,735 people [77%], dementia/census 57,283 [81%]; male < 12 years education AIBL 144 people [54%], PBS/census 9,582 people [51%], dementia/census 29,998 [58%]).

19% (111 participants) in the AIBL AD cohort,6% (3,388 participants) in the PBS/census AD cohort and 6% (9,350 participants) in the dementia/census cohort did not report their primary language. The majority of participants in both cohorts reported English as their primary language (AIBL 466 people [97%] versus PBS/census 40,897 people [80%]). Only 3% (14 participants) in the AIBL AD cohort reported their primary language to be other than English, which is a much lower culturally and linguistically diverse (CALD) population compared to 20% (10,061 participants) and 22% (33,580 participants) in the PBS/census and dementia/census cohorts respectively.

In the AIBL AD cohort, 8–11% of participants did not complete the questionnaire on the selected co-morbidities (excluding self-reporting a history of mental health condition). Mental health condition was defined as a combination of anxiety, depression and psychiatric illness. Each variable on its own has 9–10% unknown. However, combined together, only one participant did not report one of

Table 3
Baseline characteristics of participants

Baseline characteristic	*n*	AIBL	*n*	PBS/census	*P*	*n*	Dementia/census	*p*
Age, y	591	79 ± 7	54,346	81 ± 7	<0.001	164,425	83 ± 8	<0.001
65–69		59 (10)		2,849 (5)	<0.001		8,083 (5)	<0.001
70–74		144 (19)		6,920 (13)			16,369 (10)	
75–79		141 (24)		11,663 (21)			26,552 (16)	
80–84		123 (21)		14,624 (27)			37,588 (23)	
85+		154 (26)		18,290 (34)			75,833 (46)	
Gender								
Male	591	285 (48)	54,346	23.383 (43)	0.011	164,425	66, 846 (41)	<0.001
Female		306 (52)		30,963 (57)			97,579 (59)	
Highest education attainment								
≤12 years education	549	332 (60)	41,867	27,317 (65)	<0.001	122,754	87,281 (71)	<0.001
Year 8 or below		*87 (16)*		*8,067 (19)*			*29,927 (24)*	
Years 9 –12		*245 (45)*		*19,250 (46)*			*57,354 (47)*	
>12 years education		217 (40)		14,550 (35)			35,473 (29)	
Years 13–15		*100 (18)*		*13,340 (32)*			*33, 195 (27)*	
Years 15+		*117 (21)*		*1,210 (3)*			*2,278 (2)*	
Primary language								
English	480	466 (97)	50,958	40,897 (80)	<0.001	155,075	121,495 (78)	<0.001
Other		14 (3)		10,061 (20)			33,580 (22)	
Medical Co-morbidities								
None of selected condition	591	165 (28)	54,346	23,938 (44)	<0.001	164,425	52,872 (32)	0.001
One of selected condition		197 (33)		15,600 (29)			47,817 (29)	
Two of selected conditions		152 (26)		9293 (17)			35,711 (22)	
Three or more of selected conditions		77 (13)		5,515 (10)			28,025 (17)	
Arthritis								
Cancer	539	243 (45)	51,990	14,584 (28)	<0.001	164,425	56.255 (34)	<0.001
Diabetes	544	97 (18)	51,990	4,569 (9)	<0.001		17,887 (11)	<0.001
Heart disease	530	72 (14)	51,990	7,522 (14)	0.565		28,683 (17)	0.019
Kidney	535	81 (15)	51,990	9,234 (18)	0.114		38,819 (24)	<0.001
Disease	530	24 (5)	51,990	1,937 (4)	0.332		10,589 (6)	0.073
Mental health	538	205 (38)	51,990	11,443 (22)	<0.001		48,086 (29)	<0.001
Stroke	528	29 (5)	51,990	3,422 (7)	0.315		18,003 (11)	<0.001

Data are presented as mean ± standard deviation or number (percentage). *p*-values are in comparison to AIBL AD cohort. *n* is the total number of participants who self-reported to the specific question in the questionnaire. Groups were compared using a two-sample *t*-test for normally distributed continuous data, and chi-square χ^2 test for categorical data.

Table 4
Baseline characteristics of participants stratified by sex

	Male							
Baseline characteristic	*n*	AIBL	*n*	PBS/census	*p*	*n*	Dementia/census	*p*
Age, y		78 ± 7	23,283	81 ± 7	<0.001	66,846	82 ± 7	<0.001
65–69	285	29 (10)		1,340 (6)	0.001		4,302 (6)	0.001
70–74		55 (19)		3,309 (14)			8,320 (12)	
75–79		65 (23)		5,343 (23)			12,786 (19)	
80–84		58 (20)		6,455 (28)			16,380 (25)	
85+		99 (35)		6,936 (30)			25,058 (37)	
Highest education attainment								
≤12 years education	266	144 (54)	18,697	9,582 (51)	0.350	52,136	29,998 (58)	0.263
Year 8 or below		*28 (11)*		*2,909 (16)*			*10,544 (20)*	
Years 9–12		*116 (44)*		*6,673 (36)*			*19,454 (37)*	
>12 years education		122 (46)		9,115 (49)			22,138 (42)	
Years 13–15		*56 (21)*		*8,312 (44)*			*20,590 (39)*	
Years 15+		*66 (25)*		*803 (4)*			*1,548 (3)*	
Primary language								
English	224	218 (97)	22,052	17,985 (82)	Q	63,483	50,074 (79)	<0.001
Other		6 (3)		4,067 (18)			13,109 (21)	
Medical Co-morbidities								
None of selected condition	285	81 (28)	23,283	10,126 (43)	<0.001	66,846	20,815 (31)	0.145
One of selected condition		88 (31)		6,544 (28)			18,694 (28)	
Two of selected conditions		72 (25)		4,103 (18)			14,469 (22)	
Three or more of selected conditions		44 (15)		2,610 (11)			12,868 (19)	
Arthritis	265	113 (43)	22,464	5,215 (23)	<0.001	66,846	19,531 (29)	<0.001
Cancer	266	56 (21)	22,464	2,430 (11)	<0.001		9,060 (14)	<0.001
Diabetes	261	37 (14)	22,464	3,827 (17)	0.221		13,888 (21)	<0.001
Heart disease	260	52 (20)	22,464	5,065 (23)	0.328		19,217 (29)	0.002
Kidney disease	258	13 (5)	22,464	933 (4)	0.479		4,935 (7)	0.150
Mental health	261	86 (33)	22,464	4,306 (19)	<0.001		17,879 (27)	0.024
Stroke	257	14 (5)	22,464	1,815 (8)	0.123		9,185 (14)	<0.001

(*Continued*)

Table 4
(*Continued*)

	Female							
Baseline characteristic	*n*	AIBL	*n*	PBS/census	*p*	*n*	Dementia/census	*p*
Age, y	306	80 ± 8	30,963	82 ± 7	<0.001	66,846	84 ± 8	<0.001
65–69		30 (10)		1,509 (5)	<0.001		3,781 (4)	<0.001
70–74		59 (19)		3,611 (12)			8,049 (8)	
75–79		76 (25)		6,320 (20)			13,766 (14)	
80–84		65 (21)		8,169 (26)			21,208 (22)	
85+		55 (18)		11,354 (37)			50,775 (52)	
Highest education attainment								
≤12 years education	283	188 (66)	23,170	17,735 (77)	<0.001	52,136	57,283 (81)	<0.001
Year 8 or below		*59 (21)*		*5,158 (22)*			*19,383 (27)*	
Years 9 –12		*129 (46)*		*12,577 (54)*			*37,900 (54)*	
>12 years education		95 (34)		5,435 (23)			13,335 (19)	
Years 13–15		*44 (16)*		*5,028 (22)*			*12,605 (18)*	
Years 15+		*51 (18)*		*407 (2)*			*730 (1)*	
Primary language								
English	256	248 (97)	28,906	22,912 (79)	<0.001	63,483	71,121 (78)	<0.001
Other		8 (3)		5,994 (21)			20,471 (22)	
Medical Co-morbidities								
None of selected condition	306	84 (27)	30,963	13,812 (45)	<0.001	66,846	32,057 (33)	0.004
One of selected condition		109 (36)		9,056 (29)			29,123 (30)	
Two of selected conditions		80 (26)		5,190 (17)			21,242 (22)	
Three or more of selected conditions		33 (11)		2,905 (9)			15,157 (16)	
Arthritis	274	130 (47)	29,526	9,369 (32)	<0.001	66,846	36,724 (38)	0.065
Cancer	278	41 (15)	29,526	2,139 (7)	<0.001		8,827 (9)	0.001
Diabetes	269	35 (13)	29,526	3,395 (13)	0.806		14,795 (15)	0.326
Heart disease	275	29 (11)	29,526	4,169 (14)	0.090		19,602 (20)	<0.001
Kidney disease	272	11 (4)	29,526	1,004 (3)	0.560		5,654 (6)	0.217
Mental health	277	119 (43)	29,526	7,137 (24)	<0.001		30,207 (31)	<0.001
Stroke	271	15 (5)	29,526	1,607 (5)	0.947		8,818 (9)	0.045

Data are presented as mean ± standard deviation or number (percentage). *p*-values are in comparison to AIBL AD cohort. Groups were compared using a two-sample *t*-test for normally distributed continuous data, and chi-square χ^2 test for categorical data.

the three. In comparison, only 4% (2,356 participants) of the PBS/census AD cohort did not complete the questionnaire on the selected co-morbidities. All participants in the dementia/census cohort completed the questionnaire on co-morbidities. In all cohorts, there was a declining proportion of people who self-reported having more than three of the selected conditions compared to only one of the selected conditions, while the AIBL AD cohort has a higher portion of people with three or more medical co-morbidities compared to that for the PBS/census cohort, but a lower portion of people with three or more medical co-morbidities in the dementia/census cohort (one co-morbidity – AIBL 197 people [33%], PBS/census 15,600 people [29%], dementia/census 47,817 [29%]; three or more co-morbidities – AIBL 77 people [13%], PBS/census 5,515 people [10%], dementia/census 28,025 people [17%]). A lower proportion of people reported having none of the selected medical co-morbidities in the AIBL AD cohort (165 people [28%]) than in both the PBS/census AD cohort (24,050 people [44%]) and dementia/census cohort (52,872 people [32%]).

The most commonly self-reported co-morbidities in all cohorts were arthritis and mental health, with strong evidence that the proportion was higher in the AIBL AD cohort compared to the PBS/census and dementia/census cohorts (arthritis – AIBL 243 people [45%], PBS/census 14,584 people [28%], $p < 0.001$, dementia/census 56,255 [34%], $p < 0.001$; mental health AIBL 205 people [38%], PBS/census 11,443 people [22%], $p < 0.001$, dementia/census 48,086 [29%]). The proportion of people in the AIBL AD cohort that reported a history of cancer was two-fold higher compared to people in PBS/census AD cohort (AIBL 97 people [18%] versus PBS/census 4,569 people [9%], $p < 0.001$) and higher in proportion to the dementia/census cohort (17,887 people [11%], $p < 0.001$).

DISCUSSION

To our knowledge, this is the first study that compares an Australian observational AD cohort to a community-based AD population. People from a CALD background were underrepresented in the AIBL study (3%) compared to the PBS/census AD cohort (20%) and dementia/census cohort (22%). English was the predominant language spoken in the AIBL AD cohort, with 97% of the cohort reporting English as their primary language. However, this proportion is affected by 19% of participants in the AIBL AD cohort not reporting their primary language. This information bias would have caused differential misclassification, resulting in potentially under or overestimating of the proportion. This observation in AIBL is comparable to The Sydney Memory and Ageing Study, an Australian observational older adult cohort monitoring cognition, where 94% of participants reported English as their primary language.[14] Compared to a non-Australian cohort study, the CALD proportion in the AIBL study (3%) was lower than that reported by the ADNI study in the USA, where 11% of the ADNI participants were identified as being from ethnocultural populations such as Black and Latinx.[7]

In Australia, First Nations people account for 3.8% of the Australian population in 2021.[15] The Koori Growing Old Well study (KGOWS) was a prospective longitudinal cohort study investigating aging and dementia across five Aboriginal communities in New South Wales, Australia across two metropolitan Sydney sites and three regional mid-North Coast sites from 2010 to 2018. The study identified that older age, male sex, unskilled work history, polypharmacy, past smoking and carrying an *APOE* $\varepsilon 4$ allele to be associated with incident mild cognitive impairment/dementia.[16] However, there are currently no AD cohort studies actively recruiting First Nations people in Australia. First Nation status is not collected in the AIBL study nor in The Sydney Memory and Ageing Study, while the Prospective Imaging Study of Ageing: Genes, Brain and Behaviour (PISA), an Australian observational cohort study of prodromal AD reported only 0.2% of participants identified as First Nation.[17] Given that the prevalence rate of people with dementia is thought to be 3–5 times greater in the First Nations population than the general Australian population,[18,19] more efforts are required to improve recruitment and retention of First Nations people to participate in AD cohort studies to improve our understanding of the natural history of AD in this population.

Increasing the CALD population in dementia research in high-income countries has been recognized as an area that requires improvement.[20,21] This study suggests that there needs to be more efforts to improve the CALD population recruitment and retention in the AIBL study. A systematic review into potential barriers in recruitment and retention of underrepresented populations in trials has iden-

tified issues with mistrust, stigma, a lack of access to information of results and competing demands to participants in studies.[22] One of the potential barriers for AIBL to recruit CALD participants could be that the study consent form, questionnaires, and cognitive tests were only in English, which makes it challenging to establish trust and make potential participants understand how the study runs. In addition, participants would be involved in multiple investigations over multiple days which include invasive tests such as a lumbar puncture (although optional for AIBL) and can be burdensome. Recruitment and retainment of First Nations people in research has been challenging due to issues of mistrust in research within First Nation communities and poor engagement with the First Nation people from researchers.[23] The AIBL research group could engage people from the CALD Australian communities and First Nations people to identify the barriers and develop enablers to promote CALD recruitment. Since 2020, ADNI has addressed concerns of low underrepresented ethnocultural communities in their AD cohort by forming an ADNI3 Diversity Task Force, which established less burdensome investigations making lumbar punctures optional and having an advertising agency to develop culturally tailored digital media campaigns to improve the outreach effort.[24] This campaign has increased screening and enrollment of ethnoculturally underrepresented communities from 11% in ADNI to 26.7% in the ADNI 3 cohort. The AIBL study could adopt a similar approach. Questionnaires specifically asking social determinants of health would also be critical to understanding its association with AD. This would enhance our knowledge of the influence of culture and ethnicity on the natural history of AD and determine future treatment options.

40% of participants with a diagnosis of AD dementia in the AIBL study reported greater than 12 years education, which was higher than 35% in the PBS/census cohort and 29% in the dementia/census cohort. While there was strong statistical evidence of a difference ($p < 0.001$), caution should be noted that the PBS/census AD cohort had 23% of participants and the dementia/census cohort had 25% of participants who did not report their highest education attainment. Differential misclassification would have resulted from the information bias, resulting in potentially under or overestimating the population's highest education attainment above or below 12 years. In comparison to AIBL participants with a diagnosis of AD dementia, 84% of ADNI participants had reported an education greater than 12 years,[7] which was higher than 56.3% in the 2019 United States census. Globally in AD observational cohorts, the average education of participants was approximately 14 years.[25] Low education has been identified by the Lancet commission on dementia prevention as a key risk factor for the development of dementia.[26] Cohort studies like AIBL should ensure to recruit not only those with more years of education but also those with less years of education for better generalizability of research findings.

There was strong statistical evidence of a higher proportion of participants in the AIBL AD cohort self-reporting having one or more of the selected medical co-morbidities compared to the PBS/census AD cohort taking medications for AD ($p < 0.001$) and the dementia/census cohort ($p < 0.001$). This is an intriguing paradoxical finding, as other observational AD cohorts have reported less co-morbidities than in the general population,[5] likely due to selection bias from healthy volunteer bias. A potential contributor to this finding is information bias since 8–11% of AIBL participants did not fill out the questionnaire on selected medical co-morbidities. It is also possible that the AIBL AD cohort self-reported more medical comorbidities than the PBS/census cohort and census dementia cohort due to seeing their GP/specialists more often whilst they were on the study and thus able to report more comorbidities.

Several limitations of the current study must be noted. Firstly, the overall AIBL AD cohort was used instead of using a cross-section of AIBL data in 2021, which may lead to bias when used as a comparator to the PBS/census cohort. In our study we used PBS/census data that only included participants with a diagnosis of AD dementia for comparison, which limited us using all the AIBL participants who were assessed in 2021. To increase the sample size of AIBL participants with a diagnosis of AD dementia, we used cumulative AIBL data. Although the mean age of the AIBL 2021 AD cohort was comparable to the overall AIBL AD cohort (mean age $\pm$ SD, AIBL 2021 78 ± 6 years versus AIBL 79 ± 7 years, $p = 0.409$), using the cumulative data rather than cross-sectional data can potentially introduce artifacts. Secondly, the overall AIBL AD cohort reported the age of participants at the time of diagnosis of AD dementia (the incidence), while the PBS/census cohort reported the prevalence of AD dementia in Australia in 2021. This difference has likely contributed to the younger age of the AIBL

cohort to the PBS/census cohort. Thirdly, we are limited in the community-based PBS/census cohort where we only have a population that has been dispensed medications for AD. Not all people with AD would have been prescribed medications for AD leading to selection bias. There are potentially people in Australia who do not have access to pharmacological treatment for AD due to health inequities such as being unable to see a specialist for a diagnosis of AD dementia and then procuring the medications. There is an underdiagnosis of dementia.[27] People with AD dementia identified via the PBS are also younger and more educated compared to other administrative datasets in Australia (hospital inpatient records, aged care assessments, aged care funding instruments, death certificates) given that medications are prescribed at the early stages of AD dementia.[28] Geographic remoteness and socioeconomic disadvantage have also been associated with reduced cholinesterase inhibitor prescription rates in Australia.[29] Anticholinesterase inhibitors and memantine can also sometimes be prescribed to patients for other types of dementia or conditions, but for their use under the PBS, it requires a diagnosis of AD by a specialist/consulting physician. We included the 2021 census self-reported dementia cohort as an additional comparator since it would include who were diagnosed with AD dementia but were not on PBS-listed pharmacological treatment. This is however limited that the census dementia cohort is not AD specific, encompassing all types of dementia, the underdiagnosis of dementia,[27] and that there are different estimates of the prevalence of dementia in Australia depending on the dataset used (estimated age- and sex-standardized prevalence in Australians aged 60 years or more – 31.4 per 1000 people (2021 census), 21.4 per 1000 people (2018–19 NPS MedicineWise survey), and 65.9 per 1000 people (2021 Australian Institute of Health and Welfare).[30] Finally, self-reporting for co-morbidities via a questionnaire were used for all cohorts, which could contribute to potential recall bias,[31] especially for medical history obtained from participants with known cognitive impairment or family members. AIBL participants were asked to self-report 28 conditions including date of diagnosis and include details such as kind, severity, and treatment where possible. The AIBL questionnaire did not ask if the conditions were diagnosed by a doctor or if the conditions were long term (lasting for longer than six months or more). In comparison, in the 2021 census, people were asked if a doctor or nurse had told them if they had ten health conditions and if it had lasted or was expected to last for six months or more. The different self-reported questionnaires could have influenced how participants responded. In the AIBL cohort, arthritis could have been self-diagnosed by the participant rather than diagnosed by a doctor. A mental health condition reported by a participant in the AIBL cohort may not have been long term and current, and thus would not been reported by participants in the census. Self-reported long-term medical conditions was a new question in the census in 2021 compared to the census performed in 2011 and 2016. A report on the quality of the 2021 census data suggested that long-term health conditions results compared similarly to the 2017–2018 National Health survey for all ages, with the exceptions that cancer was reported higher in the census than the National Health survey, and mental health condition was reported higher in the National Health survey than the census (National Health survey – cancer 1.8%, mental health condition 20.1%; 2021 census – cancer 2.9%, mental health condition 8.8%).[32] Further investigation with other datasets in older Australians with dementia is warranted to validate the self-reported long-term health conditions in the 2021 census. A more systematic approach to compare AD cohort studies and the general population should ideally be incorporated at the design phase of future cohort studies, and it can be implemented in AIBL study.

Future studies are encouraged to compare the AIBL cognitively normal and mild cognitive impairment cohort to a community-based cohort in Australia and comparing other observational AD cohorts in Australia and globally to a community-based population to determine generalizability of their findings. The Australian Dementia Network registry encompassing patients newly diagnosed with mild cognitive impairment or dementia from memory clinics and specialists in Australia was commenced in 2020,[33] and could be used in future studies as a community-based comparative cohort.

Overall, compared with the older adults who used medications for AD dementia in Australia in 2021 linked with the Australian census, people with a confirmed diagnosis of AD dementia in the AIBL cohort were younger, received more years of education, and had more medical co-morbidities. The AIBL study has facilitated AD research, improved our understanding on the natural history of AD, and helped in the design of interventional clinical AD trials. However, care is required regarding the generalizability of the AIBL cohort and the interpretation of the find-

ings from the AIBL study, in particular in the CALD population. Increased efforts are required to enrich the AIBL cohort with a more culturally diverse population.

AUTHOR CONTRIBUTIONS

Andrew Liem Hieu Huynh (Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft); Yihan Wang (Data curation); Liwei Ma (Formal analysis); Yi Ling Clare Low (Formal analysis; Writing – review & editing); Weisi Chen (Data curation; Formal analysis; Visualization); Christopher Fowler (AIBL data collection); Edwin CK Tan (Data curation; Writing – review & editing); Colin L Masters (AIBL data collection); Liang Jin (Conceptualization; Methodology; Supervision; Writing – review & editing); Yijun Pan (Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Writing – review & editing).

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CONFLICT OF INTEREST

Colin Masters is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review. All other authors have no conflicts of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author, which is subject to the approval from AIBL scientific committee. The data is not publicly available due to privacy or ethical restrictions.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-240241.

REFERENCES

1. Fowler C, Rainey-Smith SR, Bird S, et al. Fifteen years of the Australian Imaging, Biomarkers and Lifestyle (AIBL) study: Progress and observations from 2,359 older adults spanning the spectrum from cognitive normality to Alzheimer's disease. *J Alzheimers Dis Rep* 2021; 5: 443–468.
2. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7: 280–292.
3. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. *Lancet Neurol* 2014; 13: 614–629.
4. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. *Lancet Neurol* 2013; 12: 357–367.
5. Brayne C and Moffitt TE. The limitations of large-scale volunteer databases to address inequalities and global challenges in health and aging. *Nat Aging* 2022; 2: 775–783.
6. Gianattasio KZ, Bennett EE, Wei J, et al. Generalizability of findings from a clinical sample to a community-based sample: A comparison of ADNI and ARIC. *Alzheimers Dement* 2021; 17: 1265–1276.
7. Ashford MT, Raman R, Miller G, et al. Screening and enrollment of underrepresented ethnocultural and educational populations in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimers Dement* 2022; 18: 2603–2613.
8. Ellis KA, Bush AI, Darby D, et al. The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: Methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. *Int Psychogeriatr* 2009; 21: 672–687.
9. Department of Health and Aged Care. Memantine, Pharmaceutical Benefits Scheme (PBS), https://www.pbs.gov.au/medicine/item/1956Y-2492E-2513G-9306T (2023).
10. Department of Health and Aged Care. Donepezil, Pharmaceutical Benefits Scheme (PBS), https://www.pbs.gov.au/medicine/item/11922l-11924n-2479l-2532g-8495d-8496e (2023).
11. Department of Health and Aged Care. Rivastigmine, Pharmaceutical Benefits Scheme (PBS), https://www.pbs.gov.au/medicine/item/10538P-10541T-11901J-11903L-11904M-11912Y-11916E-11923M-11925P-2475G-2477J-2493F-2494G-2526Y-2551G-8497F-8498G-8499H-8500J-9161E-9162F(2023).
12. Department of Health and Aged Care. Galantamine, Pharmaceutical Benefits Scheme (PBS), https://www.pbs.gov.au/medicine/item/11899G-11917F-11918G-2463P-2531F-2537M-8770N-8771P-8772Q (2023).
13. Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull* 1988; 24: 709–711.
14. Tsang RS, Sachdev PS, Reppermund S, et al. Sydney Memory and Ageing Study: An epidemiological cohort study of

brain ageing and dementia. *Int Rev Psychiatry* 2013; 25: 711–725.
15. Australian Bureau of Statistics. Estimates of Aboriginal and Torres Strait Islander Australians, https://www.abs.gov.au/statistics/people/aboriginal-and-torres-strait-islander-peoples/estimates-aboriginal-and-torres-strait-islander-australians/30-june-2021 (2021).
16. Lavrencic LM, Delbaere K, Broe GA, et al. Dementia incidence, APOE genotype, and risk factors for cognitive decline in Aboriginal Australians: A longitudinal cohort study. *Neurology* 2022; 98: e1124-e1136.
17. Lupton MK, Robinson GA, Adam RJ, et al. A prospective cohort study of prodromal Alzheimer's disease: Prospective Imaging Study of Ageing: Genes, Brain and Behaviour (PISA). *Neuroimage Clin* 2021; 29: 102527.
18. Radford K, Mack HA, Draper B, et al. Prevalence of dementia in urban and regional Aboriginal Australians. *Alzheimers Dement* 2015; 11: 271–279.
19. Smith K, Flicker L, Lautenschlager NT, et al. High prevalence of dementia and cognitive impairment in Indigenous Australians. *Neurology* 2008; 71: 1470–1473.
20. Brijnath B, Croy S, Sabates J, et al. Including ethnic minorities in dementia research: Recommendations from a scoping review. *Alzheimers Dement* 2022; 8: e12222.
21. Low LF, Barcenilla-Wong AL and Brijnath B. Including ethnic and cultural diversity in dementia research. *Med J Aust* 2019; 211: 345–346.
22. George S, Duran N and Norris K. A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific Islanders. *Am J Public Health* 2014; 104: e16-e31.
23. Guillemin M, Gillam L, Barnard E, et al. "We're checking them out": Indigenous and non-Indigenous research participants' accounts of deciding to be involved in research. *Int J Equity Health* 2016; 15: 1–10.
24. Mindt MR, Okonkwo O, Weiner MW, et al. Improving generalizability and study design of Alzheimer's disease cohort studies in the United States by including under-represented populations. *Alzheimers Dement* 2023; 19: 1549–1557.
25. Birkenbihl C, Salimi Y, Domingo-Fernandez D, et al. Evaluating the Alzheimer's disease data landscape. *Alzheimers Dement* 2020; 6: e12102.
26. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020; 396: 413–446.
27. Lang L, Clifford A, Wei L, et al. Prevalence and determinants of undetected dementia in the community: A systematic literature review and a meta-analysis. *BMJ Open* 2017; 7: e011146.
28. Welberry HJ, Brodaty H, Hsu B, et al. Measuring dementia incidence within a cohort of 267,153 older Australians using routinely collected linked administrative data. *Sci Rep* 2020; 10: 8781.
29. Zilkens RR, Duke J, Horner B, et al. Australian population trends and disparities in cholinesterase inhibitor use, 2003 to 2010. *Alzheimers Dement* 2014; 10: 310–318.
30. Dobson AJ, Flicker L, Almeida OP, et al. Different estimates of the prevalence of dementia in Australia, 2021. *Med J Aust* 2023; 218: 320.
31. Althubaiti A. Information bias in health research: Definition, pitfalls, and adjustment methods. *J Multidiscip Healthc* 2016: 211–217.
32. Harding SL, L., McDonald, P., Morrison, P., Trewin, D., Walters, S. Report on the quality of 2021 Census data, https://www.abs.gov.au/census/about-census/census-statistical-independent-assurancepanel-report (2022).
33. Lin X, Wallis K, Ward SA, et al. The protocol of a clinical quality registry for dementia and mild cognitive impairment (MCI): The Australian dementia network (ADNeT) Registry. *BMC Geriatr* 2020; 20: 330.