Factors Associated with the High Prevalence of Dementia in Older Aboriginal Australians

Kylie Radford[a,b,*], Louise M. Lavrencic[a], Kim Delbaere[a,b], Brian Draper[b,c], Robert Cumming[d], Gail Daylight[a], Holly A. Mack[e], Simon Chalkley[a], Hayley Bennett[a], Gail Garvey[f], Thi Yen Hill[a,c], Danielle Lasschuit[a,c] and Gerald A. Broe[a,b]

[a]*Neuroscience Research Australia, Randwick, NSW, Australia*
[b]*University of New South Wales, Sydney, NSW, Australia*
[c]*Prince of Wales Hospital, Randwick, NSW, Australia*
[d]*The University of Sydney, Camperdown, NSW, Australia*
[e]*University of Technology Sydney, Ultimo, NSW, Australia*
[f]*Menzies School of Health Research, Brisbane, QLD, Australia*

Abstract. Dementia prevalence in Aboriginal and Torres Strait Islander Australians is three to five times higher than the general Australian population. A better understanding of the underlying biomedical and social risk factors is needed to guide dementia prevention in Aboriginal Australians. The current study is the first to examine potential risk factors for dementia in the majority urban and regional population, with a representative sample of 336 Aboriginal Australians aged 60 years and older. Participants included 45 people with a dementia diagnosis ($n = 27$ probable/possible Alzheimer's disease); and 286 people without dementia. Univariate logistic regression analyses (controlling for age) identified childhood trauma, mid-life factors (history of unskilled work, past high-risk alcohol use), and medical factors (history of stroke, head injury with loss of consciousness, epilepsy) as risk factors for dementia. Multivariable analysis revealed age, childhood trauma, unskilled work, stroke, and head injury as independent predictors of all-cause dementia. A range of comorbid factors related to dementia was also identified (i.e., functional impairment, incontinence, recent hospital admission, low body mass index, living in residential care, depression, current high-risk alcohol use, social isolation, low physical activity levels). These findings extend previous outcomes in a remote Aboriginal population by highlighting that life-course social determinants of health, in addition to neurological disorders, likely play an important role in elevating dementia risk. Certain psychosocial and medical exposures are highly prevalent in Aboriginal Australians, similar to other indigenous populations, and should be considered when designing targeted and culturally appropriate prevention initiatives to reduce the burden of dementia.

Keywords: Aged, Alzheimer's disease, indigenous population, neurocognitive disorders, social determinants of health

INTRODUCTION

The global burden of dementia is increasing dramatically [1]. This is of particular concern for Aboriginal and Torres Strait Islander Australians (respectfully referred to hereon as Aboriginal Australians) as dementia prevalence is 3 to 5 times higher compared to the general Australian population [2–4]. Alzheimer's disease (AD) is the most common type of dementia in Aboriginal and non-Aboriginal populations, but effective treatments remain elusive. There is, however, increasing evidence that sheds light on the underlying risk factors of this late-onset dementia epidemic; with up to half of global AD cases thought to be attributable to modifiable risk factors [5, 6].

Low education, smoking, physical inactivity, depression, midlife obesity, midlife hypertension, and diabetes have all been identified as major

---

*Correspondence to: Kylie Radford, Neuroscience Research Australia, Randwick, NSW, Australia. Tel.: +61 2 9399 1269; Fax: +61 2 9399 1005; E-mail: k.radford@neura.edu.au.

worldwide risk factors for AD [5]. Recent systematic review evidence has shown distinct risk factors across different types of dementia, highlighting particularly strong associations for depression and type 2 diabetes mellitus, and, additionally, frequency of social contacts and benzodiazepine use [7]. However, an even broader range of factors is thought to contribute to the risk of dementia and AD. The Alzheimer's disease risk scale by Anstey et al. [8] identified both risk and protective factors encompassing age, sex, body mass index (BMI), diabetes, depression, cholesterol, traumatic brain injury, smoking, alcohol use, social engagement, physical activity, cognitive activity, fish intake, and exposure to pesticides. A number of these previously identified risk factors (such as low education, smoking, hypertension, diabetes, and depression) disproportionately affect Aboriginal Australians [9, 10]. Recently, there has also been a move toward considering factors across the life course, including childhood, which may increase the risk of dementia in late life (see [11–13] for general discussions); however, primary studies investigating these factors are limited.

Despite the extensive research on dementia risk factors to date, there is a striking lack of population-based research on dementia risk factors in Aboriginal Australians, with only two studies examining these factors [14, 15]. In a cross-sectional study of 363 Aboriginal Australians aged 45 years and older from the remote Kimberley region of Western Australia, dementia was associated with older age, being male, and having no formal education [14]. After controlling for these factors, dementia was also associated with current smoking, stroke, epilepsy, head injury, poor mobility, incontinence, and falls [14]. In a follow-up study of this same cohort ($n = 189$), only age and head injury emerged as significant longitudinal risk factors for cognitive decline (further cross-sectional associations with higher systolic blood pressure, low BMI, and analgesic medications were also identified) [15]. In addition, we have previously reported a significant association between childhood stress exposure and dementia diagnosis in the current cohort of older Aboriginal people, which was independent of adult mental health disorders (e.g., history of depression) and current symptoms of psychological distress [16].

Given the concentrated dementia risk, the Australian Aboriginal population provides a window for understanding dementia risk and prevention, applicable to many populations globally. However, it is important to consider that the Kimberley cohort is from a remote location, and these results may not generalize to the majority urban and regional Aboriginal population, or other populations more broadly. High rates of illiteracy, lack of formal education, and largely non-English speaking background could contribute to higher dementia rates in remote Aboriginal people [14]. Yet, urban Aboriginal people have similarly high dementia rates (21.0% versus 23.8% remote, at ages 60+), despite being English speaking and typically literate, with at least some secondary education [2]. While better educational outcomes will likely contribute to dementia prevention, there is a need to consider a broader array of social risk factors in indigenous populations.

The current study examined the potential risk factors for dementia in a population-based sample of Aboriginal Australians aged 60 years and older from urban and regional communities in New South Wales (NSW). It was hypothesized that the factors related to the high rates of dementia observed in this population would be multifaceted and apparent across all phases of the lifespan, from childhood through to mid- and late-life. It was also expected that the factors associated with dementia would be similar to those reported in other populations, given the similar pattern of dementia types diagnosed (i.e., AD, mixed and vascular dementia most prevalent) [2].

MATERIALS AND METHODS

Study setting and participants

The cross-sectional Koori Growing Old Well Study (KGOWS) was set in five Aboriginal communities across NSW in eastern Australia—two in metropolitan Sydney and three in regional coastal areas. NSW has the largest Aboriginal population of any state or territory in Australia, at 33% of the total Aboriginal and Torres Strait Islander Australian population [17]. These communities and the study participants encompass a diverse range of traditional cultural and language groups, from many regions of Australia. The study sample comprised 62% of the total Aboriginal and Torres Strait Islander population aged 60 years and older across five catchment areas (i.e., all contactable and willing/consenting participants) and this sample was representative of the total population in terms of age, sex, and urban/regional distribution. Study data collection was undertaken from March 2010 to September 2012. Full details of the study protocol have been described previously, including recruitment, sampling and assessment procedures

(see [2, 18]). We worked in partnership with local Aboriginal Community Controlled Health Organizations (ACCHOs) and other key community organizations, and employed local community members to support recruitment, data collection, feedback, and culturally safe engagement with participants. Variables relevant to the current analyses are briefly described below.

Ethics

The study was approved by the Aboriginal Health and Medical Research Council (AHMRC; 615/07), the University of New South Wales Human Research Ethics Committee (HREC 08003), and NSW Population & Health Services Research Ethics Committee (AU RED Ref: HREC/09/CIPHS/65; Cancer Institute NSW Ref: 2009/ 10/187). All ethical requirements were adhered to. Participants gave written informed consent or, in cases where capacity to consent was lacking, gave verbal assent and written informed consent was obtained from an appropriate relative or a caregiver.

Measures

Dementia diagnosis

The main outcome for the current study was a diagnosis of "all-cause" dementia or probable/possible AD according to National Institute on Aging and Alzheimer's Association (NIA-AA) criteria [19]. We also applied DSM-IV diagnostic criteria for AD [20], which yielded consistent results. Diagnoses were based on data obtained through comprehensive medical assessment (including cognitive, behavioral, neurological, and collateral/caregiver measures) carried out by specialist geriatricians or general physicians with experience in dementia assessment [18]. A panel of at least three clinicians (including geriatricians and psychologists) reviewed these data to determine diagnosis by consensus.

Potential social and biomedical risk factors

All risk factor data were collected using a structured interview protocol, separate to the diagnostic assessment [18]. We assessed demographic factors, including age, sex, area of residence (urban/regional), years of formal education, source of income, and Indigenous status. The 'years of formal education' variable was derived based on the highest level of education achieved [see [21], for full details].

Self-reported clinical history was obtained (coded as 1 = present, 0 = absent), including stroke or transient ischemic attack, head injury with loss of consciousness, epilepsy, lifetime diagnosis of depression, lifetime diagnosis of anxiety or post-traumatic stress disorders (PTSD), diabetes, hypercholesterolemia, hypertension, heart disease, and current smoking. Self-reported hearing loss was recorded (nil/mild versus moderate/severe). Lifetime smoking was also recorded using the pack-year history method. Past alcohol use (highest lifetime level) was assessed using the short-form of the Alcohol Use Disorders Identification Test (AUDIT-C) [22]. Scores on the AUDIT-C were classified as 0 = 'no alcohol', 1–5 = 'low-risk alcohol use', ≥ 6 = 'high-risk alcohol use' [23]. When missing or discrepant with medical assessment, self-reported clinical data were supplemented by data obtained from a nominated contact person or caregiver (i.e., typically a close relative or friend).

Social factors included occupational history (lifetime 'main job'), which was recorded and coded as unskilled (i.e., Labourers) versus partially-skilled/skilled (other occupational categories), according to the Australian and New Zealand Standard Classification of Occupations [24]. Lifetime rates of unemployment were low in this sample (n = 13; 4%), and hence these cases were also included in the unskilled work category. History of any time spent in police custody was recorded (yes/no). Aboriginal cultural and community connection were assessed using the questions: "How much is your Aboriginal culture a source of strength to you?" (coded 'a great deal' versus 'not at all/a little/somewhat'), and "Do you feel connected to the local Aboriginal community?" (yes/no). Potential early life risk and protective factors included exposure to early life stress and trauma, measured using the Childhood Trauma Questionnaire (CTQ) [25], and informal education and cultural experiences, measured using the Retrospective Indigenous Childhood Enrichment (RICE) 'Community' subscale [21]. We also considered where participants mainly grew up (major city versus inner regional versus outer regional/remote areas), the Index of Relative Socioeconomic Disadvantage (IRSD) for the postal area in which they mainly grew up (lower index scores indicate higher levels of socioeconomic disadvantage) [26], their self-reported childhood health (poor/fair versus good/very good/excellent), and death of one or both parents during childhood.

Comorbid factors

The relative prevalence of a range of factors anticipated to be comorbid with dementia diagnosis was examined, including the following variables. Functional disability was measured as impairment of activities of daily living using the total score of the Kilsyth Disability Scale [27]. Incontinence and mobility impairment were assessed using the relevant items from this same scale (present/absent). Self-reported falls over the previous year were recorded (0 versus ≥1). Self-reported number of hospital admissions over the past year (0 versus ≥1) and currently living in a residential aged care facility (RACF; yes/no) were also examined. Height and weight were assessed and used to calculate BMI (weight(kg)/height(m)^2). BMI ≤ 25 was classified as Low BMI (code = 1 versus BMI > 25, code = 0). Systolic and diastolic blood pressure was also measured (while seated, average of 2 measurements). We used validated self-report scales to assess current symptoms of depression (modified Patient Health Questionnaire 9; mPHQ-9) [28], as well as current alcohol use (AUDIT-C; coded as for past alcohol use) [23]. Engagement in physical activities, classified as mild (e.g., walking, housework, gardening) or moderate (e.g., swimming, dancing, lawn mowing), was assessed over the past three months (yes/no). Social networks and engagement were evaluated using the following variables: marital status (married/de-facto versus other), currently living alone (yes/no), subjective loneliness (almost never versus sometimes/often), and participation in different social activities over the previous three months (e.g., attending a sporting or community event, going shopping with a friend; total number /10).

Data analysis

All analyses were completed using IBM SPSS v25 (IBM Corp., Armonk, NY). Level of significance was set at 0.05. To examine potential risk factors and comorbidities of dementia in this population, we used univariate logistic regression analysis with dementia as the criterion variable and other variables as predictors. The independent effects of basic demographic variables (age, sex, years of education, current urban/regional location) were examined using a multivariable logistic regression model, which revealed age to be the only significant factor. All subsequent 'risk factor' regression analyses were performed with adjustment for age. Odds ratios with 95% confidence intervals are reported for these analyses. The

current sample size provides >95% power to detect small-to-moderate univariate effects (based on effect size $w = 0.2$). Second, to identify key independent predictors, we evaluated all significant ($p < 0.05$) age-adjusted univariate 'risk factor' associations in multivariable models for dementia. Models were tested for the outcomes of all-cause dementia as well as probable/possible AD. All predictors were entered into the initial model and predictors with $p > 0.1$ were subsequently removed. As such, only predictors with $p < 0.1$ were retained in the final multivariable model. Age, years of education, CTQ, RICE Community sub-scale, IRSD, smoking pack years, number of recent social activities, mPHQ-9, systolic blood pressure and diastolic blood pressure were analyzed as continuous variables. Variables not meeting assumptions regarding normality of distribution (i.e., age, CTQ, smoking pack years, mPHQ-9) were transformed according to the guidelines of Tabachnick and Fidell [29] for use in regression analyses. Continuous variables were converted to standardized scores prior to regression analysis to enable comparison of effects across different scales/variables. For multivariable 'risk factor' analysis, missing values for continuous variables were imputed using the expectation-maximization procedure, to maximize inclusion of participants in the analysis.

RESULTS

Participants

A representative sample of 336 Aboriginal and Torres Strait Islander people aged 60 years and older participated in the current study. Almost all of these participants identified as being an Aboriginal person ($n = 328$; 98%), with a smaller number identifying as a Torres Strait Islander ($n = 2$) or both Aboriginal and Torres Strait Islander person ($n = 6$). The majority of participants reported receiving current income from a government pension (82.4%, including 100% of people with dementia). This cohort has been previously described in detail [2]. Forty-five participants were diagnosed by clinical consensus with "all-cause" dementia, of whom 27 met criteria for probable ($n = 18$) or possible ($n = 9$) AD. Five participants were diagnosed with longstanding cognitive disorders related to schizophrenia or intellectual disability, and were excluded from further analyses. The remaining 286 participants classified as 'no dementia' were cognitively intact and/or not diagnosed with a cognitive disorder ($n = 248$) or diagnosed with mild

cognitive impairment (MCI) ($n = 38$). Demographic and clinical descriptive statistics for the sample by dementia diagnosis are shown in Table 1.

Factors associated with dementia

Univariate analyses revealed older age was significantly associated with an increased likelihood of dementia diagnosis ($B = 0.74$, $SE = 0.15$, $p < 0.001$). There was also a borderline significant trend association ($B = 0.62$, $SE = 0.32$, $p = 0.06$) for males to be more likely to be diagnosed with dementia compared to females, and for higher levels of education to reduce the likelihood of dementia ($B = -0.29$, $SE = 0.17$, $p = 0.09$), but there was no association

between dementia and currently residing in urban compared to regional areas ($B = 0.01$, $SE = 0.33$, $p = 0.97$). Of these demographic variables, only age remained a significant independent associated factor in multivariable analyses (controlling for other demographic variables), as shown in Table 1. In terms of potential early life risk factors, higher levels of exposure to childhood stress and trauma (i.e., CTQ score) and growing up in areas with higher IRSD scores (indicating lower levels of socioeconomic disadvantage) were associated with dementia diagnosis, in age adjusted analyses. High-risk alcohol use, past or current, was significantly associated with dementia (relative to abstinence), as well as moderate-severe hearing loss (borderline significance, $p = 0.05$).

Table 1
Descriptive statistics, logistic regression analyses, and adjusted odds ratios according to diagnosis, for factors potentially associated with dementia

Factor / Exposure	Dementia (N = 45)			No Dementia (N = 286)			Logistic Regression			Adjusted Odds Ratio*		
	N / Mean	% / SD	Missing	N / Mean	% / SD	Missing	B	SE	p	OR	95% CI lower	95% CI upper
Demographic												
Age (y)[†]	71.29	8.20	0	65.95	5.63	0	0.67	0.16	<0.001	1.96	1.43	2.68
Sex (male)	24	53	0	109	38	0	0.50	0.34	0.140	1.66	0.85	3.24
Urban site	19	42	0	120	42	0	–0.02	0.35	0.945	0.98	0.49	1.93
Education (y)[†]	8.39	3.46	1	9.39	2.73	0	–0.19	0.17	0.260	0.82	0.59	1.15
Childhood												
Childhood trauma[†]	42.06	22.77	15	35.89	15.24	22	0.49	0.20	0.013	1.63	1.11	2.39
Grew up – major city	12	27	0	90	32	2				REF		
Inner regional	16	36	0	106	37	2	0.24	0.43	0.568	1.276	0.55	2.95
Outer regional/remote	17	38	0	88	31	2	0.27	0.43	0.530	1.308	0.57	3.02
IRSD[†]	947.8	54.52	0	932.02	60.87	2	0.33	0.17	0.050	1.39	1.00	1.94
Poor/fair child health	8	18	1	67	24	4	–0.05	0.43	0.904	0.95	0.41	2.22
Death of parent(s)	9	20	0	63	22	2	–0.12	0.42	0.779	0.89	0.39	2.02
RICE Community[†]	23.54	7.53	8	24.23	6.32	20	–0.14	0.18	0.435	0.87	0.61	1.24
Adult social/behavioral												
Smoking (pack/y)[†]	25.63	37.51	4	25.06	34.19	14	0.13	0.18	0.465	1.14	0.80	1.64
Alcohol (past) – nil	10	22	0	80	29	14				REF		
Low risk	10	22	0	78	29	14	0.01	0.51	0.980	1.01	0.38	2.73
High risk	25	56	0	114	42	14	0.96	0.44	0.031	2.60	1.09	6.21
Culture a source of strength	17	49	10	194	70	10	–0.67	0.38	0.080	0.514	0.24	1.08
Connected to community	32	89	9	262	92	0	–0.50	0.60	0.401	0.61	0.19	1.95
Main job unskilled	26	59	1	102	37	7	0.81	0.35	0.019	2.25	1.14	4.44
Police custody	17	39	1	90	33	12	0.63	0.36	0.085	1.87	0.92	3.82
Clinical												
Depression (lifetime)	19	42	0	93	34	11	0.58	0.35	0.098	1.79	0.90	3.58
Anxiety/PTSD (lifetime)	11	24	0	89	32	11	–0.04	0.40	0.914	0.96	0.44	2.08
Diabetes	24	53	0	117	42	9	0.51	0.34	0.138	1.66	0.85	3.24
Hypercholesterolemia	20	45	1	130	48	15	0.03	0.35	0.941	1.03	0.52	2.02
Hypertension	26	59	1	175	64	11	–0.33	0.35	0.359	0.72	0.36	1.45
Heart disease	17	38	0	122	44	10	–0.46	0.35	0.187	0.63	0.32	1.25
Hearing loss (mod/severe)	20	44	0	65	23	0	0.68	0.35	0.052	1.98	0.99	3.96
Stroke	23	51	0	54	20	10	1.47	0.36	<0.001	4.36	2.16	8.77
Head injury with LOC	21	48	1	73	26	9	1.06	0.35	0.003	2.87	1.44	5.74
Epilepsy	7	16	1	17	6	12	1.54	0.54	0.004	4.65	1.62	13.34

*Demographic factors (age, sex, education and urban/regional location) adjusted for other demographic factors; all other associations adjusted for age. [†]Continuous variable, mean and standard deviation reported. IRSD, Index of Relative Socioeconomic Disadvantage; RICE, Retrospective Indigenous Childhood Enrichment Scale; PTSD, post traumatic stress disorder; LOC, loss of consciousness.

Vascular risk factors, including smoking, diabetes, hypercholesterolemia, hypertension, and heart disease were not significantly associated with dementia diagnosis. Neurological disorders of stroke, head injury with loss of consciousness, and epilepsy were all significantly associated with dementia. Individuals with a history of one or more of these neurological disorders were approximately 2.5 times more likely to be diagnosed with dementia, although the prevalence was high in both the dementia (67%) and no dementia groups (45%).

As predicted, common comorbid factors (i.e., disability, incontinence, mobility impairment, RACF, recent hospitalization, low BMI) were strongly associated with dementia, with the exception of falls, which were not significantly more prevalent in the dementia group (see Table 2). Current symptoms of depression were significantly associated with dementia ($p = 0.02$), but lifetime history of depression or history of anxiety/PTSD were not. Dementia diagnosis was significantly associated with lower levels of current mild or moderate physical activity, as well as with lower levels of social engagement across indicators including living alone, feeling lonely, and participating in fewer recent social activities.

Multivariable models for potential risk factors associated with all-cause dementia and Alzheimer's disease

Multivariable models included age, childhood trauma (CTQ score), unskilled work history, past alcohol use (based on AUDIT-C score), history of stroke, history of head injury with loss of consciousness, and epilepsy. Despite its significance as a univariate factor associated with dementia, past alcohol use was not included in the final all-cause dementia model given its diminished association ($p > 0.1$) with dementia outcome in the context of other factors. The final model for all-cause dementia (Table 3) revealed age, childhood trauma (CTQ), unskilled work, stroke, and head injury were independently and significantly associated with dementia diagnosis. There was also a non-significant trend ($p = 0.08$) for epilepsy to be independently associated with dementia in this model. When the multivariable analysis was limited to dementia cases diagnosed with probable or possible AD (Table 4), age, childhood trauma, and stroke remained significant independent associated factors; the effect of head injury was reduced and no longer included as a factor in the final AD model; epilepsy was a significant

Table 2
Descriptive statistics, logistic regression analyses, and adjusted odds ratios according to diagnosis, for factors potentially comorbid with dementia

Factor / Exposure	Dementia (N = 45)			No Dementia (N = 286)			Logistic Regression			Adjusted Odds Ratio*		
	N / Mean	% / SD	Missing	N / Mean	% / SD	Missing	B	SE	p	OR	95% CI lower	95% CI upper
ADL impairment[†]	17.82	6.95	0	9.57	2.97	11	1.38	0.21	<0.001	3.98	2.66	5.96
Incontinence	19	42	0	33	12	14	1.72	0.38	<0.001	5.56	2.63	11.76
Mobility impaired	23	51	0	63	23	11	0.87	0.36	0.014	2.40	1.20	4.80
Falls (past year)	15	34	1	63	23	10	0.42	0.37	0.257	1.52	0.74	3.15
Hospitalized (past year)	25	58	2	106	39	12	0.74	0.35	0.033	2.09	1.06	4.14
RACF	12	27	0	2	1	0	3.87	0.81	<0.001	47.72	9.76	233.34
Depression (mPHQ9)[†]	6.37	5.03	10	4.77	4.81	13	0.47	0.20	0.019	1.60	1.08	2.37
Low BMI	10	37	18	28	12	49	1.24	0.47	0.008	3.44	1.38	8.61
Systolic BP[†]	136.17	22.86	9	135.34	20.48	50	0.12	0.19	0.529	1.12	0.78	1.62
Diastolic BP[†]	84.53	14.51	9	82.1	12.79	50	0.24	0.19	0.208	1.27	0.88	1.83
Smoking (current)	13	29	0	70	25	11	0.57	0.34	0.14	1.77	0.83	3.77
Alcohol (current) – nil	30	67	0	162	59	11	REF					
Low risk use	8	18	0	89	32	11	−0.36	0.44	0.424	0.70	0.29	1.67
High risk use	7	16	0	24	9	11	1.17	0.52	0.024	3.23	1.17	8.93
Physical activity, mild	25	71	10	247	90	11	−1.09	0.44	0.013	0.34	0.14	0.79
Physical activity, mod.	9	26	10	134	49	11	−0.83	0.42	0.046	0.44	0.19	0.99
Married	13	29	0	107	38	7	−0.42	0.37	0.25	0.66	0.32	1.34
Live alone	15	38	5	62	22	10	0.76	0.37	0.043	2.13	1.03	4.43
Loneliness	37	82	0	147	51	0	1.35	0.42	0.001	3.86	1.70	8.75
Social activities (/10)[†]	3.39	2.49	12	5.37	2.11	17	−0.89	−.21	<0.001	0.41	0.27	0.62

*Adjusted for age. [†]Continuous variable, mean and standard deviation reported. ADL, activities of daily living; mPHQ9, modified Patient Health Questionnaire 9; BMI, Body Mass Index; BP, blood pressure; RACF, Residential Aged Care Facility.

Table 3
Multivariable logistic regression model for all-cause dementia

Factor	B	SE	p	OR	95% CI lower	95% CI upper
Age	1.06	0.21	<0.001	2.88	1.93	4.31
Childhood trauma	0.47	0.21	0.026	1.59	1.06	2.40
Unskilled work	0.88	0.39	0.024	2.41	1.12	5.19
Stroke	1.21	0.39	0.002	3.35	1.57	7.15
Head Injury	0.95	0.39	0.015	2.58	1.20	5.56
Epilepsy	1.15	0.66	0.079	3.17	0.88	11.49

Table 4
Multivariable logistic regression model for clinical diagnosis of Alzheimer's disease

Factor	B	SE	p	OR	95% CI lower	95% CI upper
Age	1.20	0.26	<0.001	3.31	2.01	5.46
Childhood trauma	0.64	0.26	0.013	1.90	1.15	3.16
Unskilled work	0.89	0.49	0.067	2.43	0.94	6.28
Alcohol: Abstinent				REF		
Low risk	−1.52	0.77	0.049	0.22	0.05	1.00
High risk	0.26	0.54	0.629	1.30	0.45	3.74
Stroke	1.13	0.48	0.019	3.08	1.21	7.88
Epilepsy	1.60	0.79	0.042	4.95	1.06	23.20

independent predictor of dementia diagnosis; and lifetime low risk alcohol consumption was associated with a lower likelihood of AD relative to abstinence, while high risk alcohol use was not associated with AD. However, while plausible, these results need to be interpreted more cautiously given there were fewer AD cases than the recommended minimum of five per predictor variable [30].

DISCUSSION

This study is the first to examine factors associated with dementia in a representative urban and regional community-based sample of older Aboriginal Australians. In this cohort, dementia diagnosis was associated with older age, in the context of other demographic factors. When controlling for age, dementia was also associated with childhood trauma, past high-risk alcohol use, unskilled work history, stroke, head injury, and epilepsy. Of these variables, age, childhood trauma, unskilled work, stroke, and head injury were all significantly associated with all-cause dementia when entered in a multivariable model, while epilepsy and past alcohol use were not. When restricted to only possible or probable AD cases, results remained reasonably consistent: the effect of childhood trauma and epilepsy was strengthened in relation to AD diagnosis, but head

injury was no longer a significant independent factor in the model. These findings are generally in accordance with previous research, and replicate a study in remote Aboriginal Australians that found age, stroke, head injury, and epilepsy were associated with dementia [14]. Although high-risk alcohol use was initially associated with dementia, this did not hold when past alcohol use was entered into the multivariable models; rather, low risk alcohol use was associated with a lower likelihood of AD. This is generally consistent with previous studies examining the links between alcohol consumption and dementia [31].

In contrast to other studies, years of education was not associated with dementia in the current sample. Almost everyone in the current sample (99%) reported at least four years of schooling (ranging up to 19 years of formal education), compared to high rates of no formal education (40%) in the previous remote population study [14]. Although there is evidence that years of education is associated with both prevalent and incident dementia in other populations (see [32, 33]), it is possible that 'years of education' is not a sensitive measure of learning, quality of education or educational attainment in this cohort; many participants (48%) completed 8–10 years of schooling, likely reflecting compulsory education requirements. Instead, it appears that low occupational complexity (i.e., unskilled work, also linked to fewer education/training opportunities and achievements, as well as probable lower mid-life income) is a more indicative factor associated with dementia in urban and regional Aboriginal Australians. In other populations, unskilled work has also been shown to associate with dementia [34].

Childhood stress and trauma was confirmed as a significant factor associated with dementia, and AD diagnosis in particular, after controlling for other potential dementia risk factors. In Aboriginal Australians, such childhood stress exposure has been linked, in part, to personal and family experiences of the *Stolen Generations* (i.e., forced child removal policies) [16]; and, therefore, is especially pertinent in this population. There is increasing evidence of the role that early life stress exposure could play in the pathogenesis of AD [13]. However, overall, associations between adverse childhood experiences and dementia in various populations have been inconclusive [35–38], possibly reflecting the diversity of childhood exposures assessed across studies [39]. The current study specifically measured childhood psychological trauma exposure arising from abuse and neglect, as opposed to childhood socioeconomic

deprivation, which may not necessarily confer risk for cognitive decline and dementia in all populations [35].

This study also identified factors likely reflecting dementia comorbidity including incontinence, impaired mobility, difficulties with activities of daily living, being hospitalized at least once in the past year, low BMI, current symptoms of depression, current high-risk alcohol use, social isolation (i.e., living alone, feelings of loneliness, and engagement in fewer social leisure activities), lower recent participation in physical activity, and living in residential aged care. Falls in the past year were not significantly associated with dementia, but this may relate to the relatively low prevalence of falls, or underreporting of falls, in this cohort [40]. These findings highlight the vulnerability of older individuals with dementia and provide important insights into the burden of living with dementia in urban Aboriginal communities, as well as ways to improve dementia care and support.

The current study found no significant associations between dementia and current or lifetime smoking, lifetime depression, diabetes, and other cardiovascular risk factors that have been shown to increase dementia risk globally (e.g., [5]). It is well documented that Aboriginal Australians have high rates of many chronic health conditions, notably cardiovascular and metabolic diseases, as well as mental health disorders and smoking [9, 10, 41, 42]. It could be that significant associations between dementia and these factors were not evidenced in this late-life (60+) cohort due to the particularly high prevalence of chronic conditions at older ages and the need to measure these exposures in mid-life; or due to the lack of sensitivity afforded by the dichotomous self-report measures used. Similarly, a high prevalence of potentially protective factors, such as connection to an individual's Aboriginal culture and community, was observed across both dementia and no dementia groups. Nevertheless, the somewhat elevated proportion of participants in the no dementia group who indicated that they derived a lot of strength from their Aboriginal culture suggests a role of cultural connection for aging well in this population.

This study has a number of strengths, particularly in terms of the representativeness of the sample. Participants were recruited from five study sites across urban and regional NSW and were identified via community census and snowballing techniques, thereby allowing access to all members of those communities [43]. Importantly, 79% of the Aboriginal and Torres Strait Islander Australian population reside in urban or regional communities [44]. Our sample therefore adds substantially to previous work in remote locations, in terms of representativeness and generalizability of findings. Another strength of this study is that participants were extensively assessed on their social and medical history across the life-course. There has been a move toward exploring the effect of early life factors on late-life diseases such as dementia [11, 12], and our results support the importance of examining exposures throughout early, mid-, and late-life. Finally, the diagnosis of dementia was based on a comprehensive medical assessment and clinical consensus panel review. This provided a more accurate diagnosis of participants than, for instance, using a dementia screening score or algorithmic method.

There are some limitations of this study that should be acknowledged, most notably its cross-sectional nature. Also, early and mid-life exposures were reported retrospectively, which can be subject to recall biases (and may be differentially impacted by current cognitive impairment). Longitudinal research is needed to determine whether these factors are associated with incident dementia and cognitive decline. In addition, although the current sample was representative and population-based, a larger sample likely would have provided greater power for detecting effects. In particular, results of the multivariable model predicting AD may not be reliable, given the smaller number of dementia cases in this analysis relative to the number of predictor variables, and thus warrant further investigation and replication. Further, our 2-phase protocol did not include diagnostic assessment for all participants; only those meeting cognitive screening criteria and a 20% random sample of those with cognitive screening scores in the higher (intact) range completed diagnostic assessments and underwent clinical consensus review [18]. We estimate that approximately 15% of the cognitively intact group would have been diagnosed with MCI if all participants had undergone diagnostic assessment and review [2]. As such, we did not exclude participants with MCI from the 'no dementia' group in our analyses, but this conservative approach may have attenuated some effects. Finally, neuroimaging and further clinical investigations were not available to inform diagnosis of dementia type in this study, particularly to rule out other possible causes in cases diagnosed with AD.

Converging evidence indicates that Aboriginal Australians are disproportionately affected by

dementia, with some of the highest rates reported globally observed in this population [2–4, 15]. As such, there is a pressing need to understand the major causes and risk factors for dementia in this population, to guide targeted prevention initiatives and reduce the burden of dementia as this population continues to transition to aging. The current results highlight that life-course social determinants of health (e.g., childhood trauma, unskilled work opportunities) likely play an important role in elevating dementia and AD risk. This study also confirms, in urban and regional dwelling older people, the association between dementia and the high prevalence of neurological disorders (i.e., stroke, traumatic brain injury, epilepsy), previously observed in a remote Aboriginal population [3, 14, 15]. As Barnes and Yaffe [5] note, "the most important AD risk factors for a given country or community are probably the ones that are most prevalent" (p. 826). The high prevalence of cardiovascular and metabolic risk factors in this population, however, has not been directly linked to dementia to date, but the prominent effect of stroke history (on both all-cause and AD/mixed diagnoses) indicates that a focus on reducing risk for vascular brain disease is also important. Future research is needed to more closely consider the underlying causes of dementia in this population, which mostly presents clinically as AD. Neuroimaging and established genetic risk factors (such as Apolipoprotein E) are yet to be examined in the context of dementia in Aboriginal Australians, and further longitudinal studies are also needed to enhance our understanding of dementia in this population.

The global prevalence of dementia is forecast to rise rapidly over the coming decades, but this increase will not affect all populations equally [1]. There is an urgent need to understand the factors contributing to dementia risk in culturally, ethnically and socioeconomically diverse populations in order to work effectively towards global dementia prevention and reducing inequalities in brain health and aging. Low education in particular has been highlighted as a key modifiable risk factor for dementia worldwide [5, 45]. Addressing disparities in education is clearly important, but also likely insufficient, for dementia prevention. We need a more comprehensive understanding of the life course social and environmental determinants contributing to population disparities in dementia, both across and within low, middle, and high income countries. The current study adds substantially to a limited body of evidence on dementia in First Nations peoples. It also provides data on the impact of early life stress and trauma exposure, linked to histories of colonization, racial discrimination, and ongoing disadvantage, that are common across many indigenous populations in post-colonial settler societies, as well as overlapping with other marginalized or disadvantaged populations within high income countries.

REFERENCES

[1] Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP (2013) The global prevalence of dementia: A systematic review and metaanalysis. *Alzheimers Dement* **9**, 63-75.e62.

[2] Radford K, Mack HA, Draper B, Chalkley S, Daylight G, Cumming R, Bennett G, Delbaere K, Broe GA (2015) Prevalence of dementia in urban and regional Aboriginal Australians. *Alzheimers Dement* **11**, 271-279.

[3] Smith K, Flicker L, Lautenschlager NT, Almeida OP, Atkinson D, Dwyer A, LoGiudice D (2008) High prevalence of dementia and cognitive impairment in Indigenous Australians. *Neurology* **71**, 1470-1473.

[4] Li SQ, Guthridge SL, Aratchige PE, Lowe MP, Wang Z, Zhao Y, Krause V (2014) Dementia prevalence and incidence among the Indigenous and non-Indigenous populations of the Northern Territory. *Med J Aust* **200**, 465-469.

[5] Barnes DE, Yaffe K (2011) The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* **10**, 819-828.

[6] Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C (2014) Potential for primary intervention of Alzheimer's disease: An analysis of population-based data. *Lancet Neurol* **13**, 788-794.

[7] Bellou V, Belbasis L, Tzoulaki I, Middleton LT, Ioannidis JPA, Evangelou E (2017) Systematic evaluation of the associations between environmental risk factors and dementia: An umbrella review of systematic reviews and meta-analyses. *Alzheimers Dement* **13**, 406-418.

[8] Anstey KJ, Cherbuin N, Herath PM (2013) Development of a new method for assessing global risk of Alzheimer's disease for use in population health approaches to prevention. *Prev Sci* **14**, 411-421.

[9] Gubhaju L, McNamara BJ, Banks E, Joshy G, Raphael B, Williamson A, Eades SJ (2013) The overall health and risk factor profile of Australian Aboriginal and Torres Strait Islander participants from the 45 and up study. *BMC Public Health* **13**, 661.

[10] Vos T, Barker B, Begg S, Stanley L, Lopez AD (2009) Burden of disease and injury in Aboriginal and Torres Strait Islander peoples: The Indigenous health gap. *Int J Epidemiol* **38**, 470-477.

[11] Borenstein AR, Copenhaver CI, Mortimer JA (2006) Early-life risk factors for Alzheimer disease. *Alzheimer Dis Assoc Disord* **20**, 63-72.

[12] Whalley LJ, Dick FD, McNeill G (2006) A life-course approach to the aetiology of late-onset dementias. *Lancet Neurol* **5**, 87-96.

[13] Hoeijmakers L, Lesuis SL, Krugers H, Lucassen PJ, Korosi A (2018) A preclinical perspective on the enhanced vulnerability to Alzheimer's disease after exposure to stress in early-life. *Neurobiol Stress* **8**, 172-185.

[14] Smith K, Flicker L, Dwyer A, Atkinson D, Almeida OP, Lautenschlager NT, LoGiudice D (2010) Factors associated with dementia in Aboriginal Australians. *Aust N Z J Psychiatry* **44**, 888-893.

[15] LoGiudice D, Smith K, Fenner S, Hyde Z, Atkinson D, Skeaf L, Malay R, Flicker L (2016) Incidence and predictors of cognitive impairment and dementia in Aboriginal Australians: A follow-up study of 5 years. *Alzheimers Dement* **12**, 252-261.

[16] Radford K, Delbaere K, Draper B, Mack HA, Daylight G, Cumming R, Chalkley S, Minogue C, Broe GA (2017) Childhood stress and adversity is associated with late-life dementia in Aboriginal Australians. *Am J Geriatr Psychiatry* **25**, 1097-1106.

[17] ABS, 2071.0 - Census of population and housing: Reflecting Australia - Stories from the Census, 2016, http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/2071.0~2016~Main%20Features~Aboriginal%20and%20Torres%20Strait%20Islander%20Population%20Data%20Summary~10.

[18] Radford K, Mack HA, Robertson H, Draper B, Chalkley S, Daylight G, Cumming R, Bennett G, Pulver LJ, Broe GA (2014) The Koori Growing Old Well Study: Investigating aging and dementia in urban Aboriginal Australians. *Int Psychogeriatr* **26**, 1033-1043.

[19] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Theis B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.

[20] American Psychiatric Association (2000) *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*, American Psychiatric Association, Washington, DC.

[21] Minogue C, Delbaere K, Radford K, Broe GA, Forder WS, Lah S (2018) Development of initial validation of the Retrospective Indigenous Childhood Enrichment scale (RICE). *Int Psychogeriatr* **30**, 519-526.

[22] Bush K, Kivlahan DR, McDonnell MB, Fihn SD, Bradley KA (1998) The AUDIT Alcohol Consumption Questions (AUDIT-C): An effective brief screening test for problem drinking. *JAMA Intern Med* **158**, 1789-1795.

[23] Calabria B, Clifford A, Shakeshaft AP, Conigrave KM, Simpson L, Bliss D, Allan J (2014) Identifying Aboriginal-specific AUDIT-C and AUDIT-3 cutoff scores for at-risk, high-risk and likely dependent drinkers using measures of agreement with the 10-item Alcohol Use Disorders Identification Test. *Addict Sci Clin Pract* **9**, 17.

[24] ANZSCO, Australian and New Zealand Standard Classification of Occupations, Version 1.2, http://www.abs.gov.au/ausstats/abs@.nsf/DirClassManualsbyTopic/4AF138F6DB4FFD4BCA2571E200096BAD?OpenDocument,

[25] Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, Stokes J, Handelsman L, Medrano M, Desmond D, Zule W (2003) Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl* **27**, 169-190.

[26] ABS (2013) Australian Bureau of Statistics, Canberra.

[27] Akhtar AJ, Broe GA, Crombie A, McLean WM, Andrews GR, Caird FI (1973) Disability and dependence in the elderly at home. *Age Ageing* **2**, 102-111.

[28] Esler D, Johnston F, Thomas D, Davis B (2008) The validity of a depression screening tool modified for use with Aboriginal and Torres Strait Islander People. *Aust N Z J Public Health* **32**, 371-321.

[29] Tabachnick BG, Fidell LS (1996) *Using multivariate statistics*, Harper Collins, New York.

[30] Vittinghoff E, McCulloch CE (2007) Relaxing the rule of tem events per variable in logistic and Cox regression. *Am J Epidemiol* **165**, 710-718.

[31] Anstey KJ, Mack HA, Cherbuin N (2009) Alcohol consumption as a risk factor for dementia and cognitive decline: Meta-analysis of prospective studies. *Am J Geriatr Psychiatry* **17**, 542-555.

[32] Xu W, Tan L, Wang H-F, Tan M-S, Tan LL, J.-Q., Zhau Q-F, Yu J-T (2016) Education and risk of dementia: Dose-response meta-analysis of prospective cohort studies. *Mol Neurobiol* **53**, 3113-3123.

[33] Meng X, D'Arcy C (2012) Education and dementia in the context of the cognitive reserve hypothesis: A systematic review with meta-analyses and qualitative analyses. *PLoS One* **7**, e38268.

[34] Karp A, Andel R, Parker MG, Wang HX, Winblad B, Fratiglioni L (2009) Mentally stimulating activities at work during midlife and dementia risk after age 75: Follow-up study from the Kungsholmen Project. *Am J Geriatr Psychiatry* **17**, 227-236.

[35] Barnes LL, Wilson RS, Everson-Rose SA, Hayward MD, Evans DA, Mendes de Leon CF (2012) Effects of early-life adversity on cognitive decline in older African Americans and whites. *Neurology* **79**, 2321-2327.

[36] Moceri VM, Kukall WA, Emanual I, van Belle G, Starr JR, Schellenberg GD, McCormick WC, Bowen JD, Teri L, Larson EB (2001) Using census data and birth certificates to reconstruct the early-life socioeconomic environment and the relation to the development of Alzheimer's disease. *Epidemiology* **12**, 383-389.

[37] Persson G, Skoog I (1996) A prospective population study of psychosocial risk factors for late onset dementia. *Int J Geriatr Psychiatry* **11**, 15-22.

[38] Pilleron S, Guerchet M, Ndamba-Bandzouzi B, Mbelesso P, Dartigues JF, Preux PM, Clement JP (2015) Association between stressful life events and cognitive disorders in Central Africa: Results from the EPIDEMCA Program. *Neuroepidemiology* **44**, 99-107.

[39] Ritchie K, Jaussent I, Stewart R, Dupuy AM, Courtet P, Malafosse A, Ancelin ML (2011) Adverse childhood environment and late-life cognitive functioning. *Int J Geriatr Psychiatry* **26**, 503-510.

[40] Lukaszyk C, Radford K, Delbaere K, Ivers R, Rogers K, Sherrington C, Tiedemann A, Coombes J, Daylight G, Drane DL, Broe GA (2017) Risk factors for falls among older Aboriginal and Torres Strait Islander people in urban and regional communities. *Australas J Ageing* **37**, 113-119.

[41] Shen Y-T, Radford K, Daylight G, Cumming R, Broe GA, Draper B (2018) Depression, suicidal behaviour, and mental disorders in older Aboriginal Australians. *Int J Environ Res Public Health* **15**, 1-14.

[42] Broe GA, Radford K (2018) Multimorbidity in Aboriginal and non-Aboriginal Australians. *Med J Aust* **209**, 16-17.

[43] Atkinson R, Flint J (2001) *Accessing hidden and hard-to-reach populations: Snowball research strategies. Social Research Update No. 33*, Department of Sociology, University of Surrey, Guilford.

[44] ABS, 3238.0.55.001 - Estimates of Aboriginal and Torres Strait Islander Australians, June 2011, http://www.abs.gov.au/ausstats/abs@.nsf/mf/3238.0.55.001.

[45] Livingston G, Sommerlad A, Ortega V, Costafreda SG, Huntley J, Ames D, Ballard C, Banerjee S, Burns A, Cohen-Mansfield J, Cooper C, Fox N, Gitlin LN, Howard R, Kales HC, Larson EB, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbaek G, Teri L, Mukadam N (2017) Dementia prevention, intervention, and care. *Lancet* **390**, 2673-2734.