Statistical Analysis Plan

for

Koori Growing Old Well Study (KGOWS)

Dementia incidence and risk factors in urban and regional Aboriginal Australians

SAP Version Number: 1.0

Date: 30 August 2019

Contents

1 ADMINISTRATIVE INFORMATION

Statistical Analysis Protocol

Version history

Version	Date	Description
SAP Version 1		Final version

List of contributors

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2 SIGNATURE PAGE

We, the undersigned, have reviewed and approve this Statistical Analysis Plan.

The signatories confirm that:

a) They believe the procedures for the statistical analysis of the data from the *Koori Growing Old Well* study described in this document are appropriate;
b) Their intention is to analyse the data from the *Koori Growing Old Well* study using the statistical procedures described in this document; and
c) If, subsequently, the statistical analysis of the data is conducted in a way that differs importantly from the procedures described in this document, those differences will be explicitly outlined in reports of those analyses.

Signature	Date
Dr Louise Lavrencic Postdoctoral Fellow, NeuRA	5 September 2019
Dr Kylie Radford Research Fellow, NeuRA	5 September 2019
A/Prof Kim Delbaere Principal Research Scientist, NeuRA	30 August 2019
Prof Robert Cumming Professor of Epidemiology, University of Sydney	

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Signature	Date
Dr Louise Lavrencic Postdoctoral Fellow, NeuRA	
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3 INTRODUCTION

Gaining a better understanding of dementia in Aboriginal communities is of great importance given that the Aboriginal population is ageing, with the number of Aboriginal people aged 65 years and over expected to more than double from 2011 to 2026 (ABS, 2014). In the past decade, research has consistently demonstrated a higher dementia prevalence for urban, regional and remote Aboriginal and Torres Strait Islander people (respectfully referred to hereon as Aboriginal) compared to the 'mainstream' Australian population (Li et al., 2014; Radford, Mack, Draper, Chalkley, Daylight, et al., 2015; Smith et al., 2008). However, to date there has only been one prospective study examining dementia incidence in a remote sample of Aboriginal Australians from the Kimberley region in Western Australia. This study found that there is also a higher rate of incident dementia (21.0 per 1000 person-years) and cognitive decline (52.6 per 1000 person-years) in Aboriginal people aged 60 years and older compared to Australian estimates for the broader population (Lo Giudice et al., 2016). Whilst this study has shed additional light on the profile of dementia in a remote Aboriginal population, there are currently no estimates of dementia incidence for the majority urban and regional Aboriginal population (accounting for 80% of all Aboriginal Australians) (ABS, 2016).

In recent years, risk and preventive factors for dementia have been a focus in epidemiological and cohort studies. A number of recent articles have summarised the literature on life-course risk factors for dementia and identified that dementia risk is related to early life (educational attainment), midlife (hearing loss, hypertension, obesity and traumatic brain injury), late-life (smoking, depression, physical inactivity, social isolation, diabetes and hyperlipidaemia) and genetic (ApoE ε4) factors (Barnes & Yaffe, 2011; Baumgart et al., 2015; Deckers et al., 2014; Livingston et al., 2017). Whilst extensive research has occurred to identify these factors, there is limited evidence of risk factors for dementia in an Aboriginal Australian context. This is imperative given the elevated rates of dementia for Aboriginal Australians, giving rise to the possibility that the dementia risk factor profile differs from other populations.

4 STUDY AIMS AND METHODS

This study aims to identify the incidence rates and risk factors for dementia and cognitive decline in a population-based sample of urban and regional Aboriginal Australians aged 60 years and older. It was hypothesised that high rates of incident dementia and cognitive decline would be observed compared to incidence rates reported for non-Indigenous populations. Furthermore, it was expected that the risk factors for dementia and cognitive decline would be similar to those previously reported in Aboriginal Australians as well as other populations, and would span the life-course.

Participants were part of the longitudinal Koori Growing Old Well Study (KGOWS), a population-based study spanning five Aboriginal communities in New South Wales (NSW), Australia with two metropolitan Sydney sites and three regional mid-North Coast sites. The baseline study has been described elsewhere, including dementia prevalence rates and cross-sectional factors associated with dementia (Radford et al., 2018; Radford & Mack, 2012; Radford, Mack, Draper, Chalkley, Daylight, et al., 2015; Radford et al., 2014). Baseline data collection occurred from March 2010 to September 2012 (n=336). Baseline participants who

were contactable and willing to participate were recruited for a follow-up study, with follow-up data collection occurring from July 2016 to April 2018 (n=165).

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).

5 STUDY POPULATION AND SUBGROUPS

Baseline inclusion criteria were identifying as an Aboriginal and/or Torres Strait Islander person, aged 60 years or older, and having resided in one of the five study catchment areas for at least 6 months. All baseline participants were eligible to take part in the follow-up study.

At baseline, dementia screening instruments included the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975); the modified Kimberley Indigenous Cognitive Assessment (mKICA (Radford & Mack, 2012); and the Rowland Universal Dementia Assessment Scale (RUDAS) (Storey, Rowland, Basic, Conforti, & Dickson, 2004). At baseline, all participants who screened positive for cognitive impairment (≤26 on the MMSE, ≤35 on the mKICA, and/or ≤25 on the RUDAS) and a 20% random sample of those who screened negative, proceeded to medical/cognitive assessment and contact person interview. At follow-up, based upon validation of the MMSE and mKICA (Radford, Mack, Draper, Chalkley, Delbaere, et al., 2015), participants who screened positive for cognitive impairment (<26 on the MMSE and/or <37 on the mKICA) proceeded to medical/cognitive assessment and contact person interview.

Diagnosis of dementia and cognitive impairment were based on comprehensive medical data, with assessment by specialist geriatricians or general physicians experienced in dementia assessment; cognitive, neurological and behavioural measures, as well as contact person interview were used for diagnosis. “All-cause” dementia or probable/possible Alzheimer’s disease (AD) were diagnosed according to National Institute on Aging and Alzheimer’s Association (NIA-AA) (McKhann et al., 2011) and DSM-IV diagnostic criteria. Other types of dementia were diagnosed according to available criteria and detailed in previous reports (Radford, Mack, Draper, Chalkley, Daylight, et al., 2015). Diagnosis of mild cognitive impairment (MCI) was also based on clinical consensus review using internationally recognised criteria (Winblad et al., 2004). Where there was objective cognitive impairment but no decline reported at baseline, participants were classified as ‘cognitive finding no dementia’ (CFND). Where impairment was due to another cause at baseline (e.g., disability, mental health condition), a classification of ‘other cognitive impairment’ was given.

For participants unable to complete a medical assessment at follow-up, evidence of decline was based on changes to cognitive screening test scores from baseline to follow-up. Participants were categorised as having MCI if they experienced a 2SD drop (i.e., ≥3 points) in MMSE score (based on published norms for intact participants of the baseline study) (Radford, Mack, Draper, Chalkley, Delbaere, et al., 2015) from baseline to follow-up and had no evidence of functional impairment (Akhtar et al., 1973). Participants with an MMSE score <22 and evidence of functional impairment were diagnosed with dementia, consistent with baseline procedure (Radford, Mack, Draper, Chalkley, Daylight, et al., 2015).

6 STATISTICAL ANALYSIS

The primary analyses will be conducted using binary logistic regression analyses. All tests will be 2-tailed and the nominal level of α will be 5%. Where data are missing for outcome measures, the number of observations will be reported; no imputation of missing values for the primary outcome will be carried out. P-values will not be adjusted for multiple comparisons; however, outcomes are clearly categorised by importance (i.e., primary and secondary). P-values will be rounded to three decimal places and values less than 0.001 will be reported as <.001. Subgroup analyses are exploratory and should be treated with caution due to absence of correction for multiple comparisons and likely small sample size.

6.1 Primary Outcomes

Incident cognitive decline is the primary outcome measure. Cases of incident cognitive decline will be identified as shifting to a more severe diagnostic category from baseline to follow-up. Cognitive decline is identified as falling into the following categories from baseline to follow-up: intact to MCI/dementia, CFND to MCI/dementia, MCI to dementia, or other cognitive impairment to dementia. Participants will be categorised as not having declined if their diagnosis remained stable from baseline to follow-up, or they reverted from baseline MCI diagnosis to intact at follow-up. Participants with dementia diagnosis at baseline will be excluded from the cognitive decline variable.

6.2 Secondary Outcomes

Incident dementia is the secondary outcome measure. Incident dementia is defined as participants who did not have a dementia diagnosis at baseline, but were diagnosed with dementia at follow-up. Participants with a dementia diagnosis at baseline will be excluded from incidence calculations.

6.3 Additional Measures

Demographic data were collected at baseline, including information on age, sex, urban/regional location, educational attainment and work history. Comprehensive lifecourse and medical history was also taken (see Table 1 for list of measures).

Continuous predictor variables will be standardised (z-scored) prior to inclusion in models.

Table 1. *List of baseline measures to be used as predictor variables in statistical analyses.*

Measure	**Details**
Age	Continuous
Sex	1=female, 2=male
Urban/regional	0=regional, 1=urban
Educational attainment	Continuous
Unskilled work history	0=no, 1=yes
Childhood trauma questionnaire	Continuous
Childhood socioeconomic disadvantage (IRSD scores)	Continuous
Past alcohol use	0=abstinent, 1=low risk, 2=high risk
Current alcohol use	0=abstinent, 1=low risk, 2=high risk
Vision problems	0=no/mild, 1=moderate/severe
Hearing problems	0=no/mild, 1=moderate/severe
Smoking (pack year history)	Continuous

Smoking status	0=never smoked, 1=ex-smoker, 2=current smoker
Diabetes	0=no, 1=yes
Hypercholesterolemia	0=no, 1=yes
Hypertension	0=no, 1=yes
Body mass index	Continuous
Waist-hip ratio	Continuous
Heart disease	0=no, 1=yes
Stroke/TIA	0=no, 1=yes
Head injury	0=no, 1=yes
Epilepsy	0=no, 1=yes
Disability	0=no, 1=yes
Incontinence	0=no, 1=yes
Mobility impairment	0=no, 1=yes
Resides in Residential Aged Care Facility	0=no, 1=yes
Hospitalisation (past year)	0=no, 1=yes
Falls (past year)	0=no, 1=yes
Depressive symptoms (mPHQ9)	Continuous
History of depression (in lifetime)	0=no, 1=yes
History of anxiety/PTSD (in lifetime)	0=no, 1=yes
Physical activity (moderately energetic)	0=no, 1=yes
Lives alone	0=no, 1=yes
Feels lonely	0=almost never, 1=sometimes/quite often
Social activity participation	Continuous
Death of a parent in childhood	0=no, 1=yes
Resilience (CD-RISC)	Continuous
Retrospective Indigenous Childhood Enrichment (RICE) scale	Continuous
Culture is a source of strength	0=none/a little, 1=somewhat/a lot
Number of missing teeth	Continuous
Mean arterial pressure	Continuous
Polypharmacy	0=no, 1=yes
Number of childhood middle ear infections	0=none/one, 1=two or more

ApoE genotype data was also obtained at follow-up from saliva samples and will be examined for associations with outcome variables (i.e., ApoEε4 coded 0=nil/absent, 1=1 or 2 alleles present).

6.4 Analyses of Primary Outcome

Descriptive statistics for continuous (mean, standard deviation, median, interquartile range, range) and categorical/dichotomous variables (number and percentage in each group) will be reported (for both original and imputed data), as will frequency of ApoE genotypes.

Crude and age-adjusted incidence rates by 1,000 person-years will be calculated for cognitive decline. All rates (crude and age adjusted) will be calculated using the mid-point method, in line with methods published for large-scale epidemiological cohort studies investigating dementia incidence (Matthews et al., 2016; Prince et al., 2012). Therefore, to estimate crude incidence rates, participants with incident dementia/cognitive decline at follow-up will be assumed to have declined mid-way between the two study waves. 95% confidence intervals

will be calculated according to a Poisson distribution. Age-adjusted incidence rates will be estimated by standardisation to an Australian population (Access Economics, 2009) by calculating incidence rates for the following age groups: 60-69, 70-79, and 80+. 95% confidence intervals for the age-adjusted incidence rates will be calculated by approximating the standard error according to the formula $SE = R/\sqrt{N}$, where R is the age-adjusted rate and N is the number of events (Keyfitz, 1966).

Univariable comparisons will be made between groups (incident cognitive decline vs no decline) using logistic regression analyses for all variables. These analyses will be adjusted for age (entered as a covariate). Significant variables ($p<.05$) from univariable analyses will then be entered into a multivariable logistic regression model predicting incident cognitive decline. Predictors in this model with $p>.01$ will subsequently be removed; as such, only predictors with $p<.01$ will be retained in the final model.

6.5 Analyses of Secondary Outcome

Crude and age-adjusted incidence rates will be calculated for dementia using the same methods specified for the primary outcome. These analyses will only be conducted provided they meet sample size requirements (criteria being a minimum of 5 events per variable for logistic regression) (Vittinghoff & McCulloch, 2006).

6.6 Additional Analyses

Due to the smaller sample size of people with ApoE data, the final model will be re-run including ApoE as a covariate (if ApoE is a significant predictor of incident cognitive decline in univariable analysis).

Differences between incident cognitive decline and incident dementia cases will also be analysed in relation to all head injury, stroke and onset of epilepsy/seizures, including baseline and follow-up (i.e., more recent) cases. It is expected that the incidence rates will be low, but this is important to examine in order to account for the impact of recent history.

If no effects of cardiovascular/metabolic risk factors are seen (hypertension, hypercholesterolemia, diabetes, heart disease), sensitivity analyses will be conducted examining age of diagnosis of these factors, to tease apart potential reasons for lack of effects such as mid- versus late-life onset and the impact of chronic disease management.

6.7 Missing Data and Outliers

Missing values will not be imputed for the outcome measures or ApoE genotype. To maximise inclusion of participants in analyses, for cases where psychological or cognitive tests have less than 25% missing items, total scores will be prorated according to the suggested formulas (from relevant test manual) or based on previous literature. Multiple imputation will be conducted for predictor variables prior to conducting analyses.

If outliers are present in the data or the model assumptions are grossly violated, sensitivity analyses will be conducted for those specific models.

10 RATIONALE FOR ANY DEVIATION FROM PRE-SPECIFIED ANALYSIS PLAN

Logistic regression analyses will not be conducted if the following criteria is not met: minimum of 5 events per variable for logistic regression analyses (Vittinghoff & McCulloch,

2006). Instead, in the event of separation or quasi-separation, either Firth's penalised regression for rare events procedure (Firth, 1993) or Bayesian logistic regression will be conducted depending on appropriateness.

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Addendum to Statistical Analysis Plan – KGOWS incidence paper

1. 6.2 Secondary Outcomes (Page 7): In response to Reviewer comments, we also categorised cases of incident MCI (excluding baseline dementia and baseline MCI cases). Crude incidence rates were calculated and reported for incident MCI using the same method as incident cognitive decline and dementia.
2. 6.3 Additional Measures (Table 1, pages 7-8): Disability was not included in analyses for the associated paper as the incontinence and mobility items were drawn from that scale, hence it was removed prior to analysis due to overlap. However, we did report descriptive statistics for the total activities of daily living score (from which the dichotomous Disability variable was derived). This was done in response to Reviewer comments and was purely descriptive (not included in analysis).
3. 6.4 Analyses of Primary Outcome (page 9): For the final model, the Analysis Plan states "Predictors in this model with $p>.01$ will subsequently be removed; as such, only predictors with $p<.01$ will be retained in the final model." This is a typo and should read "$p<.1$". As such, variables with $p<.1$ were retained in the final model presented in the associated paper.
4. 6.4 Analyses of Primary Outcome (page 9): In response to Reviewer comments, we adjusted for follow-up time (in addition to age) for all analyses.
5. 6.5 Analyses of Secondary Outcome (page 9): Incidence rates for dementia were reported. However, logistic regression analyses were not reported in the associated paper due to the large amount of information already presented and the number of additional tests this would have required.
6. 6.6 Additional Analyses (page 9): In addition to the stated analyses, upon co-author review of the paper it was suggested that the final model (excluding *APOE*) be re-run restricted to the sample included in the final model including *APOE*. Therefore, this additional analysis was run and included in the associated paper, to enable comparisons between models with and without *APOE*, amongst the same sample.
7. 6.6 Additional Analyses (page 9): In addition to the stated analyses, a logistic regression model was run to determine the relative risk of developing dementia for baseline mild cognitive impairment/other cognitive impairment (not dementia) versus intact (excluding baseline dementia cases). This was based upon a co-author suggestion, and included to better understand cognitive trajectories from baseline to follow-up.
8. 6.6 Additional Analyses (page 9): Sensitivity analyses for cardiovascular/metabolic risk factors were not reported in the associated paper as, upon review, a more thorough investigation into these potential nuanced effects (and interactions with *APOE*) would be more appropriate. These analyses will be carried out but that level of detail is beyond the scope of the associated paper.