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## Fingernail cortisol as a marker of chronic stress exposure in Indigenous and non-Indigenous young adults

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### ABSTRACT

Cumulative exposure to stress over a long period can negatively impact an individual's health. Significant advancements in biomarkers of chronic stress have been made, with the use of fingernails recently explored. Cross sectional data from the Australian Aboriginal Birth Cohort (Indigenous) and Top End Cohort (non-Indigenous) were used to investigate the associations (sociodemographic and emotional) of fingernail cortisol in Indigenous and non-Indigenous young adults. Details on sociodemographic (age, gender, and Indigenous identification), smoking and alcohol use, emotional wellbeing, and emotional stress (perceived stress and stressful events), and fingernail samples were obtained face-to-face. Fingernail samples were analyzed for 179 Indigenous and 66 non-Indigenous participants (21–28 years). Indigenous participants were subjected to higher rates of stressful events compared to non-Indigenous (Median 6.0; interquartile range (IQR) 4, 9 vs. 1.0; IQR 0, 2;  $p < .001$ ). Median cortisol levels were similar between Indigenous and non-Indigenous participants (4.36 pg/mg; IQR 2.2, 10.0 vs. 3.87 pg/mg; IQR 2.0, 9.7;  $p = .68$ ). However, Indigenous participants had a higher cortisol level on adjustment for emotional distress and exposure to stressful events (Geometric Mean 1.82; 95CI: 1.07–3.09), with a negative association with increasing number of stressful events (Geometric Mean 0.94; 95CI 0.90, 0.99). Collection of fingernails was an easily conducted, well-tolerated method to measure stress markers in this multicultural cohort. Indigenous young adults experienced a high number of stressful events which was associated with a lowering of fingernail cortisol levels.

### LAY ABSTRACT

- Chronic stress can impact negatively on health and emotional wellbeing. A fingernail sample provided a culturally acceptable, noninvasive method of measuring chronic stress in Indigenous and non-Indigenous young adults. Cortisol levels, a marker of chronic stress, were different between Indigenous and non-Indigenous young adults and were influenced by emotional status and occurrence of multiple stressful events.

### ARTICLE HISTORY

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### KEYWORDS

Fingernail cortisol; young adults; Indigenous; stressful events; chronic stress; non-Indigenous

## Introduction

Indigenous Australians are at an increased risk of exposure to a high-stress environment, stemming from colonization, socio-economic and political marginalization, and racial discrimination (Gracey & King, 2009; Kelly, Dudgeon, Gee, & Glaskin, 2009). They often experience multiple stressful events, such as death of a family member, alcohol/drug problems or abuse/violent crime associated with an increased risk of psychological distress and lower emotional wellbeing (Blair, Zubrick, & Cox, 2005; Davison, Nagel, & Singh, 2017). Exposure to high levels of stress over a long period has been shown to have a negative influence on emotional and physical health (Miller, Chen, & Zhou, 2007; Schwarzer & Schulz, 2012). The high stress environment experienced by Indigenous Australians, a factor that might be present early and persists through life and across generations, might be an explanation for the high rates of emotional distress present in this population.

In assessing the impact stress has on emotional wellbeing, survey questionnaires and interviews are often used. However, questionnaires can be complex and are not necessarily suitable in all cultural and literacy groups. Interviews, while providing in-depth data, are time consuming. There is a substantial diversity in language and cultural groups in Australian Indigenous peoples, with more than 150 languages spoken. On average Indigenous Australians have lower education levels and high rates of illiteracy compared to non-Indigenous Australians. Aboriginal languages are traditionally oral, with no written component (Bailie, Stevens, & McDonald, 2011; Phillips, 2009; Dingwall & Cairney, 2010). Given these difficulties, a reliable objective method such as cortisol, could provide a beneficial measure of, or useful adjunct for, assessing chronic stress response.

Exposure to stress activates the hypothalamic–pituitary–adrenal (HPA) axis, inducing the release of corticotropin-releasing factor (CRF) from the hypothalamus, which binds to CRF receptors on the anterior pituitary gland, with

adrenocorticotrophic hormone (ACTH) being released. ACTH binds to receptors on the adrenal cortex stimulating the release of cortisol. While cortisol is necessary to regulate or support several physiological processes including mental functions, excess amounts over a prolonged time can be harmful to these systems (Rabkin & Struening, 1976). Correspondingly, when high levels of cumulative, ongoing stress are experienced a blunting of the HPA axis and low levels of cortisol can be seen (Susman, 2006). Therefore, cortisol levels at either end of the spectrum, high and low, may set the stage for the pathogenic process that predisposes individuals to mental illness (Miller et al., 2007).

In the past decade, hair samples have been the most commonly used measure of long-term accumulation of cortisol due to its predictable, consistent growth and ease of collection and storage (Stalder et al., 2017). However, limitations have been identified including; availability of hair, cultural acceptability, and suggestion that the mechanism is independent of central cortisol (Sharpley, Kauter, & McFarlane, 2010; Davison, Singh, & McFarlane, 2019; Sharpley, McFarlane, & Slominski, 2012). Due to the similarities in form and structure between nail and hair, the use of fingernail samples has recently been explored (De Berker, André, & Baran, 2007; Herane-Vives et al., 2018).

Nail samples have been used to provide information on long-term exposure to environmental stressors such as toxins (arsenic), and drugs (Karagas et al., 1996; Palmeri, Pichini, Pacifici, Zuccaro, & Lopez, 2000). The growth of the fingernail in adults is relatively consistent, taking an average of three months to grow from the nail matrix to become a free nail (De Berker et al., 2007; Warnock et al., 2010). Drugs are thought to be incorporated into nails by a double mechanism via the nail bed as well as at the point of nail generation (Warnock et al., 2010; De Berker et al., 2007). Although thought to be similar to drugs, little is known about the incorporation of cortisol.

Warnock et al. (2010) were one of the first to report the use of fingernail cortisol in a pilot study involving university students (Warnock et al., 2010). Although limited, current research has shown its potential as a marker of chronic stress. Elevated fingernail cortisol levels have been associated with the occurrence of stressful events (Izawa, Matsudaira, Miki, Arisaka, & Tsuchiya, 2017) and depression (Herane-Vives et al., 2018). Fingernail cortisol has been shown to reflect saliva cortisol obtained 4–5 months earlier (Früge et al., 2018; Izawa et al., 2015), with a moderate association seen with hair cortisol (Izawa et al., 2015).

Currently, there is a paucity of information available on chronic stress biomarkers in the Australian context, particularly in Indigenous Australians. Research to date has shown cortisol levels at either end of the spectrum, high and low, in response to stress. High urinary cortisol levels have been reported in remote residing Indigenous adults undergoing rapid socio-cultural change (Schmitt, Harrison, & Spargo, 1998). More recently, a blunted cortisol awakening response was seen in Indigenous students associated with increased chronic stress (Berger et al., 2017). Our previous research has shown no difference in hair cortisol levels between Indigenous and non-Indigenous young adults (Davison,

Singh, & McFarlane, 2019). However, Indigenous women who were at an increased risk of psychological distress and experiencing high levels of stress exposure had higher cortisone levels than their non-Indigenous counterparts (Davison, Singh, & McFarlane, 2019). In these Indigenous women, a curvilinear relationship between hair cortisone and the number of stressful events experienced was present (i.e. levels increased in those experiencing up to 6 events and then decreased up to 13 events) (Davison, Nagel, & Singh, 2019).

In this multi-cultural cohort, we tested the hypothesis that increased exposure to a high-stress environment, as experienced by Indigenous young adults, would be reflected in an increase in fingernail cortisol levels. The aims of this study were two fold; (i) to investigate fingernail cortisol levels in Indigenous and non-Indigenous young adults; (ii) to investigate whether the association of health indicators (substance use, emotional wellbeing, and emotional stress) with fingernail cortisol differed amongst comparable Indigenous and non-Indigenous young adults.

## Methods

### Study participants

The Life Course Program, based in Darwin, Northern Territory (NT), Australia involves two distinct but complementary cohorts; the Aboriginal Birth Cohort (ABC) and the Top End Cohort (TEC). Participants of the ABC and TEC undertake periodical, face-to-face comprehensive health assessment involving questionnaires (sociodemographic, lifestyle, emotional and dietary), anthropometry, blood and urine sampling, and ultrasounds and cardiovascular assessment. During the fourth follow-up (August 2013 and June 2015), participants were invited to take part in this study by providing a fingernail sample.

The recruitment and previous follow-up of the ABC (Sayers et al., 2009) and TEC (Davison, Cunningham, & Singh, 2011) studies have been described in detail elsewhere. In brief, between 1987 and 1990, 686 (54% of those eligible) babies born to Indigenous mothers were recruited from the Royal Darwin Hospital, the main referral hospital for the NT at the time, to the ABC study (Sayers & Powers, 1993; Sayers et al., 2009). Subsequent follow-up has occurred at the participant's residence in over 40 urban and remote communities across the NT at age 11 years (1999–2002) (Sayers, Mackerras, Halpin, & Singh, 2007) and age 18 years (2006–2008) (Sayers et al., 2009). Between 2007 and 2009, 196 non-Indigenous adolescents were recruited to form the TEC, so named due to the recruitment geographical area being locally known as the "Top End" (Davison, Cunningham, & Singh, 2011). Adolescents born in Darwin between 1987 and 1991, age-matched to the ABC study, were invited to participate. The invitation to participate was widely disseminated including schools (public and private), sporting clubs, youth services, media platforms, and snowball sampling.

### **Ethics approval**

This study was approved by the Human Research Ethics Committee of NT, Department of Health and Menzies School of Health Research, including the Aboriginal Ethical Subcommittee which has the power of veto (ABC Reference no. 2013-2022 and TEC Reference no. 2013-1986). All research was performed in accordance with the National Health and Medical Research Council guidelines (National Statement on Ethical Conduct in Human Research, 2007). Informed written consent was obtained from all participants.

### **Cohort demographics**

Participants of the ABC and TEC reside in over 40 urban and remote communities across an area covering approximately 400,000 km<sup>2</sup> of the “Top End” of the NT. Three-quarters (76%) of ABC participants reside in remote communities which vary in population size from 200 to 2200 people, with many small family groups living in outstations (<50 people). Given the remoteness of these locations, lack of traditional communication methods and the cost and logistics involved in accessing these areas, it was not feasible to contact participants prior to the time of assessment (Sayers, Mackerras, & Singh, 2017; Lawrance, Sayers, & Singh, 2014).

### **Fingernail sample**

Samples were obtained if the following criteria were met: willingness to provide sample, sufficient nail growth in at least one finger, sample weight >1 mg and nail polish was not currently present or had not recently been used. Fingernail samples were clipped directly into a plastic zipped bag, thereby avoiding losing any parts of the sample. Fingernail clippings were stored in the plastic bag in a cool room until processing (approx. 40 months).

### **Sample analysis**

Fingernail samples were prepared similar to previously described for hair with some modification (Sharpley, Kauter, & McFarlane, 2009). Briefly, the fingernails were washed with 1 ml of methanol, agitated for 5 min, decanted and allowed to dry prior to being cut into small pieces <1 mm<sup>2</sup>, weighed (median and range) and then placed into a glass vial and extracted for 24 h with 1.5 ml methanol on a platform shaker. The methanol was decanted into 1.5 ml microfuge tubes and the methanol evaporated under vacuum. The samples were extracted twice more and the methanol decanted into the same microfuge tube each time and evaporated under vacuum. Further extractions beyond 3 gave no increase in hormone concentrations. Finally, the samples were dissolved in 50 ul of 50% methanol:water and then centrifuged before transfer into autosampler vials in duplicate.

Samples were analyzed in duplicate by liquid chromatography–mass spectrometry using the method of Ionita et al. (2009) with minor modifications as follows (Ionita, Fast, and Akhlaghi, 2009). Briefly, a Shimadzu UPLC and 8050 triple quadrupole mass spectrometer equipped with a heated electrospray ionization source (HESI) operating in positive ion

mode were used. The samples (10 ul) were separated using a Kinetex 2.6 u Evo C18 column (2.1 × 50 mm 2 u particle size; Phenomenex, Lane Cove, NSW, Australia). Samples were eluted with a gradient from 10% to 100% methanol with 0.2 mM ammonium fluoride over 6 min. Cortisol eluted with a retention time of 2.5 min, and quantitative analysis was performed in multiple reaction monitoring mode (MRM) of the most abundant product ions ( $m/z$  363.2 > 121.2 & 309.3). The calibration curve demonstrated a linear relationship ( $r^2 > 0.995$ ) between the 25 ug/ml and 40 pg/ml with detection limits of cortisol <0.4 pg. The inter and intra assay coefficients of variation were determined to be 4.7%.

### **Sociodemographic, substance use and medical history**

Questionnaires either self-completed or researcher assisted, were used to provide information on: sociodemographic factors including gender, age, marital status (married/defaulto relationship or single), children and employment (in regular employment or not); substance use measures including alcohol consumption (consumes alcohol ≥ once a week) and smoking behavior (current smoker or non-smoker). Health records were checked for diagnosis of mental illness (depression, anxiety, and schizophrenia).

### **Emotional markers**

Details on emotional status were obtained by a specifically designed, pictorial computerized questionnaire using the following questionnaires (Davison et al., 2017). Each questionnaire enquired about the previous 4 weeks, with the questions using a 5-point Likert scale.

Psychological distress was assessed by the Kessler-5, which has been used with Indigenous and non-Indigenous Australians in state-wide and national surveys (Australian Bureau of Statistics [ABS], 2013; McNamara et al., 2014). This questionnaire asked how often participants felt; “nervous? without hope? restless or jumpy? everything was an effort? and so sad that nothing could cheer them up?” Individual question scores were added together to create a continuous variable.

Positive wellbeing was assessed by the Short Warwick-Edinburgh Mental Well-being Scale (Bartram, Sinclair, & Baldwin, 2013). Although there is a scarcity of research from Australia, this scale has been used widely in the United Kingdom and Scotland in teenagers and young adults (Clarke et al., 2011). This questionnaire asked how often participants felt; “happy about the future? Useful? Relaxed? dealt with problems well? thought clearly? close to other people? and been able to make up their own mind?” Individual question scores were combined to create a continuous variable as per previously used criteria (Bartram et al., 2013).

### **Stress markers**

Subjective stress was assessed by the Short Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983), which has been previously used in Australian Indigenous and non-Indigenous adults (Wiggers et al., 2001). This questionnaire enquired

about the previous 4 weeks using a 5-point Likert scale and asked how often participants felt they were: “able to control the important things in their life? handle personal problems? that things were going their way? and that difficulties were piling up so high that they could not overcome them?” Individual question scores were combined to create a continuous variable.

The occurrence of stressful events (yes/no) in the past 6 months were adapted from the Negative Life Events Scale (Kowal, Gunthorpe, & Bailie, 2007) and included: “a close family member has been in an accident; has been in hospital; has been arrested; is in prison; has an alcohol problem; has a drug problem; needs their care most days; has passed away; they didn’t have enough money to buy food or pay bills; them or someone in the house gambles a lot and it gives them money problems; they felt their house doesn’t have enough space for all the people who live there; they were scared by other peoples’ behavior; and physically hurt by someone.”

### Statistical analysis

All statistical analysis was performed in Stata 15.1 (StataCorp, College Station, TX, USA). Representativeness of the participants providing an adequate fingernail sample compared to those of the available Indigenous and non-Indigenous participants was assessed by Wilcoxon rank-sum test. Categorical demographic data was examined by Indigenous status and gender through Pearson Chi-square tests, with continuous emotional and stress variables through Wilcoxon rank-sum.

Fingernail cortisol data were log transformed to correct skewness. For descriptive purposes, medians and interquartile range (IQR) in original units (pg/mg) are presented. Association with fingernail cortisol was assessed through linear regression and multivariable linear regression with adjustment for confounding factors. Age, gender, and Indigenous status were considered as fixed confounders to be adjusted in the multivariable analysis. Other risk factors (categorical; relationship, employment status, smoking status, alcohol consumption per week and continuous; psychological distress, positive wellbeing, perceived stress and stressful events) for fingernail cortisol were included as covariates in the adjusted analysis if they were statistically significant at  $p = .2$  in the univariate analysis. The results of the regression analysis are reported as regression coefficients of the log-transformed fingernail cortisol variable, the geometric mean, their 95% confidence limits (95%CI) and  $p$  value. The significance level was set at  $p < .05$ .

## Results

### Fingernail samples

Of the 576 young adults (aged 21–28 years) available for assessment 73% ( $n = 418$ ) consented to provide a fingernail sample, similar in non-Indigenous and Indigenous participants (79% vs. 71%) (see Figure 1). No difference in consent rates was seen between men and women in either group (Indigenous men 75% and women 67% and non-Indigenous

men 84% and women 77%). Of those who consented, an adequate sample ( $\geq 1$  mg) was obtained from 61% ( $n = 257$ ). Rates were higher in non-Indigenous young adults compared to Indigenous young adults (72% vs. 59%;  $p = .018$ ). Similar rates of obtainment were seen between men and women in both groups (Indigenous men 56% and women 61% and non-Indigenous men 78% and women 68%). For men and women in both groups, the inability to provide a sample was largely due to having no free nail available or use of nail polish.

Fingernail cortisol levels were available on 190 Indigenous and 67 non-Indigenous young adults. Two people (one Indigenous woman and one non-Indigenous man) were excluded from analysis due to extreme cortisol levels ( $> 250$  pg/mg), with a further 9 Indigenous participants (5 men and 4 women) excluded due to preexisting mental illness, resulting in 245 participants (179 Indigenous and 66 non-Indigenous) available for analysis (see Figure 1).

### Cohort sociodemographic

After stratifying by Indigenous identification, no difference in sex, sociodemographic, substance use or emotional markers were seen between those who provided a sample and the cohort as a whole (data not shown). Significant differences in sociodemographic and substance use were seen between Indigenous and non-Indigenous participants (see Table 1). Indigenous participants were more likely to have children and had lower rates of employment compared to their non-Indigenous counterparts. They were significantly more likely to smoke, but less likely to regularly consume alcohol.

Indigenous young adults reported a higher number of stressful events than their non-Indigenous counterparts. Rates of individual stressful events were higher in Indigenous participants, with 30–70% of young adults reporting the occurrence of each event compared to  $\leq 15\%$  of non-Indigenous for the majority. Rates for each stressful events for Indigenous vs. non-Indigenous participants were as follows: Family member in an accident (43% vs. 13%); Family member in hospital (62% vs. 39%); Family member arrested (49% vs. 5%); Family member in prison (52% vs. 0%); Family member has alcohol problem (56% vs. 16%); Family member has drug problem; (50% vs. 7%); Family member needs their care most days (47% vs. 5%); Family member has passed away (72% vs. 10%); No money to buy food or pay bills (42% vs. 7%); Them or family member has a gambling problem (31% vs. 2%); House is overcrowded (39% vs. 12%); They were scared by other peoples’ behavior; (34% vs. 5%); They were physically hurt by someone (20% vs. 0%).

No differences in psychological distress or perceived stress levels were seen between Indigenous and non-Indigenous young adults. However, Indigenous young adults reported higher rates of positive wellbeing. See Table 1 for details. Women had higher median psychological distress and lower positive wellbeing levels compared to men, but no difference in perceived stress level or rates of stressful events was seen (see Table 2 for details). No difference in emotional markers was seen between non-Indigenous women and men.

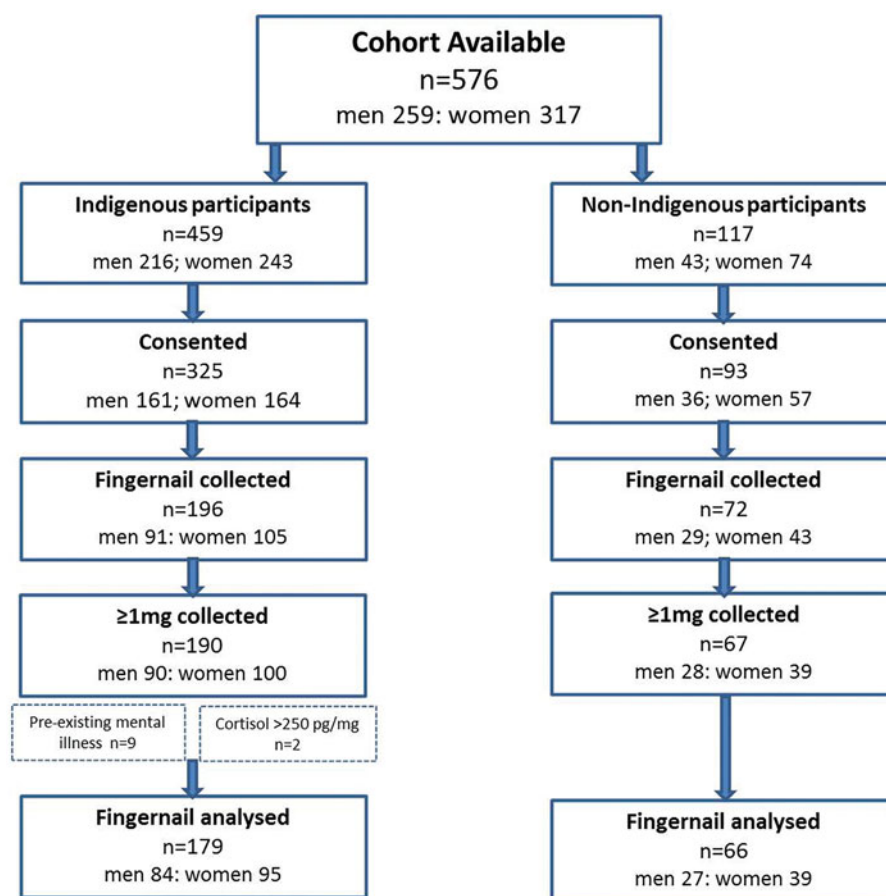


Figure 1. Flowchart of fingernail sample availability for Indigenous and non-Indigenous young adults.

Table 1. Demographics, emotional status and fingernail cortisol levels for Indigenous and non-Indigenous young adults.

	Indigenous young adults n = 179	Non-indigenous young adults n = 66	p-value
Age (years)	25.3 (23–28)	23.6 (21–27)	<.001
% Men	47% (84)	41% (27)	.40
Employed	29% (51)	90% (59)	<.001
Married or defacto	61% (109)	49% (32)	.07
Children	69% (117)	6% (4)	<.001
Current smoker <sup>#</sup>	70% (110)	16% (10)	<.001
Alcohol ≥ weekly <sup>#</sup>	34% (56)	63% (39)	<.001
<b>Emotional markers</b>			
Psychological distress <sup>†</sup>	10.0 (7, 13)	10.0 (8, 13)	.14
Positive wellbeing <sup>†</sup>	25.0 (22, 28)	23.2 (21, 25)	.007
Perceived stress <sup>†</sup>	4.0 (3, 6)	4.0 (3, 6)	.99
Stressful events <sup>‡</sup>	6.0 (4, 9)	1.0 (0, 2)	<.001
<b>Fingernail analysis</b>			
Nail weight (mg)	6.3 (3.6, 9.5)	3.4 (2.5, 5.4)	.004
Cortisol (pg/mg)	4.36 (2.2, 10.1)	3.87 (2.0, 9.7)	.68

Median (interquartile range) presented for continuous variables and percentage (number) for categorical; p values presented from Pearson Chi-square test for categorical and Wilcoxon rank-sum regression for continuous; <sup>#</sup>Available numbers: Indigenous 157 & non-Indigenous 61; <sup>†</sup>Available numbers: Indigenous 159 & non-Indigenous 64; <sup>‡</sup>Available numbers: Indigenous 133 & non-Indigenous 61.

### Fingernail cortisol

Median cortisol levels for the whole cohort was 4.20 pg/mg (IQR 2.1, 9.9), with no difference seen between Indigenous and non-Indigenous young adults (4.36 pg/mg; IQR 2.2, 10.1 vs. 3.87 pg/mg; IQR 2.0, 9.7). Despite a numerical increase in median cortisol levels for women compared to men (4.80 pg/mg; IQR 2.4, 11.0 vs. 3.53 pg/mg; IQR 1.7, 9.2), this was not significant ( $p = .13$ ) (see Tables 1 and 2).

### Association with substance use and emotional stress

Table 3 shows the results of regression analysis. There was little evidence of independent association between sociodemographic or substance use and cortisol levels following the univariate analysis. Similarly, little evidence of association was evident with cortisol level and psychological distress or perceived stress as a cohort or when stratified by Indigenous identification or sex. However, stressful events showed

evidence of strong association with fingernail cortisol in the cohort: a 6% decrease in average (geometric) cortisol level was associated with a unit increase in number of stressful events ( $GM = 0.94$ ; 95% CI: 0.90–0.99;  $p = .016$ ).

Multivariable regression adjusting for sex, age, Indigenous status, and factors associated with fingernail cortisol at 20% following a univariate analysis, showed strong evidence of association with fingernail cortisol by Indigenous status ( $GM = 1.82$ ; 95% CI: 1.07–3.09,  $p = .027$ ) and number of stressful events ( $GM = 0.90$ ; 95%CI: 0.85–0.96;  $p = 0.001$ ). An 82% increase in average (geometric) cortisol level was seen in Indigenous young adults compared to non-Indigenous. A negative association was present, with a 10% decrease in average (geometric) cortisol level associated with a unit increase in number of stressful events.

**Table 2.** Demographics, emotional status and fingernail cortisol levels for men and women.

	Men <i>n</i> = 111	Women <i>n</i> = 134	<i>p</i> -value
Age (years)	25.1 (22–28)	24.6 (21–28)	.05
% Indigenous	76% (84)	71% (95)	.40
Employed	52% (58)	39% (52)	.035
Married or defacto	59% (65)	57% (76)	.77
Children	46% (51)	52% (70)	.034
Current smoker <sup>#</sup>	65% (64)	47% (56)	.009
Alcohol $\geq$ weekly <sup>#</sup>	58% (59)	29% (36)	<.001
<b>Emotional markers</b>			
Psychological distress <sup>†</sup>	9.0 (7, 11)	11.0 (8, 24)	<.001
Positive wellbeing <sup>†</sup>	25.0 (22, 27)	23.2 (21, 27)	.033
Perceived stress <sup>†</sup>	4.0 (3, 6)	4.5 (3, 6)	.36
Stressful events <sup>‡</sup>	4.0 (1, 7)	4.0 (1, 8)	.88
<b>Fingernail analysis</b>			
Nail weight (mg)	6.5 (3.6, 11.3)	4.2 (2.7, 7.1)	.004
Cortisol (pg/mg)	3.53 (1.7, 9.2)	4.80 (2.4, 11.0)	0.13

Median (interquartile range) presented for continuous variables and percentage (number) for categorical: *p* values presented from Pearson Chi-square test for categorical and Wilcoxon rank-sum regression for continuous;

<sup>#</sup>Available numbers: Men 95 & women 130; <sup>†</sup>Available numbers: Men 99 & women 124; <sup>‡</sup>Available numbers: Men 90 & women 104.

This association between stressful events and fingernail cortisol levels differed between the Indigenous and non-Indigenous young adults. The association in non-Indigenous young adults was not strong ( $GM = 1.01$ ; 95% CI: 0.79–1.28;  $p = .94$ ). However, Indigenous young adults showed a stronger negative association with cortisol level ( $GM = 0.89$ ; 95% CI: 0.84–0.95;  $p = .001$ ) suggesting 11% decrease in geometric mean of cortisol level with a unit increase in stressful events. Stronger evidence of negative association between cortisol level and stressful events was seen in women ( $GM = 0.88$ , 95% CI: 0.811–0.96,  $p = .003$ ) compared to men when the cohort was stratified by sex. In women, there was a significant association between increasing fingernail cortisol levels and increasing levels of psychological distress ( $GM = 1.07$ ; 95%CI: 1.01–1.14,  $p = .02$ ), which was not present in men ( $GM = 0.98$ ; 95% CI: 0.91–1.06,  $p = .62$ ) (see Figure 2).

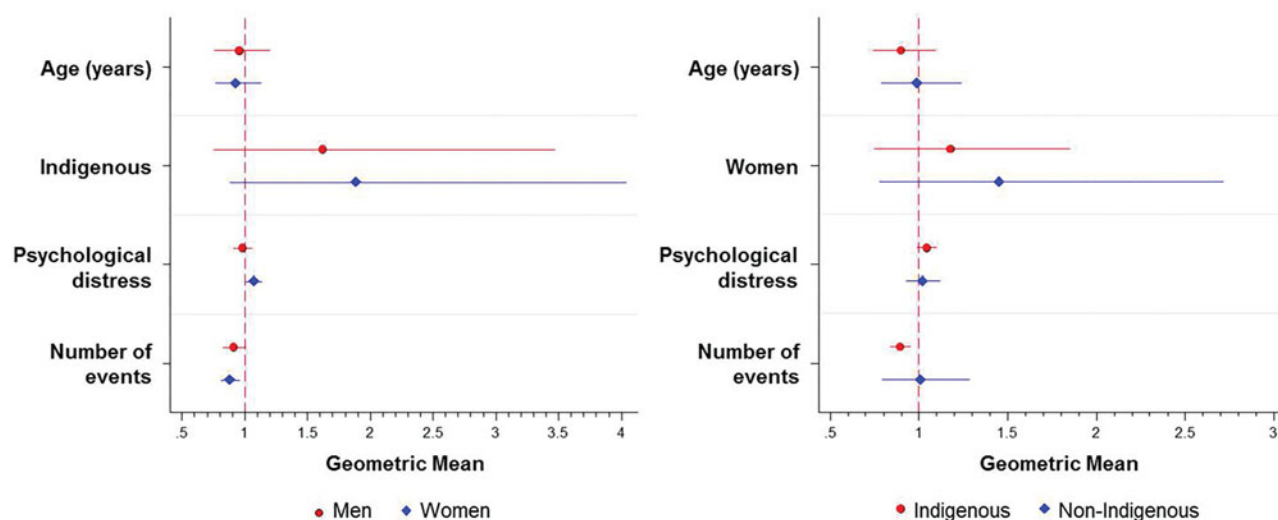
## Discussion

In this study, we were able to assess the potential of fingernail samples as a marker of long-term cortisol concentration in a multi-cultural cohort at increased risk of stressful events and psychological distress. In this large health assessment, a simple, not time dependent method was required to assess stress levels. In this cohort, where cultural considerations and varying literacy levels exist, survey questionnaires can be complex and not necessarily reliable. Collection of fingernail samples provided a noninvasive, easy to collect and store method, acceptable in both Indigenous and non-Indigenous young adults. Similar to other elements, minimal sample was required for the detection of cortisol in fingernails (He, 2011).

In this cohort, similar to other Australian Indigenous cohorts (Blair et al., 2005), significantly higher numbers of stressful events were reported in Indigenous young adults compared to non-Indigenous (6 vs. 1) (Davison, Nagel, & Singh, 2017). Despite these significant differences in stress exposure,

**Table 3.** Fingernail cortisol concentrations associations with sociodemographic and emotional status.

	<i>n</i>	Univariate regression			Multivariable regression		
		Log-coefficient (95% CI)	Geometric mean (95% CI)	<i>p</i> Value	Log-coefficient (95% CI)	Geometric mean (95% CI)	<i>p</i> Value
Age (years)	245	−0.02 (−0.12, 0.09)	0.98 (0.88, 1.09)	.73	−0.06 (−0.20, 0.09)	0.94 (0.82, 1.09)	.44
<b>Sex</b>							
Men	111	(Reference group)	–	–	–	–	–
Women	134	0.24 (−0.06, 0.54)	1.27 (0.94, 1.72)	.12	0.23 (−0.12, 0.59)	1.26 (0.88, 1.80)	.20
<b>Indigenous status</b>							
Non-Indigenous	66	(Reference group)	–	–	–	–	–
Indigenous	179	−0.03 (−0.37, 0.31)	0.97 (0.69, 1.36)	.87	0.60 (0.07, 1.13)	1.82 (1.07, 3.09)	.027
<b>Relationship status</b>							
Single	103	(Reference group)	–	–	–	–	–
Married	141	0.06 (−0.25, 0.37)	1.06 (0.78, 1.44)	.70	–	–	–
<b>Employment status</b>							
Unemployed	110	(Reference group)	–	–	–	–	–
Employed	134	0.08 (−0.22, 0.39)	1.09 (0.80, 1.47)	.59	–	–	–
<b>Tobacco use</b>							
Non-smoker	98	(Reference group)	–	–	–	–	–
Smoker	120	−0.15 (−0.47, 0.17)	0.86 (0.62, 1.19)	.36	–	–	–
<b>Alcohol use</b>							
No alcohol	130	(Reference group)	–	–	–	–	–
Alcohol use	95	−0.11 (−0.43, 0.22)	0.90 (0.65, 1.24)	.52	–	–	–
<b>Emotional and stress markers</b>							
Psychological distress	223	0.03 (−0.01, 0.07)	1.03 (0.99, 1.07)	.18	0.03 (−0.0, 0.08)	1.03 (0.99, 1.08)	.14
Perceived stress	223	0.01 (−0.05, 0.06)	1.01 (0.95, 1.07)	.78	–	–	–
Emotional wellbeing	222	−0.01 (−0.05, 0.02)	0.99 (0.95, 1.02)	.50	–	–	–
Stressful events	194	−0.06 (−0.11, −0.01)	0.94 (0.90, 0.99)	.016	−0.10 (−0.1, −0.04)	0.90 (0.85, 0.96)	.001



**Figure 2.** Association of fingernail cortisol, events and physiological distress by sex and Indigenous status.

univariate analysis showed no difference in fingernail cortisol levels between Indigenous and non-Indigenous young adults. However, when age, sex, psychological distress level, and exposure to stressful events were adjusted for, a significant increase in cortisol levels was evident in Indigenous young adults. The increased exposure of Indigenous Australians to a high-stress environment, possibly from a young age, is well documented. Indigenous Australians are often exposed to high rates of unemployment, social change, and cultural conflict (Hunter & Milroy, 2006). This study highlights the effect of this exposure to high levels of stress in Indigenous Australians, particularly Indigenous women, on the HPA axis and cortisol release is likely to be complex and warrants further research.

A discordance in the association of cortisol to increasing number of stressful events was seen between Indigenous and non-Indigenous young adults. A negative association was evident between cortisol level and increasing number of stressful events in Indigenous young adults, particularly Indigenous women. This result is not unexpected and has been reported in other high-stress cohorts (Bourne, Rose, & Mason, 1968; Wolff, Friedman, Hofer, & Mason, 1964; Yehuda et al., 1995; Yehuda et al., 2000; Faresjo et al., 2013). In response to acute stress, the HPA axis normal response is one of hyperactivity and increased glucocorticoid release. However, if the stress exposure is cumulative, or over a long period, and the person is unable to cope with this exposure, a state of exhaustion is reached and the system turns to hypoactive functioning.

Early research measuring cortisol levels indicated that chronic stress (e.g. being a soldier in combat or having a child with cancer) was associated with reduced daily output of cortisol (Bourne et al., 1968; Wolff et al., 1964). Yehuda et al. (1995) examined the influence of chronic stress across generations, showing a decrease in urine cortisol levels in Holocaust survivors (Yehuda et al., 1995) and their children in adulthood (Yehuda et al., 2000). More recently, lower levels of hair cortisol were reported in young Greek adults living in an environment with increased level of economic and social pressure (Faresjo et al., 2013).

In this cohort, we have previously reported a decrease in hair cortisone in Indigenous women experiencing a high level of stressful events (6 or more) (Davison et al., 2019). The findings in this cohort, differ from the limited research currently available on fingernail cortisol, where elevated cortisol levels were associated with the occurrence of 1 or more stressful events (Izawa et al., 2017). This discordance in findings, high and low levels of cortisol, in response to stress may, in part, be reflective of the level of stress exposure. The high number of stressful events experienced in Indigenous Australians (mean 6.0 in this cohort) and the negative association on cortisol levels in Indigenous young adults may reflect the ongoing nature of the high-stress environment and its effect on HPA axis and cortisol response.

Another possible explanation of the lower cortisol levels in Indigenous participants exposed to an increased number of stressful events, may be due to an adaptive change and associated with increased resilience in response to chronic (even possibly transgenerational) stress. Despite the high rates of stressful events, higher levels of emotional wellbeing were evident in Indigenous young adults. In this cohort majority (70%) resided in remote communities where a strong connection to culture, family, and country is present (Burgess, Johnston, Bowman, & Whitehead, 2005). The benefit of living on, and caring for, country has been shown to decrease the risk of psychological distress and an improvement in social, cultural, and behavioral pathways (Burgess et al., 2009).

The lack of strong evidence of relationships between fingernail cortisol and self-reported stress and psychological distress is consistent with other markers of chronic stress, such as hair cortisol studies that reported null findings (Dettenborn, Tietze, Bruckner, & Kirschbaum, 2010; Dowlati et al., 2010). This may indicate that there is no relationship; however methodological explanations need to be considered. One consideration is the differences in time frames covered. Fingernails take on average 3 months to reach a free nail, whereas the questionnaires used enquired about the past month. This insufficient indication of association may mean that fingernails are reflective of the experience of stress over a longer period as opposed to the current stress reported by questionnaires. However, it is



worth noting the exact mechanism for incorporation of cortisol in fingernail is not yet clearly understood.

There are technical limitations warranting acknowledgment. As this was a one-off, often impromptu, face-to-face assessment participants could not be asked to trim nails 3 months prior and then allow them to grow. This resulted in an inability to obtain an adequate sample, or minimal sample, from some participants. We collected any free nail, irrespective of digit and did not record which digit was used. No differences in the rate of fingernail growth between the right and left hands or between men and women, has been reported (Herane-Vives et al., 2018; Higashi et al., 2016). However, a small study of young adults showed little fingernails grew slower than other fingernails (Yaemsiri, Hou, Slining, & He, 2010). Although the differences in fingers used could impact on cortisol levels, the impact is likely to be minimal but warrants further research.

Due to no available information prior to commencing collection in 2013, those who currently, or had recently, used nail polish were excluded. Izawa et al. (2015) showed no effect of polish, however, the numbers were small and further exploration is required (Izawa et al., 2015). No information on hand products, cortisone based or other, was collected as part of this study. However, their impact on cortisol levels in fingernails needs to be fully explored.

## Conclusion

This study provides valuable information on the use of fingernail cortisol as a marker of chronic stress, building on the current paucity of information available. In this multi-cultural cohort at an increased risk of stressful events, the high consent numbers demonstrate the cultural acceptability of this simple, noninvasive method. The associations present with fingernail cortisol levels in Indigenous young adults exposed to an increased number of stressful events show the potential of this noninvasive method in chronic stress research.

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All authors declare they have no conflict of interest.

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## Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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