Feasibility of biomarkers to measure stress, burnout and fatigue in emergency nurses: a cross-sectional study

Lucinda M Mithen, Natasha Weaver, Frederick R Walker, Kerry J Inder

ABSTRACT

Introduction Retaining nurses in the workforce is an urgent concern in healthcare. Emergency nurses report high levels of stress and burnout, however, there is no gold standard of how to measure these responses. This study aims to measure stress, burnout, and fatigue in emergency nurses using biomarkers and psychometric instruments. Biomarkers will be used to better understand nurses’ levels of stress and burnout and to assess the feasibility of using biomarkers as a viable stress measurement tool in a real-world setting.

Methods and analysis A two stage cross-sectional design to measure stress, burnout and fatigue in emergency nurses while they work is proposed. All registered and enrolled nurses working in the emergency department from four hospitals in Australia will be invited to participate. Validated psychometric tools will be used in stage 1 to measure depression, anxiety, acute stress, chronic stress, burnout and fatigue. Biomarkers comprising hair cortisol, saliva alpha amylase and heart rate variability will be collected as an objective measure of stress and burnout in stage 2 over one working shift per participant. Written consent will be sought for stage 2 where nurses will provide one hair sample, wear a heart rate sensor and be asked to collect their saliva at three different time points of one shift. Data analysis will measure the domains of acute stress, chronic stress and burnout and explore relationships and correlation between psychometric measures and biomarkers.

Ethics and dissemination Ethics approval obtained from the Human Research Ethics Committee of the Hunter New England Local Health District (approval number: HREC/2020/ETH01684) and University of Newcastle HREC (H-2022-0169). Results will be reported in peer-reviewed publications using the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Public dissemination will occur by presenting at conferences and to the participating local health district.

BACKGROUND

Reducing stress in nurses is an urgent issue that needs to be addressed if organisations want to improve retention rates and wellbeing in the nursing workforce. Occupational stress is a contributor to nurse attrition and is prevalent in emergency nurses globally. In Australia, SafeWork New South Wales (NSW) describes occupational stress as ‘the physical, mental, and emotional reactions of workers who perceive that their work demands exceed their abilities and/or their resources (such as time, help/support) to do the work’. Stress is linked to poor health of nurses, has implications for patient safety and is positively correlated with nurses’ intention to leave the profession.

Workforce shortages are currently being felt in emergency departments across Australia causing nurses to work overtime or extra shifts to meet roster shortfalls. Nurses who work unusual or prolonged hours are at higher risk of developing occupational stress, burnout and fatigue. Emergency department nurses face significant time-pressure demands, physical demands in an unpredictable and chaotic environment, dealing with traumatic situations and occupational violence or threats. These known workplace stressors have...
the demands put on them and the resources available to meet those demands. Chronic stress can cause wear and tear in the worker that may lead to burnout. Burnout may be the end result of persistent high chronic stress levels and may cause feelings of cynicism, emotional exhaustion and poor personal accomplishment at work. Maslach’s theory describes burnout as a state that workers experience when there is a mismatch between the worker and one or more of six factors: workload, control, reward, community, fairness or values. These factors have been identified as contributors to developing burnout in workers and their relationship can be explored using the Areas of Worklife Survey (AWS) developed by Leiter and Maslach. The relationship between burnout and fatigue has been explored with correlations demonstrated among healthcare workers. Fatigue is another complex phenomenon to define but should include emotional and physical fatigue as opposed to the term compassion fatigue which is a separate issue.

Objective measures of burnout can enhance the strength of studies that aim to measure burnout in healthcare workers. The biomarker cortisol has been used to measure chronic stress and burnout and is a hormone released during HPA axis activation. Measuring hair cortisol (hCort) has been correlated with several chronic conditions including chronic stress, depression, anxiety and burnout. Hair grows at approximately 1 cm per month and each centimetre close to the scalp has good cortisol production markers enabling segmental hair analysis to investigate retrospective levels of cortisol over monthly periods per centimetre of hair.

For emergency nurses, eustress has aided in responding to sudden increases in intensity of work demands but it is a fragile balance that can easily tip over to maladaptive responses to the work environment. Reducing stress and burnout and providing stress management techniques for nurses is critical in light of nurses expressing intention to leave the profession. Systematic reviews of intervention studies that aim to reduce stress and improve nurse retention rates have found little evidence of effectiveness long term. Interventional studies demonstrate considerable heterogeneity in study design, types of intervention and approaches to stress measurement that have not included the acute stress response.

Theories of occupational stress have used the flight or flight response that was first described by Cannon in 1915. Theorists have expanded on this idea of stress to acknowledge that the stress response is a dynamic, individual, hard to measure human reaction to their environment. This study will add to our understanding of the stress response in nurses by using new approaches to measuring stress in healthcare workers. SafeWork NSW includes both psychological and physical reactions to a stressor and recognises that organisational factors can contribute to a worker’s stress responses. This cross-sectional investigation of emergency nurses

Recent developments in biomarker use to measure stress have provided a promising new approach to defining, measuring and recording acute stress. The fight/flight/freeze response to a threat/challenge occurs predominantly in the autonomic nervous system (ANS) and the hypothalamus-pituitary-adrenal (HPA) axis where several biomarkers are released or altered to meet the challenge of a stressor. In saliva, an enzyme called alpha amylase (sAA) is released by the parotid gland during ANS activation and is highly sensitive to stress-related situations and is suitable for measuring acute stress. Several studies confirmed that sAA reaches its peak immediately following a stressful event and reduces back to base levels within 30 minutes.

Heart rate variability (HRV) has been used in research to measure the negative health effects of shift work, the benefits of aromatherapy and the efficacy of using photoplethysmography compared with electrocardiography in nursing populations. The fluctuating heart rate of a normally regulated person will show high HRV when responding to a stressful event. For people who have been exposed to childhood trauma, chronic stress and/or disease, HRV may be low and dysregulated indicating an impaired ANS response to stressors. The gap in the literature found that HRV has not been used to measure stress in emergency nurses previously due to technological and infection control limitations. New wearable technology has provided an opportunity to measure acute stress in emergency nurses and explore if HRV is correlated with sAA and perceived stress.

Chronic stress occurs when there is a persistent imbalance within the worker’s personal traits, the occupational demands put on them and the resources available to meet...
will use psychometric tools that have been validated among a nursing population to measure psychological and emotional perceptions of their stress. The use of biomarkers will provide physiological measurements of stress in a real-time occupational setting as nurses react to job demands.

Aims and research questions
The primary aim is to measure acute stress, chronic stress, burnout and fatigue in emergency room nurses while they are working. The secondary aim is to assess the feasibility of using biomarkers to measure stress and burnout for future studies. The aims are based on two research questions.

Research question 1
What are the levels of acute stress, chronic stress, burnout and fatigue of nurses working in emergency departments in public hospitals in NSW?

Research question 2
How feasible is it to use biomarkers to measure stress and burnout with validated psychometric instruments while nurses are working?

METHODS AND ANALYSIS
Study design
This study uses a two-stage cross-sectional design. Stage 1 will consist of a survey of validated psychometric instruments. Stage 2 will involve collection of biomarker data from a subsample of stage 1 participants.

Study setting
The study is set in a regional health district in the state of NSW, Australia which serves a population of over 930,000 people across 131,785 km², with 38 hospitals and multipurpose public facilities. This study will recruit nurses working in emergency departments from four hospitals within the district. These four hospitals were chosen as part of this study to assess how feasible it will be to collect biomarkers across a large land area in the time period with the limited funding available.

Hospital 1 (H1) is a Level 1 Trauma Centre and is one of the busiest hospitals in the state. H1 is a major referral hospital with 650 beds providing retrieval services for critically ill and injured patients from several regional areas of NSW. H1 services over 900,000 people with all surgical, medical, obstetric and mental health specialties provided and had 80,774 presentations to its emergency department in 2020–2021.

Hospital 2 (H2) is a regional hospital and the main rural referral hospital with 339 beds. H2 services a population of approximately 85,000 providing maternity, medical, surgical, high dependency, intensive care, mental healthcare, palliative and rehabilitation services with 45,512 emergency department presentations for the 2020–2021 period.

Hospital 3 (H3) is a small rural hospital with 63 beds serving a population of approximately 60,000 and contains a small theatre and surgical, medical, rehabilitation and palliative services, a high dependency unit and emergency department with 16,141 emergency department presentations for the 2020–2021 period.

Hospital 4 (H4) is a rural hospital with 80 beds, including a rehabilitation referral facility and emergency department serving a population of approximately 6,000. The emergency department presentations for 2020–2021 were 1,028.

Sampling and recruitment
Convenience sampling will be used for this observational study due to time constraints, funding limitations and scope of the study. The secondary aim involves assessing the feasibility of using biomarkers to measure stress and burnout for a full-scale future study. The total pool of nurses was provided by the nurse manager from each hospital when requested by the research team. The sampling frame comprises a total of 333 casual, full time and part time registered nurses (RNs) and enrolled nurses (ENs) at the four participating hospitals and is shown in table 1.

Recruitment at each hospital site will start with a briefing of nursing staff by the author LMM, followed by an email of the information statement and providing online access to the 111-item survey in stage 1. The participant briefing will explain the aims of the study and biomarker collection processes, demonstrate access to the survey and the creation of a unique participant code. The briefing will also provide an opportunity to answer questions. The predicted data collection period will be from 1 November 2022 to 31 July 2023.

Eligibility criteria
The inclusion criteria are RNs and ENs who work full time, part time or as casual staff for the emergency department of any of the four hospitals. Exclusion criteria for participants with alopecia will exclude them from the hCort measurement of this study only. Participants with existing chronic conditions will be adjusted for in the statistical analysis.

Ethics
Ethical approval has been obtained from the Hunter New England Human Research Ethics Committee (approval

<table>
<thead>
<tr>
<th>Study recruitment</th>
<th>Hospital site</th>
<th>Total pool nurses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital 1</td>
<td>212</td>
<td></td>
</tr>
<tr>
<td>Hospital 2</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Hospital 3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Hospital 4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>353</td>
<td></td>
</tr>
</tbody>
</table>

Table 1  Participant recruitment strategy

Hospital site Total pool nurses
number: HREC/2020/ETH01684) and the University of Newcastle Human Research Ethics Committee (H-2022-0169) and the study design aligns with the ethical principles of the Declaration of Helsinki and will be observed through every stage of the study. The participants will be given 2 weeks to consider their participation in the study to avoid potential coercion and no incentives will be offered to join the study. Stage 1 requires participants to access the survey by clicking a web link or scanning a QR code which sends them to the eligibility question then the participant information statement that explains the aims, procedures and rights of the participants who join the study. Once participants have reviewed the participant information statement they click ‘to the survey’ to continue to the first question of the survey. For participants who complete the hardcopy or online survey, consent is implied when they return the survey. Participants will remain anonymous in this stage as no identifying details are required.

Written informed consent will be necessary for stage 2 and participants will provide a 10-item numeric code known only to the participants and research team. The written consent form will record the participant’s name, email address and their 10-item code. This will enable the researchers to contact participants to organise biomarker collection and to match the participants survey results to their biomarker data. Reporting using aggregate data and pooled results will ensure that no individual participant is recognisable in the reporting of the results.

**Data collection procedure**

The stage 1 survey contains items on demographics, occupational details and four validated psychometric tools to measure depression, anxiety, stress, burnout and fatigue. Participants will be given a minimum of 2 weeks to complete the stage 1 survey, which will be available in hard copy or accessed online via a REDCap (Research Electronic Data Capture) database hosted at the Hunter Medical Research Institute. REDCap is a secure, web-based software platform designed to support data capture for research studies.43

After written informed consent has been received, stage 2 participants will be asked to complete a brief 6-item survey asking about medication use and pregnancy status. Saliva samples, hair sample and heart rates will be collected using procedures designed to limit disruption to the flow of nurses’ work which was highlighted as a concern by nurse managers during the planning stages of this study. At the time of saliva collection, participants will record what area in the ED they are working (eg, team leader, triage) and rate their perceived level of stress at the time.

**Biomarker collection procedure**

**Saliva samples**

Saliva collection will require that participants collect their own saliva sample three times over one shift (8, 10 or 12-hour shift). The first sample will be collected at commencement of the shift (before nursing handover), the second sample will be before participants eat lunch/meal, and the third sample will be collected at the end of the shift. The three saliva collection timepoints are designed to avoid possible contamination of saliva from recent ingestion of food, coffee, tobacco use or recent brushing of teeth. The second saliva sample will provide a mid-shift level of sAA while nurses are deep into their workday. This may help to identify sustained acute stress levels occurring in participants.

The absorbent device method will be used to collect saliva from participants for increased ease of use. The SalivaBio oral swabs are a small non-toxic inert polymer with good validity and reliability for collection of analytes from saliva and may help with filtering large macro molecules and other particulate matter that can improve the assay results.44 Participants will use a non-touch technique to place the SalivaBio swab in their mouth for 2 minutes then into a labelled tube and into a chiller box that will be <4°C.44 To minimise variation in saliva collection, a 2-minute timer will be used to help participants determine when saliva swab saturation has occurred. The saliva samples will be transported to the wet lab and stored in the freezer (−80°C) until processing using the alpha amylase Salivary Assay Kit recommendations.44

**Hair sample**

The hair sample of approximately 3–5 mm in one clump from the posterior vertex of the scalp will be collected by LMM once per participant. The sample will be secured with tape, placed in a labelled envelope and transported to the wet laboratory for processing.45

**Heart rates**

Heart rate monitoring will use the POLAR OH1 heart rate sensor worn in a simple arm band on the upper arm compiling with infection prevention and control policies in healthcare of ‘bare below the elbow’46 and will be applied at the beginning and removed at the end of the nurse’s shift by LMM. The sensor uses optical heart rate monitoring by detecting blood flow using light-emitting diodes (LEDs) through the skin.47 The heartbeat is measured using photoplethysmogram (volumetric changes of an organ) via the LEDs in the sensor shining a constant light onto the skin.47 The OH1 sensor stores heart rate data which will be uploaded into the POLAR Flow database then downloaded to a computer and exported as a comma separated values (csv) file.47 Application of the OH1 sensor will begin with a baseline measure where participants will sit for 5 minutes before commencing work.

**Measures**

This study will measure demographic and occupational data as well as psychometric data in stage 1. Questions regarding education levels, occupational status, experience as an emergency nurse and possible life stressors are addressed in the survey. Psychometric data are collected...
### Table 2  Psychometric and biological measurements

#### Psychometric instruments

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Measures</th>
<th>Data content/items</th>
<th>Cronbach’s alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression Anxiety Stress Scale-21 (DASS-21)</td>
<td>Perceived stress, anxiety or depressive symptoms in the past week (21 items)</td>
<td>A 4-point Likert scale where 0=never and 3=almost always three domains: Stress (seven items) ► Moderate=19–26 ► Severe=26–33 ► Extremely severe core=34+ Anxiety (seven items) ► Moderate=10–14 ► Severe=15–19 ► Extremely severe=20+ Depression (seven items) ► Moderate=14–20 ► Severe=21–27 ► Extremely severe=28+ NB: scores should be multiplied by 2</td>
<td>Total scale 0.93, depression 0.86, anxiety 0.84 and stress 0.85</td>
</tr>
<tr>
<td>The Maslach Burnout Inventory-Medical Personnel tool (MBI-MP)*</td>
<td>Daily experiences of emotional exhaustion, feelings of personal accomplishment and depersonalisation (28 items)</td>
<td>A 7-item Likert scale from never=0 to everyday=6 in three domains of burnout: ► Depersonalisation (DP; five items) ► Personal accomplishment (PA; eight items) ► Emotional exhaustion (EE; nine items) High burnout=EE≥27, DP≥13, PA≤13 Moderate burnout=EE is 17–26 DP 7–12, PA 38–32 Low burnout=EE≤16, DP≤6, PA≥39</td>
<td>Total=0.902 EE=0.938 DP=0.876 PA=0.887</td>
</tr>
<tr>
<td>Areas of Worklife Survey (AWS)*</td>
<td>Degree of congruence between the worker and their job environment (28 items)</td>
<td>six domains: workload, control, reward, community, fairness and values. Higher congruence&gt;3 Incongruence&lt;3</td>
<td>Workload 0.67, control 0.83, reward 0.78, community 0.80, fairness 0.80 and values 0.73</td>
</tr>
<tr>
<td>Fatigue Assessment Scale (FAS)</td>
<td>Levels of fatigue (how a person usually feels; 10 items)</td>
<td>The Likert scale ranges from 1=never 5=always Low fatigue=10 Moderate fatigue≥22 Extreme fatigue&gt;33</td>
<td>0.72</td>
</tr>
<tr>
<td>Visual analogue scale (VAS)</td>
<td>Rate of current feelings of perceived stress (one item)</td>
<td>The current feelings of perceived stress on a 0–10 scale ‘0’=no stress ‘10’=extreme stress</td>
<td>n/a</td>
</tr>
</tbody>
</table>

#### Biological markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Units of measure</th>
<th>Measures in previous studies</th>
<th>This study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva alpha amylase</td>
<td>Units per millilitre (U/mL of fluid volume</td>
<td>11.5 U/mL (6.7–20.9) to 37.2 U/mL (14.5–73.4) (p value &lt; 0.001)</td>
<td>Acute stress≥50 U/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean 38.0±40.7 U/mL to mean 51.3±47.1 (p value &lt; 0.0038)</td>
<td></td>
</tr>
<tr>
<td>Hair cortisol</td>
<td>Picogram per milligram unit (pg/mg)</td>
<td>Hair cortisol (hCort) 34.9 pg/mg with IQR 55.0 (CI 95% 36.7 to 63.8) hCort of 83.1 (33.0 to 204.9) hCort &lt;40 and &gt;128 pg/mg correlated with stress (r=0.230, p=0.026) and DP (burnout; r=0.221, p=0.033)</td>
<td>Chronic stress≥50 pg/mg Burnout≥40 pg/mg</td>
</tr>
<tr>
<td>Heart rate variability</td>
<td>Standard deviation of the normal- to-normal (SDNN) beats using milliseconds (ms)</td>
<td>SDNN&lt;100 ms</td>
<td></td>
</tr>
</tbody>
</table>

*License and permission obtained for MBI-MP and AWS.
using four standardised instruments and are summarised in table 2.

The Depression Anxiety Stress Scale (DASS-21) enables targeted measurement of perceived stress in participants and helps separate stress symptoms from anxiety or depressive symptoms. The DASS-21 measures the three domains of depression, anxiety and stress from the past week.

The Maslach Burnout Inventory-Medical Personnel (MBI-MP) tool will measure the daily experiences in three domains of burnout that includes emotional exhaustion, personal accomplishment and depersonalisation which is often referred to as cynicism in the literature. The MBI-MP has been validated in a nursing population and is summarised in table 2.

The AWS concentrates on the degree of congruence between the worker and their job environment and has been validated in different working populations including nurses. There are five profiles identified in the AWS that include burnout, overextended, ineffective, disengaged, or engagement and include the MBI scores to determine the profile and degree of burnout.

The Fatigue Assessment Scale (FAS) measures how a person usually feels using fatigue as a single factor. Physical and mental fatigue are represented in the FAS and has reported fatigue in nurses before the COVID-19 pandemic and correlated with burnout among nurses during the pandemic.

The visual analogue scale (VAS) measures perceived stress at the time of scoring using a 0–10 scale with ‘0’ indicating no stress and ‘10’ indicating extreme stress, providing a quick option to record perceived stress. This one-item assessment tool is effective in the real-world healthcare setting and was significantly correlated with salivary cortisol to measure work stress in nurses.

Saliva alpha amylase is measured in units per millilitre (U/mL) of fluid volume. A conservative estimate of sAA expressing acute stress is >50 U/mL for this study based on previous research using this biomarker to measure the stress response in healthcare workers (see table 2 for p values of significance). hCort will use a threshold of >40 mg/pg based on a positive correlation between perceived stress, burnout and hCort concentration among healthcare workers that were involved in direct patient contact.

Calculating HRV using a time-domain measurement of SD of the normal to normal beats (SDNN) is considered the gold standard when considering cardiac risk and will be used in this study. The POLAR OH1 device captures heartbeats in 1 s epochs. These will be converted to interbeat intervals by taking the reciprocal and converting to milliseconds (ms). SDNN will be calculated for the 15 minute period surrounding each saliva sample collection. A measure of SDNN less than 50 ms is considered unhealthy, 50–100 ms as compromised health and greater than 100 ms as a healthy cardiac response. An overall calculation will also occur for each participant using mean, median and SD for group comparisons.

Sample size
Participants will be recruited using convenience sampling from the total pool of 353 nurses at the four hospitals. Recent research conducted on the stress of healthcare workers demonstrates a response rate ranging from 55.5% to 66%. Assuming a conservative response rate of 20%, we expect a sample of 70 participants.

Data analysis
All analyses will be performed in Stata software. Demographic and occupation-related characteristics of participants will be summarised using descriptive statistics. Continuous variables will be summarised as means with SD or medians with IQR, as appropriate for the distribution. Categorical variables will be summarised as frequency count and percentage. Gender and age distribution of the sample will be compared with that of the population of health district nursing staff.

To meet the primary aim of measuring acute stress, chronic stress, burnout and fatigue in emergency room nurses, numeric summaries for psychometric scores and biomarkers will be reported. Acute stress will use sAA, VAS score and HRV. Chronic stress will use hCort and the DASS-21 domain of stress. Burnout will use hCort, MBI-MP and AWS. Fatigue will be measured using the FAS only.

Acute and chronic stress scores will be summarised by subgroups defined by regional location (regional vs metropolitan), sex (female vs male), nursing experience (senior vs novice) and compared using t-tests or Wilcoxon-Mann-Whitney test if distributional assumptions are violated. Categorical measures will be compared between subgroups using χ² tests or Fisher’s exact test if sample size assumptions are not met. Finally, a retrospective examination of emergency department statistics will take place to understand the workload of nurses on the day of biomarker sampling using the Emergency Department Information System data available to the public in NSW, Australia.

The secondary aim of assessing the feasibility of using biomarkers to measure stress in a real-world setting will follow conventional tests for feasibility found in interventional studies and will use two main objectives. First, issues around recruitment will be assessed including how long it took to reach the recruitment target, examining refusal rates, eligibility restrictions and obstacles encountered when collecting the biomarkers.

Second, an assessment of how appropriate the data collection procedures and outcome measures were for meeting the aims of the study. This will include examining missing data, participant capacity to complete data collection procedures and the time frame for collection to determine participant burden for emergency nurses while they were working. Internal consistency will be
Validity of using biomarkers to measure acute and chronic stress and burnout will test the association with psychometric tools using Pearson’s correlation coefficient or a rank correlation coefficient (eg, Spearman’s) based on examining scatterplots for linearity. Cronbach’s alpha will be calculated for psychometric scales as a measure of reliability. Acute stress biomarkers of sAA and HRV will be tested for association with the VAS, and workload metrics. Chronic stress biomarkers will be assessed for validity by testing correlation among hCort and the stress parameter in the DASS-21. Burnout will be tested with hCort, the MBI and the AWS domains of workload and control.

Factors that may affect the measurement of biomarkers and may confound the association between biomarkers and psychometric measures are summarised in table 3. Regression models will be used to adjust statistically for these confounders and/or add context to any outlying values, assuming an adequate number of samples. Adjustment for life stressors such as caregiver burden, financial strain, and recent life events to isolate occupational stress will also be considered.

**Patient and public involvement**

Emergency nurses, managers and executive managers were consulted to discuss the accessibility, feasibility and barriers to conducting the study. This was especially helpful when the COVID-19 pandemic arrived in Australia and disrupted usual business in emergency departments of NSW.

**Dissemination**

The study will be part of LMM’s PhD dissertation and reporting of results will follow the Strengthening the Reporting of Observational Studies in Epidemiology guidelines format. The findings will be published in peer-reviewed journals and be presented at national and international conferences.

**DISCUSSION**

Nurses experience eustress to respond appropriately to the situations that arise at work. This can mean a sudden rush of epinephrine and energy to save a life or can also be a more maladaptive response of ongoing emotional exhaustion, fatigue and cynicism due to prolonged exposure to upsetting stressors. This study will report the levels of stress, burnout and fatigue in emergency nurses using subjective and objective data. Use of biomarkers will be assessed for feasibility in this cohort of nurses while they are in the natural environment of the workplace.

An examination of the correlation between HRV, sAA and the VAS of perceived stress for acute stress will occur. The correlation between chronic stress and burnout with hCort will be explored. The degrees of these variables using aggregated data such as metropolitan versus rural/regional nurses, senior versus novice nurses, male versus female nurses and part-time versus full-time employment were compared with prior studies and assessed if outcome measures using proposed thresholds were reasonable.

### Table 3  Factors affecting biomarker measurement

<table>
<thead>
<tr>
<th>Possible confounder</th>
<th>Effect on biomarker</th>
<th>Cortisol</th>
<th>Alpha amylase (sAA)</th>
<th>Heart rate variability (HRV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids, topical steroid creams, immunosuppressant (inhaled, systemic or both)</td>
<td>Can inflate cortisol levels in hair</td>
<td>Some medications can influence sAA levels in the saliva including asthma treatments</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Heart rate control medications</td>
<td>Nil</td>
<td>Beta blockers and other rate control medications can influence sAA secretion</td>
<td>May suppress the HRV effects in response to a stressor</td>
<td></td>
</tr>
<tr>
<td>Antianxiety medications and antidepressation medications</td>
<td>Can suppress the hypothalamus-pituitary-adrenal axis response</td>
<td>Psychotropic substances and antidepressants can influence sAA secretion and saliva production</td>
<td>May suppress the cardiac response to stressors</td>
<td></td>
</tr>
<tr>
<td>Pain medications (opioids, naloxone, patches, S8s, S4s)</td>
<td>Nil</td>
<td>May reduce salivary flow rate</td>
<td>May reduce heart rate variability during a stress response</td>
<td></td>
</tr>
<tr>
<td>Pregnancy or recent pregnancy</td>
<td>Cortisol is elevated by pregnancy and remains increased up to 24 weeks post partum</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Nil</td>
<td>One study found smoking will inhibit amylase activity, but another study found elevated sAA in habitual smokers</td>
<td>Can affect HRV and physiological reactions</td>
<td></td>
</tr>
</tbody>
</table>
status will take place. The impact of the COVID-19 pandemic will be considered and the feasibility of using HRV, sAA and the single-item VAS to measure acute stress using statistical correlation tests will occur. The use of the AWS alongside the MBI-MP and hCort to identify burnout profiles among emergency nurses will be analysed and the feasibility of this approach will be discussed.

A detailed discussion of strengths and limitations will include the use of objective measures to explore predominantly psychological phenomena. Acknowledging that measuring stress in humans should take a holistic approach is important and will be discussed in relation to the feasibility of using biomarkers. Predicted biases in this cross-sectional study of nurses include gender bias, response bias and self-report bias. Additional limitations considered will include the potentially large proportion of part-time nurses and this effect on measurement variables and the lack of knowledge of antecedent stressors prior to sAA sampling for assessing acute stress. Shift patterns of nurses or recent absence from work were other areas of potential impact on stress levels that will be considered in the discussion of limitations.

Use of biomarkers to better understand nurses’ stress, burnout and fatigue, and how they influence nurses’ physiological responses may pave the way for future interventional studies that aim to reduce stress in the workplace. New knowledge about the feasibility of using biomarkers with a nursing population in a real-world setting may provide more precision when measuring occupational stress. The potential impact is that nurses who consider using stress reduction strategies may agree to try the new stress measurement strategy if the strength of the evidence demonstrates that it will work. This may influence how managers and organisations design policy that aims to improve staff well-being in the future.

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Contributors LMM conceptualised the study including the study design, identified the study measures and data collection processes, compilation of the surveys and saliva log, developed the analysis and management plan, obtained ethical approval, and undertook a systematic review of the literature. KJL was involved in the study design, refining the methods including survey development, ethical approval, review of literature and writing, reviewing, and editing of this protocol manuscript. NW focused on the data analysis and management strategy and survey development and the writing, reviewing, and editing of this protocol manuscript. FRW assisted with study design, methods and expertise in biomarker collection and processing and reviewing and editing of this protocol manuscript.

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