Received: 4 August 2023 | Revised: 25 October 2023 | Accepted: 31 October 2023

DOI: 10.1002/hsr2.1710

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Exploring the potential of stratum corneum biomarkers for assessing psychological distress in health care workers: An observational pilot study

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Abstract

Backgrounds: The detection of biomarkers of a stress response in the stratum corneum (SC) could be used as objective assessment of early stress symptoms and monitoring of stress reduction interventions in health care workers (HCWs).

Aim: The aim of this study is to explore SC biomarkers of immune and hormonal response and skin barrier for assessment of psychological distress (PD) in HCWs.

Methods: Twenty-five female HCWs and 25 non-HCWs participated. SC samples were collected using adhesive tapes at baseline and 3–5 days later (T1). We analyzed 24 biomarkers (immunological, vascular, hormones, and natural moisturizing factors). Stress symptoms were assessed using three scales of Copenhagen Psychosocial Questionnaire. The study involved: identifying SC biomarkers, correlating stress symptoms and biomarkers at baseline and T1, examining stress symptoms between the groups with a Mann-Whitney test, comparing stress symptoms and biomarkers between groups using Ordinary Least Regression and investigating temporal variability of SC biomarkers at baseline and T1 using a Wilcoxon-signed rank.

Results: Fourteen SC biomarkers were identified. We found correlations between general stress and "IL18" ($r = 0.55$) physical stress and "IL1b" ($r = 0.36$) and cognitive stress and "MIP3a" ($r = 0.38$) at baseline and general stress and cortisol ($r = -0.49$), physical stress and cortisol ($r = -0.60$) and cortisone ($r = -0.67$) at T1. We found no differences in stress symptoms and biomarkers between the groups, except for "MIP3a" at baseline. Differences in the biomarker levels between two time points were found for "TARC," "VEGFA," "ILRA," "IL1RA/IL1a," "NMF," and "DHEA."

Conclusion: The SC can be suitable biological material to assess biomarkers related to immune response, hormonal response, and skin barrier function. The SC biomarkers, showed strong, moderate and weak correlations with stress symptoms. Notably, these associations include cytokines of innate immunity and well-known stress hormones, cortisol and cortisone.

KEYWORDS
biomarkers, epidermis, health personnel, occupational health, psychological, stress

1 | INTRODUCTION

Health care workers (HCWs) report higher levels of psychological distress (PD) compared to the general working population.[1] PD is defined as a discomforting emotional state in response to specific (work) demands, often resulting in disability for work, ranging from stress symptoms to stress-related disorders such as burnout, depression and anxiety.[2] PD has adverse effects for the individual (e.g., higher risk of depression),[3] the organization (e.g., turnover and absenteeism) and society at large (e.g., costs).[1,4] According to studies 30%–70% of HCWs experience high levels of PD symptoms.[1] Prevention of PD in HCWs is warranted given the high prevalence and the adverse effects.[5]

Oftentimes, questionnaires are utilized for the assessment of PD. However, commonly used questionnaires that screen for PD do not appear to have adequate measurement properties and diagnostic accuracy.[6] This limitation of questionnaires negatively influences the diagnostic accuracy, leading to over-estimation or under-estimation of PD in HCW.[6] Therefore, exploring approaches for an objective assessment of PD, holds promise.

The majority of biomarker studies have primarily focused on cortisol, the key effector molecule of the hypothalamic–pituitary–adrenal axis (HPA-axis).[7] However, the predictive value of these reported biomarkers significantly varies across different studies. Moreover, biomarkers of HPA-axis insufficiently capture the downstream effects of PD on the immune and vascular systems.[8] Measuring cortisol levels in hair, urine, or saliva presents methodological challenges. Factors like baldness, hair coloring, sunlight exposure, circadian rhythm can influence biomarker levels.[9] To overcome the methodological challenges in hair, saliva or urine, measuring in the skin might be a promising option.

The stratum corneum (SC), the outermost layer of the skin, contains various molecules involved in hormonal and immune response, making it a potential source for PD biomarkers.[10,11] Similar to the HPA-axis, the skin has its own system involving the hypothalamus, pituitary gland, and adrenal glands, which regulate the production of corticotropin-releasing hormone (CRH), adrenocorticotropin (ACTH) and cortisol. Cortisol release can activate immune cells, leading to the release of immune mediators like Th1 and Th2 cytokines, as well as growth and vascular factors. These substances diffuse through the epidermis and reach the SC (Figure 1).[16]

Activation of immune cells and release of cortisol causes by PD may also occur in the skin itself (local HPA-axis) whereas CRH and ACTH are produced by skin cells. Thus, the levels of cortisol and other hormones and immune mediators in the skin will depend on both central and local HPA-axis. This brain-skin connection is evident from the clinical studies that point to PD as an important trigger for skin inflammatory diseases, such as psoriasis and atopic dermatitis.[17] Furthermore, PD has a large impact on the skin barrier by activating the HPA- axis to stimulate local and systemic stress hormone production.[11] Natural moisturizing factors (NMF), is important for skin barrier and homeostasis, PD may contribute to a disruption of NMF. It has been shown that individuals that experience PD have delayed wound healing.[18]

SC samples can be collected by a non invasive method using adhesive tapes.[19] This non invasive and relatively simple approach may be particularly suitable for workers' health surveillance in occupational health setting to early detect PD in workers with an increased risk for health problems as it enables screening of a large number of workers such as HCWs.

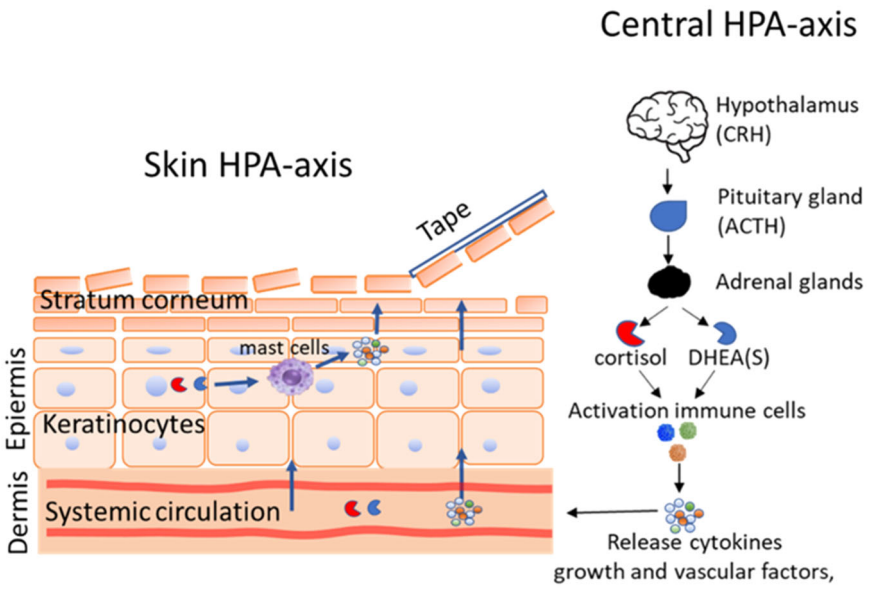

FIGURE 1 Schematic presentation of the central and local HPA-axis. Cortisol that may be generated by both central and local HP-axis activates immune cells leading to release of immunological mediators including cytokines, growth and vascular factors.[12–15] ACTH, Adrenocorticotropic hormone; APH-axis, hypothalamic-pituitary-adrenal axis; CRH, Corticotropin-releasing hormone; DHEA, Dehydroepiandrosterone; DHEA(s), Dehydroepiandrosterone sulphate.

We hypothesize that HCWs experience higher levels of PD symptoms compared to non-HCWs (nHCWs). Regarding the biomarkers, we will assess hormonal biomarkers such as cortisol, cortisone, DHEA and DHEA(s) for their role in stress response. NMF, essential for skin hydration and homeostasis, will represent the skin barrier.[20] A comprehensive range of immune mediators, including representatives of innate, Th1, Th17, and Th2 immunity, will be included due to the limited studies on immunological biomarkers in PD. Additionally, growth factors and vascular system markers will be incorporated.[10]

This study aims to explore the potential of a panel of SC biomarkers, including immune and hormonal response and skin barrier, for assessing PD in HCWs. The objectives are to (1) identify candidate PD biomarkers in the SC, (2) compare PD symptoms between HCWs and nHCWs, (3) examine associations between SC biomarkers and PD symptoms, (4) compare SC biomarker levels in HCWs and nHCWs, and (5) assess the temporal variability of the investigated biomarkers by collecting samples at two time points.

2 | METHODS

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for observational study was used to structure the reporting of this study. The completed STROBE checklist was retrieved from https://www.strobe-statement.org.[21]

2.1 | Setting and study design

This study was conducted as a single center pilot study with two groups, HCWs and nHCWs. We collected the data at an academic hospital in April–June 2022. The study protocol followed the principles of the Declaration of Helsinki. As the study was performed anonymously and the measurements were non invasive we did not need approval by the Medical Ethics Committee of the Academic Medical Center, Amsterdam, The Netherlands which issued formal exemption (reference number: W21_558 # 21.614). Informed consent was obtained from all participants before the study.

2.2 | Participants and collection of SC samples

Twenty-five female from the departments of rehabilitation and dermatology such as nurses and physicians participated in this study. Another 25 females participated from the department of experimental immunology and facility department such as laboratory workers and logistics workers as the group nHCWs. Participants were recruited via department newsletters, posters, and personal approaches by the researcher LME. Inclusion criteria were: females, aged between 18 and 65, no underlying conditions, willing to participate for the second measurement and consented for participation.

The SC samples were collected, by using round adhesive tapes (3.8 cm^2, D-Squame; CuDerm) which were attached to the middle of the forearm skin.[22] Six consecutive tapes were collected from the same skin area. The tapes were pressed onto the skin for 5 s with a standardized force (roller of 1 kg weight).[19]

The tapes were gently removed with tweezers and individually placed in cryo-vials and immediately stored at −80°C until analysis. The first tape was discarded to eliminate dirt and remnants of skin products. The 2th and 3th tapes were used for hormonal biomarkers, 5th tape strip for NMF and 4th and 6th tape strips were used for immunological biomarkers.

The optimal depth of the SC (reflected by the consecutive strip number) used for the analysis of DHEA, DHEA(s) was evaluated in the preceding pilot study showing the highest concentrations in the uppermost 4 tapes. The optimal depth of the SC for the analysis of NMF and cytokines have been described elsewhere.[14,23]

2.3 | SC biomarkers variables

Among immunological biomarkers that we included were pro inflammatory cytokines IL1RA, IL1a, IL1b, IL-6, IL18, TNFa, and CXCL8 (IL-8), macrophage inflammatory protein-3 alpha (MIP3a), a growth factor GM-CSF, CCL11 (Eotaxin), CCL17 (TARC), CXCL10 (IP-10) and IL-22 as representatives of respectively Th-2, Th1 and Th17 immunity. Among hormones we included cortisol, cortisone, DHEA and DHEA(s) as well as NMF as a skin barrier marker. Furthermore, we measured VEGFA, ICAM, and VCAM as vascular markers, C-reactive protein (CRP), brain-derived neurotrophic factor (BDNF) and epithelial-derived neutrophil-activating (ENA-78).

For data analysis, we included the SC biomarkers that could be determined in more than 50% of the samples (i.e., the concentration of a biomarker was above detection level).

2.4 | PD symptoms variables

Data on demographics, PD symptoms and psychosocial risk factors was collected using a self-reported questionnaire. The PD symptoms was collected at baseline, with the three stress scales of the Dutch version of the Copenhagen Psychosocial Questionnaire (COPSOQ).[24] The COPSOQ is a validated questionnaire for the measurement of self-reported psychosocial stress at work. The reported validity and reliability of the COPSOQ are good or very good.[24,25]

The general stress scale consists of three items ("How often have you had problems relaxing, how often have you been irritable, how often have you been tense?").

The physical stress scale consists of four items ("How often have you had stomach ache, how often have you had a headache, how often have you had palpitations, how often have you had tension in various muscles").

The cognitive stress scale consists of four items ("How often have you had problems concentrating, how often have you found it difficult to think clearly, how often have you had difficulty in taking decisions, how often have you had difficulty with remembering?").

The answering options of all scales are a 5-point Likert, where the lowest category represents the minimal value ("not at all") and the last the maximal value ("all the time"). For each scale the items were added and divided by the number of items to create the stress scales, higher means more stress symptoms.

2.5 | Psychosocial risk-factors variables

Psychosocial risk factors, measured with COPSOQ scales, were collected at baseline to describe the population and understand their impact on PD symptoms. The COPSOQ scales included quantitative demands, work pace, cognitive demands, emotional demands, influence at work, control over working time, social support from supervisor, social support from colleagues, work engagement, organizational justice, and violence at work (Supporting Information S1: File 1). The scale scores were calculated by summing and averaging the items, with higher scores indicating higher levels of experienced risk factors. Demographic data such as age, employment type, educational level, and working hours were also collected (higher means higher educated and working more hours).

2.6 | Analysis of the SC biomarkers

The concentration of all biomarkers was expressed as the concentration of a biomarker per protein/steroid hormone amount. Soluble proteins were determined by using the Pierce Micro BCA Protein Assay Kit (Thermo Fischer Scientific) with the bovine serum albumin supplied as standard.[10]

The 4th and 6th strip was used to determine the immunological biomarkers. Phosphate-buffered saline (Merck, Darmstadt, Germany) with 0.005% Tween 20 (Sigma-Aldrich) in a volume of 1.2 mL was added to a cryo-vial containing the 4th tape for the extraction of immunological biomarkers and soluble proteins. The extraction was performed in an ultrasonic bath (Branson 5800). The analysis of the immunological biomarkers was conducted using electrochemiluminescence immunoassays (MESO QuickPlex SQ 120 [MSD]) as described previously.[10,11] The limit of detection (LD) for immunological biomarkers was calculated by Discovery Workbench 4.0 software (MSD) as 2.5 standard deviations above the background signal.[26]

The 5th tape was used to determine NMF. The analysis was conducted after extraction of NMF from the tape using high-performance liquid chromatography with ultraviolet detection.[27] As the amount of SC on the tape varies, the amount of NMF in the SC on each tape was normalized by the protein content, which was determined using the Pierce Micro BCA Protein Assay Kit (Thermo Fischer Scientific) with the bovine serum albumin supplied as standard.[10] The limit of quantitation for NMF has been provided in Dapic et al.[27]

The second and third consecutive strip was used to determine cortisol, cortisone, DHEA and DHEAs which were extracted by adding 1 mL of methanol to a microtube with tape strip. After vortexing for 30 min at room temperature, methanol extracts from both tapes were pooled by transferring to another microtube and evaporated to dryness by vacuum centrifugation at 45°C (Eppendorf). The analysis was performed at the Dresden University of Technology (TU Dresden) by using Liquid chromatography coupled with tandem mass spectrometry (LCMS/MS).[23] To normalize for the variable amount of SC material on each tape, the optical density (OD) was measured using the D-Squame Scan 850 A (Monaderm) prior extraction. The amount of proteins on the tape, derived from the OD value was calculated as follows: protein ($\mu g/cm^2$) = 0.623*OD + 2.703.[26] For the analysis of cortisol, cortisone and DHEA(s) the LD was 1 nmol/L). For the samples below the LD half of the LD value was taken.[23]

2.7 | Statistical analysis

Data analysis was conducted using IBM SPSS statistics (version 27.0). The Shapiro–Wilk test was used to assess normal distribution, and the Mann–Whitney test, Wilcoxon signed-rank tests were used for skewed data. A natural log transformation was applied to the non-normally distributed data. Continuous variables were presented as median and interquartile (IQR) for non-normal distribution, while categorical variables were presented as percentages.

To examine the objectives of this study we conducted the following pre-specified statistical analyses. To describe the population, a Mann–Whitney test was conducted to assess differences in age, educational level, working hours per week, work-related risk factors and PD symptoms levels between HCWs and nHCWs. A new variable assessing inflammation was calculated by dividing IL1RA by IL1a, this variable was added as a biomarker. Partial correlation analyses, adjusted for age and group, examined the association between SC biomarkers and PD symptoms. Ordinary Least Squares regression was used to investigate differences in SC biomarkers between HCWs and nHCWs, with age and group as independent variables. Differences in SC biomarkers between baseline and T0 were analyzed using Wilcoxon signed-rank test, by pooling data from HCWs and nHCWs, the median of differences for the biomarkers between the T0 and T1 were reported.

Due to the exploratory nature of the study no correction for multiple testing and power calculations was performed. Instead, we determined our sample size by referencing previous PD biomarker studies conducted in workers, where sample sizes ranged from 12 to 102.[28,29] A 2-sided $p < 0.05$ was considered statistically significant. Correlation coefficients between 0.1 and 0.2 were considered very weak, 0.2–0.39 weak, 0.40–0.59 moderate, 0.6–0.79 strong, and 0.8–1 very strong.

3 | RESULTS

3.1 | Participants characteristics

The characteristics of the participants are described in Table 1. The median age for HCWs is 46 and for nHCWs 27. Differences between the

two groups were found for age and educational background, nHCWs are on average, higher educated than HCWs (48% Master degree or higher).

3.2 | SC biomarkers

From 24 immunological, vascular and hormonal biomarkers, 14 biomarkers could be determined in more than 50% of the samples. These included the biomarkers cortisol, cortisone, DHEA, NMF, IL18, IL1b, IL8, MIP3a, TARC, VEGFA, IL1RA, IL1a, CRP, and ICAM. The following biomarkers were below the detection level of 50% and were excluded from data analyses, i.e. IL-22, IL-6, IP-10, TNF-a, BDNF, ENA-78, Eotaxin, GM-CSF, VCAM-1, and DHEA(s).

3.3 | Comparison of PD symptoms and SC biomarker levels between HCWs and nHCWs

We found no differences between HCWs and nHCWs in the levels of PD symptoms (Table 1). Among 14 biomarkers, MIP3a showed a significant difference between HCW and nHCW at baseline ($\beta = -0.0.45$, $p = 0.02$).

TABLE 1 Characteristics between HCWs and nHCWs for demographic factors, PD symptoms and work factors.

	HCWs			nHCWs			Total			
	Median/%	IQR	*n*	Median/%	IQR	*n*	Median/%	IQR	*n*	*p* Value
Age	46.50	28.25–56.25	24	27	24–41	23	34	26–51	47	0.01
Employment type			24			24			48	0.06
Fixed	79%			50%			65%			
Temporary contract	13%			42%			27%			
Other	8%			8%			8%			
Educational level			24			25			49	0.01
High school diploma	21%			4%			12%			
Higher professional education	46%			28%			36%			
University bachelor	17%			16%			16%			
University master	8%			48%			28%			
Doctoral	8%			4%			6%			
Working hours	32	24–36	23	36	33–36	25	36	30–36	48	0.04
Stress scales[1]										
General stress scale	1.50	1.00–2.00	24	1.33	1.00–2.33	24	1.33	1.00–2.00	48	0.70
Physical stress scale	1.00	0.38–1.25	25	0.75	0.50–1.00	25	0.75	0.50–1.25	50	0.36
Cognitive stress scale	1.00	0.75–1.63	25	1.25	0.63–163	25	1.25	0.75–1.56	50	0.86
Work-factors[2]										
Quantitative demands	2.25	2.00–2.50	25	2.25	2.00–2.50	25	2.25	2.00–2.50	50	0.96
Work pace	2.33	2.00–2.83	25	2.00	1.67–2.33	25	2.33	1.92–2.67	50	0.04
Cognitive demands	2.75	2.50–3.00	25	2.38	1.81–2.75	24	2.50	2.25-2.75	49	0.10
Emotional demands	2.33	2.00–2.67	25	0.67	0.33–1.33	25	1.67	0.67–2.33	50	0.00
Influence at work	1.83	1.67–2.00	25	2.17	1.67–2.50	25	2.00	1.67–2.33	50	0.05
Control over working time	2.20	1.80–2.60	24	3.00	2.60–3.20	25	2.30	2.20–3.00	49	0.00
Social support from supervisor	2.33	1.50–2.83	25	2.67	2.00–3.17	25	2.33	2.00–3.00	50	0.29
Social support from colleagues	2.33	2.00–2.67	23	2.50	2.33–2.92	24	2.33	2.00–2.67	47	0.25
Work engagement	3.00	2.33–3.17	25	2.67	2.33–3.17	25	2.67	2.33–3.08	50	0.66
Organizational justice	2.25	2.00–2.50	23	2.37	2.00–2.75	24	2.25	2.00–2.75	47	0.41
Violence at work	0.00	0.00–0.00	25	0.00	0.00–0.00	25	0.00	0.00–0.00	50	0.04

Note: 1. A higher score indicated higher levels of stress symptoms. 2. A higher score indicates higher levels of work factors.
Abbreviation: IQR, interquartile.

3.4 | Associations between SC biomarkers and PD symptoms

We tested 14 correlations between SC biomarkers and PD (Table 2). At baseline, we found positive correlations between three biomarkers and measures of stress. Specifically, we found positive correlations between the general stress scale and IL18 ($r = 0.55$, $p < 0.001$), physical stress and IL1b ($r = 0.36$, $p = 0.04$) and cognitive stress and MIP3a ($r = 0.38$, $p = 0.03$). At T1, we found a moderate negative correlation between the general stress scale and cortisol ($r = -0.49$, $p = 0.03$), and physical stress scale and both cortisol ($r = -0.60$, $p = 0.01$) and cortisone ($r = -0.67$, $p = 0.00$).

3.5 | Differences in SC biomarkers over time within one working week

A difference between baseline and T0 was found for six out of 14 biomarkers, for all these biomarkers the Wilcoxon-sign test was in favor of T1. The median of differences between T1 and T0 for TARC was 0.003 (95% CI 0.002–0.023), for VEGFA 0.022 (95% CI 0.006–0.066), for IL1RA 9.47 (95% CI 5.544–128.2.81) for IL1RA/IL1a 0.207 (95% CI 0.112–0.284), for NMF 0.039 (95% CI 0.006–0.158) and for DHEA 4.938 (95% CI 2.250–7.703).

4 | DISCUSSION

4.1 | Main findings and interpretation of the findings

Preventing PD among HCWs is of utmost importance, given the far-reaching adverse effects it can have on their health, the organization, and society as a whole.[1,4] While preventive interventions often rely on questionnaires to detect HCWs at risk, the incorporation of objective measurements in the assessment of PD holds promise, overcoming some of the limitations associated with questionnaires.[6] In line with the objective of this study, we identified 14 out of 24 candidate PD biomarkers in the SC. Our study has demonstrated that SC is a suitable biological material for determination of biomarkers related to immune and hormonal response, as well as skin barrier function, but validation in future studies is warranted.

We compared PD symptoms and SC biomarkers between HCWs and nHCWs and examined associations between SC biomarkers and PD symptoms. Immunological biomarkers IL18, IL1b, and MIP3a, along with hormonal biomarkers cortisol and cortisone, were associated with PD symptoms, but at a very weak to strong level. These findings may be due to low stress levels and limited variability in PD symptoms within both groups. Most HCWs scored low on the PD symptoms scale, which could be attributed to the specific departments they were recruited from, known for having lower rates of PD among their staff.[30] This could also explain why we did not find any differences between the groups in SC biomarkers, except for MIP3a.

The immunological biomarkers that correlated with PD symptoms, were cytokines mediating innate immunity, such as IL18, IL1b, and the chemotactic mediator MIP3a. However, none of the Th1 or Th2 cytokines showed any association with PD symptoms. In the literature, an imbalance between Th1 and Th2 due to PD has been reported.[20] Although, the biomarkers IL18 and IL1b have been previously demonstrated to exhibit associations with PD or stress-related disorders, similar to the findings observed in our study.[31]

Cortisol is the most widely studied biomarker for PD, often measured in hair.[9] However, studies examining immunological biomarkers in relation to PD are limited. The available data on the association between hair cortisol levels and self-reported PD are inconsistent.[32] In a recent large study conducted in occupational settings, no associations was found between PD and hair cortisol levels in the overall sample, but, a positive association was observed in a subgroup with high perceived PD, suggesting that alterations in the HPA-axis become apparent beyond a certain threshold of stress symptomatology.[32] These findings imply that hair biomarkers are not suitable for detecting early or mild symptoms of PD. However, it remains unclear whether this also applies for SC biomarkers, as our study only included a sample with low PD levels.

Notably, cortisol and cortisone levels were negatively associated with PD at follow-up. Decreased cortisol in hair has been observed in individuals with anxiety or posttraumatic stress syndrome. However, in workers with high levels of PD in occupational settings, usually only increased cortisol levels were found.[28] One of the reasons might be different kinetics of cortisol in the SC as compared to hair and that SC cortisol originates from systemic circulation and from the skin itself (Figure 1). Further investigation is required to assess the contribution of the central and local HPA-axis for the SC levels of cortisol.

Finally, we assessed the temporal variability of the investigated biomarkers by collecting samples at two time points. This information is important in determining the optimal time for sampling. It is well established that changes in blood and saliva cortisol levels occur rapidly after a stress trigger and are therefore suitable indicators of current PD levels. In contrast, hair cortisol levels provide information on PD levels over a longer period.[32,33] Regarding SC, there is currently limited data on its biomarker kinetics. Based on the turnover of the SC of approximately 4 weeks,[34] it is expected that the levels of biomarkers in the SC represent a shorter time period than hair biomarkers, but a longer period than saliva or blood biomarkers. However, hair and saliva biomarkers are likely to be less practical for workplace monitoring due to the need for specialized equipment and expertise for sample collection and analysis.[32] In contrast, SC biomarkers can be easily collected using adhesive tapes, it is non invasive, relative affordable and analyzed using standard laboratory techniques, making them a more practical and accessible option for routine monitoring of PD levels in HCWs.

TABLE 2 Correlation coefficient and significance level (p) adjusted for age and group at baseline and T1.

	General stress (n = 33)		Physical stress (n = 34)		Cognitive stress (n = 34)			General stress (n = 21)		Physical stress (n = 22)		Cognitive stress (n = 22)	
Baseline	**Correlation coefficient**	***p***	**Correlation coefficient**	***p***	**Correlation coefficient**	***p***	**T1**	**Correlation coefficient**	***p***	**Correlation coefficient**	***p***	**Correlation coefficient**	***p***
Cortisol	0.10	0.59	−0.04	0.83	0.15	0.42	Cortisol	**−0.49**	**0.03**	**−0.60**	**0.01**	−0.27	0.24
Cortisone	0.31	0.09	−0.03	0.86	0.11	0.55	Cortisone	−0.42	0.07	**−0.67**	**0.00**	−0.08	0.74
DHEA	0.14	0.45	0.12	0.52	−0.03	0.88	DHEA	−0.10	0.69	−0.18	0.45	−0.16	0.49
NMF	−0.21	0.26	0.06	0.76	0.00	1	NMF	0.16	0.50	0.24	0.31	0.09	0.70
IL18	**0.55**	**0.00**	0.18	0.33	0.28	0.12	IL18	0.20	0.41	0.34	0.14	0.21	0.38
IL1b	0.30	0.11	**0.36**	**0.04**	0.00	1	IL1b	0.09	0.73	0.13	0.60	0.18	0.45
IL8	0.15	0.41	−0.07	0.71	0.07	0.69	IL8	−0.20	0.41	−0.21	0.37	0.11	0.65
MIP3a	0.27	0.15	0.09	0.63	**0.38**	**0.03**	MIP3a	0.26	0.28	−0.03	0.90	−0.03	0.91
TARC	0.27	0.15	0.03	0.87	0.21	0.25	TARC	−0.01	0.97	0.00	1	0.19	0.41
VEGFA	0.08	0.66	−0.19	0.31	−0.09	0.63	VEGFA	−0.36	0.13	−0.16	0.49	−0.07	0.77
IL1RA	0.16	0.38	0.05	0.77	−0.15	0.42	IL1RA	0.01	0.99	0.19	0.44	0.21	0.38
IL1a	0.27	0.14	0.35	0.05	0.19	0.30	IL1a	0.04	0.87	0.19	0.42	0.21	0.37
CRP	−0.01	0.97	0.15	0.43	0.11	0.54	CRP	−0.05	0.84	0.02	0.92	0.12	0.61
ICAM	0.09	0.64	0.04	0.83	−0.08	0.66	ICAM	0.09	0.73	0.21	0.39	0.12	0.62
IL1RA/IL1A	−0.03	0.88	−0.16	0.38	−0.23	0.21	IL1RA/IL1A	−0.05	0.84	0.01	0.97	0.02	0.93

4.2 | Limitations and strengths

It is important to acknowledge the limitations of the study, such as the relatively small sample size, small contrast within and between the groups in PD levels and the fact that only female participants were included. It is also important to acknowledge the lack of data on biological, spatial (i.e., depth of the SC from which the sample is taken) and temporal variability of SC biomarkers. The associations found should also be interpreted cautiously because we did not correct for multiple testing. Not correcting for multiple testing can lead to false-positive results and the reporting of spurious associations. Furthermore, it is essential to emphasize that one should not solely focus on p-values when assessing the significance of investigated associations.[35]

Although multiple testing correction was not applied in our study, it is important to note that this was an exploratory pilot study with the initial aim of exploring the potential of SC biomarkers. Nevertheless, to the best of our knowledge this is the first study that explores the potentional of immune and hormonal response, as well as skin barrier function in the SC for the assessing PD in the occupational health setting.

4.3 | Future research and generalizability

Future research in the field of evaluating SC biomarker of PD in HCWs should investigate HCWs working in medical specialties that have a higher risk of PD, such as emergency medicine or intensive care.[30] Additionally, future studies should consider incorporating interventions, to explore whether SC biomarkers are sensitive enough to detect changes in PD levels, thereby enabling objective assessment of the effectiveness of stress reducing interventions.

The kinetics of SC biomarkers could be further studied in experimental settings, for example, by examining their levels before and after acute physical or psychological stress events (e.g., exams or sporting events). Furthermore, it is important to consider the generalizability of our findings, as our study sample consisted of a small sample size, with only female HCWs with lower PD levels. Studies with larger and more diverse samples, including different sexes and varying PD levels, are necessary in further exploring the potential of SC biomarkers to assess PD in HCWs.

5 | CONCLUSION

The SC can be suitable biological material to assess biomarkers related to immune response, hormonal response, and skin barrier function. The SC biomarkers showed strong to weak correlations with stress symptoms. Notably, these associations include cytokines of innate immunity and well-known stress hormones, cortisol and cortisone.

AUTHOR CONTRIBUTIONS

Lima M. Emal: Conceptualization; data curation; formal analysis; methodology; project administration; writing—original draft. **Sietske J. Tamminga**: Conceptualization; supervision; writing—review and editing. **Frederieke G. Schaafsma**: Conceptualization; supervision; writing—review and editing. **Ivone Jakasa**: Methodology; writing—review and editing. **Ines Peremin**: Methodology. **Clemens Kirschbaum**: Methodology; writing—review and editing. **Henk F. van der Molen**: Conceptualization; methodology; supervision; writing—review and editing. **Sanja Kezic**: Conceptualization; methodology; project administration; supervision; writing—review and editing.

ACKNOWLEDGMENTS

We would like to acknowledge and thank Dr. Ehsan Motazedi for his contribution to the statistical analyses and the interpretation of the analyses. This study was internally funded by Amsterdam UMC, University of Amsterdam. L. M. E., S. J. T., F. G. S., and H. v. d. M. and S. K. declare that there was no involvement of Amsterdam UMC in the study design, data collection, data analysis, interpretation of results, writing of the study, or the decision to submit for publication. All aspects of the research, including the study design and reporting process, were conducted independently by the authors without any external influence or financial interest.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

We are committed to promoting transparency and facilitating research collaboration. Upon reasonable request, the first author of this study is prepared to provide access to the data for fellow researchers interested in further examination and validation of our findings. Please contact Lima M. Emal at Lima.emal@amsterdamumc.nl to request access to the data.

TRANSPARENCY STATEMENT

The lead author Lima M. Emal affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Emal LM, Tamminga SJ, Schaafsma FG, et al. Exploring the potential of stratum corneum biomarkers for assessing psychological distress in health care workers: an observational pilot study. *Health Sci Rep*. 2024;7:e1710. doi:10.1002/hsr2.1710