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PERSPECTIVE

Mapping the stress-skin axis: Difficulties, strategies & prospects ahead

Hong Zhang,[1] Xuelan Gu,[1,*] Yimei Tan,[2,5,6,7] Sijia Wang,[3,7] Wencai Jiang,[2,5,6] Bingjie Li,[3] and Jingjun Yang[4]

[1]Unilever R & D Shanghai, 66 Lin Xin Road, Shanghai 200335, China

[2]Department of Skin & Cosmetic Research, Shanghai Skin Disease Hospital, School of Medicine, Tongji University, Shanghai 200443, China

[3]Shanghai Institute of Nutrition and Health, Chinese Academy of Sciences, Shanghai 200031, China

[4]Unilever R & D Colworth Science Park, Sharnbrook, Bedfordshire MK441LQ, UK

[5]Professional Technical Service Platform for Clinical Evaluation of Skin Health Related Products, Shanghai Science and Technology Commission, Shanghai 200443, China

[6]NMPA Key Laboratory for Monitoring and Evaluation of Cosmetics, Shanghai 200443, China

[7]These authors contributed equally.

*Correspondence: xuelan.gu@unilever.com

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Chronic psychological stress is linked to various skin disorders such as psoriasis and acne, yet the mechanisms are still underexplored, especially in young, healthy populations. Herein, we mainly discuss the challenges in studying the impact of chronic psychological stress on skin and suggest the following approaches, (1) conduct a population-based survey to identify distinct segments and their associations with perceived stress levels as study initiative; (2) incorporate systems-level, physiological, and biological measures across biospecimens, along with psychological, self-reported subjective experiences; and (3) utilize advanced omics technologies and noninvasive measures, like Trans Epidermal Water Loss (TEWL) at baseline and after repeated tape stripping to better capture high-dimensional data and dynamic physiological property of skin; and (4) apply multi-model framework to analyze and integrate comprehensive datasets, such as causal mediation analysis. This effort is expected to decode the significance of psychological stress on skin, hair, scalp health and provide a foundation to develop novel biomarkers of healthy skin, hair and scalp, and integrate our fragmented knowledge of skin-mind, inflammation process, oxidative stress related to beauty and wellness.

CHRONIC PSYCHOLOGICAL STRESS AS AN INVISIBLE CHALLENGE FOR HUMAN HEALTH

In daily life, human bodies are continuously exposed to various stressors including both external factors, such as pollutants, chemicals, UV radiation and lifestyle choices including psychological stress, as well as internal factors, such as metabolic processes. The concept of exposome was initially described in 2005 and has emerged as a research approach from the need to decipher the comprehensive interactions between human health and exposures.[1,2] Environmental factors, such as traffic-related air pollutants, have been reported to act on human health and skin problems. Likewise, lifelong exposure to psychological stress has been recognized as a significant public concern affecting both mental and physical wellbeing.[3] Accumulated evidence indicates the link between psychological stress with fatigue, depression and anxiety, as well as cardiovascular disorders and immunodeficiency. Recent findings suggest that psychological stress is related to some common skin diseases and conditions, including psoriasis, atopic dermatitis,[4] acne, dullness and hair loss. Despite this widespread belief that psychological stress leads to onset, exacerbation and recurrence of many skin diseases and problems, the evidence supporting this claim appears to be insufficient. Moreover, the underlying mechanisms involved, especially in healthy young adults, have not been extensively studied.

CURRENT CHALLENGES

Psychological stress occurs when an individual perceives demands exceed his or her adaptive capacity. The prolonged or excessive stress will affect and may have adverse physiological consequences. The principal effectors of the stress system include the hypothalamic-pituitary-adrenal (HPA) axis, the immune system, neurotransmitters and the neural system, along with the gut-brain-skin axis, etc. Different hypotheses or pathways have been proposed to explore the interplay between psychological stress and conditions of skin and hair. Although studies are emerging, several challenges still exist.

Measurement challenges

The measurements of human stress have been intensively investigated and still debated. Cortisol, the primary stress hormone, can be measured in blood, saliva and hair fiber. Dehydroeiandrosterone (DHEA) as a sex steroid precursor, has been shown to counteract some of the effects of cortisol. This has given rise to controversies regarding the use of DHEA as a stress biomarker. Apparently, in addition to the monitoring of stress hormones, many self-reported questionnaires have been designed over past decades. One of the most popular tools for measuring subjective perception of stress is the Perceived Stress Scale (PSS-10), which was designed to determine the degree of the individual's subjective perception and emotional response to stress. However, it also raises questions due to culture disparities in the perception of stress, and the interconnections between personality and healthy aging. To date, the association between subjective and objective measurements of stress are yet to be fully elucidated.

Sampling challenges

Tape stripping has been used widely in dermatological research as a non-invasive method of epidermis sampling. However, currently there is no optimal protocol or action standard for protein extraction methods, and new developments in cost-effective RNA-sequencing technologies for low-quality or low-quantity samples are urgently needed.

Conceptual gaps

Chronic psychological stress increases the susceptibility of individuals to accelerated aging and multiple diseases including skin disorders. Longitudinal studies have demonstrated connections between chronic psychological stress and both subjective and objective health biomarkers in midlife and older populations, but there is a lack of evidence in young healthy populations. Given the lifelong impact of stress, it is necessary to predict health trajectories occurring during chronic stress and identify the mediators that connect stress to phenotypic changes through high-dimensional mediation analysis, therefore providing meaningful insights to unlock the intricate connection between psychological wellbeing and skin health.

CONSIDERATIONS IN STUDY DESIGN

Herein, we highlight four core design principles which are central to the rationale of studying the impact of psychological stress on health and beauty in the context of clinical study. A body of aging research proposed that there were different wave patterns of features throughout the lifespan, such as a critical change at 34 years old in Caucasian,[5] early change at age 30 in Chinese.[6] Here, young, female adults aged 18-35 years was defined as the target population, a demographic characterized by unique physiological and psychosocial attributes which may result in substantial physiological dysregulation underlying the nonlinear aging process. Moreover, this group represents a critical early-life window preceding the onset of age-related skin damage or complex comorbidities. Investigating psychological stress within the relative "uncomplicated" system offers several advantages, including the establishment of a "healthy" baseline, the absence of confounding variables, and improved clarity in multi-omics data. Additionally, young females experience more frequent hormonal fluctuations and are exposed to heightened psychosocial stressors from academics, career and family, which can inten-

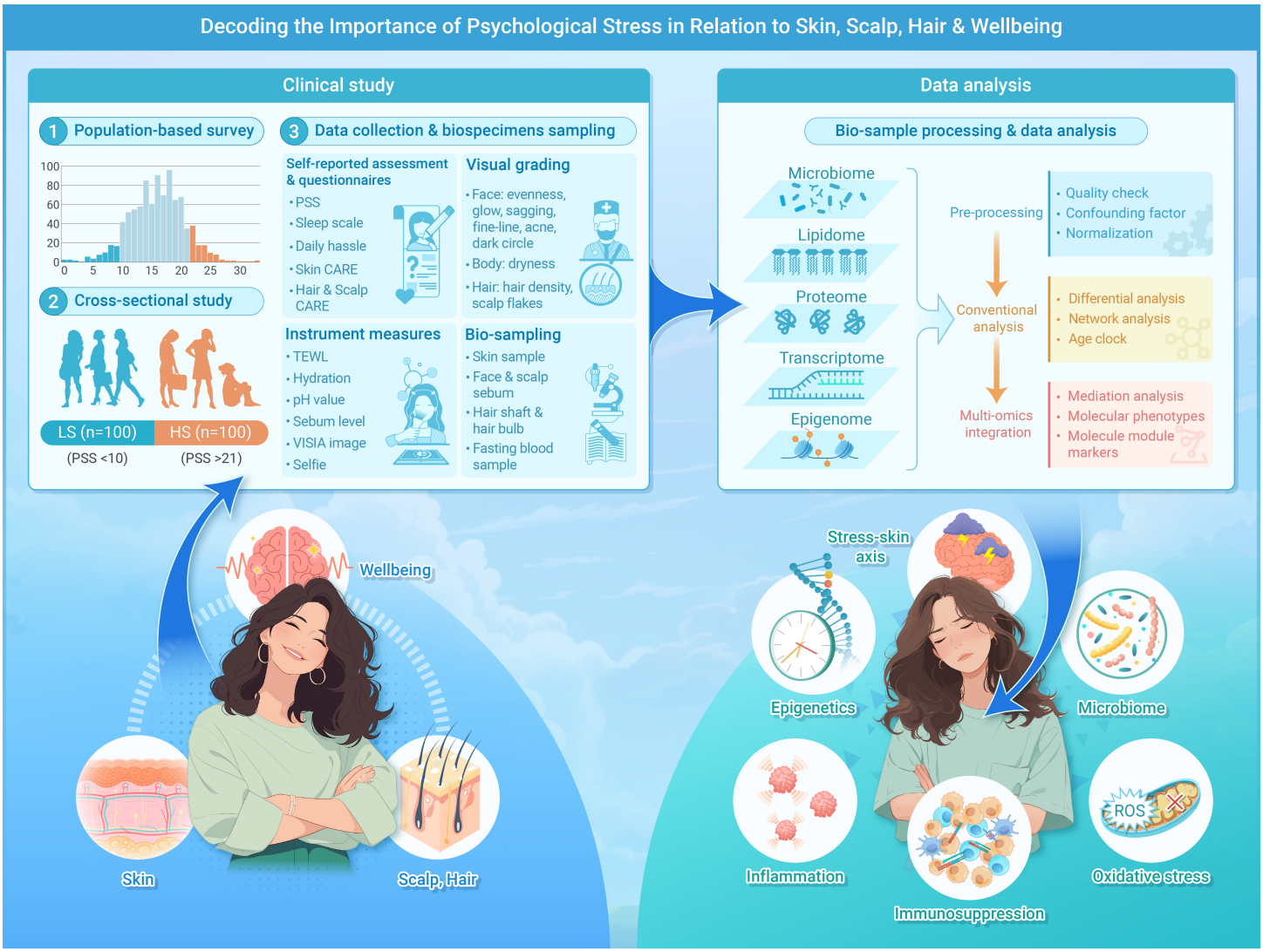

Figure 1. Flowchart of clinical study to decode the impact of psychological stress on the skin, scalp, hair and wellbeing.

sify the adverse effects of chronic stress on their health and well-being.

Principle 1: Define distinct segments within the target population (high stress & low stress)

To comprehensively assess the stress dynamics within our target demographic, an initial population-based survey is essential to map out stress levels, identify prevalent concerns among those under stress, and guide subsequent cross-sectional study. The total score of PSS ranging from 0 to 40 indicates either a low, moderate, or high level of perceived stress. In our cohort, the mean score of PSS was 15.9 (n=954, aged 18-35, Shanghai China), which is commensurate with the findings of other studies. Scores ranging from 21 to 40 are considered high perceived stress, while scores from 0-10 are regarded as low stress. It's worth mentioning that the PSS only reflects stress over the past month, and self-report outcomes may be influenced by factors such as social desirability or recall bias.

Principle 2: Include 'physic', 'psycho' and 'bio' measurements fit for purpose

Psychological stress, systemic and skin health are inseparable co-regulation processes. To holistically investigate the multifaceted interplay between psychological stress, dermatological health, and systemic biological markers, the study must adopt mixed methods and include multiple domains of analysis ranging from subjective experiences to the basic molecular and cellular biomarkers. We suggest to create a comprehensive dataset as can, including dermatologist-assessed signs (visual grading on acne IGA (Investigator's Global Assessment), dark circles, skin evenness, skin glow, facial sagging, and skin fine lines), instrumental readouts (pH, skin color, VISIA image, sebum levels, hydration and Trans Epidermal Water Loss (TEWL) on skin and scalp); and self-reported outcomes (self-report experiences, PSS, sleep scale, daily hassle, wellbeing related scores). Biospecimen collection via non-invasive sampling techniques is highly recommended. Hair cortisol concentration, as the neuroendocrine marker of stress, reflects the long-term cumulative cortisol secretion during the period of hair growth. It has been recognized as a stable and relevant biological maker to assess chronic stress. Furthermore, brain-derived neurotrophic factor and oxytocin are centrally secreted neuropeptides. Quantifying the levels of these major stress mediators in blood or skin have immense potential to explore the mind-skin connection.

Principle 3: Conduct hypothesis-driven multi-OMICS study

Recent years have witnessed rapid development in 'Omics' technologies. The integrative muti-omics approach application presents a comprehensive understanding of underlying mechanisms and unravel novel association. The upper layer of the skin plays a pivotal role in skin barrier function. Researchers have developed various noninvasive skin surface sampling methods for proteomics, lipidomic and microbiome analysis, and transcriptomics, including tape-striping, swabbing and patching. Among these, the tape-stripping method is commonly used for obtaining skin cells. Olink® Target 96 panels have been widely used for proof-of-concept studies.[7] It is hypothesized that stress may accelerate aging progress through the oxinflammation pathway and immunosuppression. Therefore, applying panels, such as inflammation and immune oncology, can generate a versatile dataset in a single run. In addition to the targeted proteome technology,

untargeted proteome should also be considered for hypothesis-driven exploration. With this regard, four-dimensional data-independent acquisition-based proteomics is a promising technology with an increased coverage and high sensitivity. Skin surface lipids are crucial to the structure and function of skin. Analysis of the totality of skin lipids requires tailored sample process against selected analytical platform. Non-invasive sampling often represents a particular challenge to extracting RNA of adequate quality for the whole transcriptome profiling analysis. The SMART-seq® HT kit is commercially available and designed for generating cDNA from single cells or 10 pg^{-1} ng of total RNA,[8] thus exceeding the limit of tape strips on sampling coverage. Increasing evidence indicates that gut microbiome plays a critical role in modulating skin disorders such as psoriasis and affect mood, cognition and behavior. Probing subtle changes in skin and scalp microbiome could elucidate how it interacts with skin cells. DNA methylation is currently the most promising molecular marker for monitoring the aging process. It is worth exploring the evidence linking DNA methylation to stress-accelerated phenotypes.

Principle 4: Network-based approach to integrate and analysis high-dimensional dataset

Analysis on individual omics dataset provides a snapshot of the effect of psychological stress at different levels, including RNA expression, protein expression, and metabolites like lipids. Undoubtedly, an integration analysis of multi-omics offers a comprehensive view of the molecular landscape of skin under stress conditions. The integrative analysis not only covers the data from different layers of skin or hair but also merges individual datasets from different levels into one unified platform. Confounding factors including demographic information such as age, body mass index (BMI), and sampling information such as sampling time and operators, are all considered and evaluated. Various methods for removing the batch effect and normalization such as RUVg are included in analysis to precisely address the chronic psychological stress effect on genes, proteins and lipid level. Afterwards, similarity fusion network analysis of integrated transcriptomics and proteomics enables us to unravel the molecular phenotype of chronic psychological stress on skin. Most importantly, employing advanced analysis tools, such as causal mediation analysis, dissects the role of the intermediate variables involved in the causal pathway between stressors (chronic psychological stress) and outcomes (stress related phenotypic changes), ultimately unraveling the molecular driver of stress acceleration effect. This potentially can provide the basis to win cosmetic personalization strategy. Studying the younger demographic allows for a simplification of the multi-omics approach, as biological variability is lower and confounding factors are fewer. This clarity enhances the detection of stress-related molecular changes, making it easier to break down clear mechanisms and find early biomarkers.

CONCLUDING REMARKS

Based on the above-mentioned core principles, the schematic of study design aiming to decode the fundamental mechanisms of stress-skin interaction is proposed, as shown in Figure 1. The rich multi-omics dataset generated from the young population, 18-35 years old, is the first of its kind and allows revealing early molecular signatures of the impact of psychological stress on skin, and discovering 'precocious derangements',[9] the potential precursors in still-healthy individuals, these insights can aid preventive strategies and inspire research in older populations and personalized skin care approaches.

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AUTHOR CONTRIBUTIONS

Conceptualization, X. G., Y.T., and S.W.; methodology, H.Z., W.J., and B.L.; writing—original draft preparation, H.Z. and X.G.; writing—review and editing, H.Z., X.G., Y.T. and S.W.; visualization, H. Z.; funding acquisition, X.G., and J.Y.. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.