Jie, Ma, et al. (2024) "Evaluation of sweat-based biomarkers using wearable biosensors for monitoring stress and fatigue: a systematic review." *International Journal of Occupational Safety and Ergonomics*. Accepted version

Evaluation of sweat-based biomarkers using wearable biosensors for monitoring stress and fatigue: a systematic review

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Acknowledgements

The authors acknowledged the following funding grants: 1. General Research Fund (GRF) Grant (15201621) entitled “Monitoring and managing fatigue of construction plant and equipment operators exposed to prolonged sitting”; 2. General Research Fund (GRF) Grant (BRE/PolyU 15210720) entitled “The development and validation of a non-invasive tool to monitor mental and physical stress in construction workers”; and 3. Start-up Fund for RAPs under the Strategic Hiring Scheme (1-BD34).

Abstract

Purpose*:* This systematic review aims to report the evaluation of wearable biosensors for the real-time measurement of stress and fatigue using sweat biomarkers.

Methods: A thorough search of the literature was carried out in databases such as PubMed, Web of Science, and IEEE. A three-step approach for selecting research articles was developed and implemented.

Results: Based on a systematic search, a total of 17 articles were included in this review. Lactate, cortisol, glucose, and electrolytes were found as sweat biomarkers. Sweat-based biomarkers are frequently monitored in real-time using potentiometric and amperometric biosensors. Wearable biosensors such as an epidermal patch or a sweatband have been widely validated in scientific literature.

Conclusions: Sweat is an important biofluid for monitoring general health, including stress and fatigue. It is becoming increasingly common to use biosensors that can measure a wide range of sweat biomarkers to detect fatigue during high-intensity work. Even though wearable biosensors have been validated for monitoring various sweat biomarkers, such biomarkers can only be used to assess stress and fatigue indirectly. In general, this study may serve as a driving force for academics and practitioners to broaden the use of wearable biosensors for the real-time assessment of stress and fatigue.

Keywords: Fatigue; Stress; Biomarkers; Lactate; Cortisol; Sweat analysis

1. INTRODUCTION

Stress and fatigue are common symptoms among healthy adults. According to self-reported subjective (i.e., perceived) fatigue scores, fatigue affects 14% to 60% of the healthy population [1]. In particular, people working in various industries, including construction, manufacturing, and mining, are susceptible to developing stress and fatigue due to labor-intensive, physically demanding activities, and repetitive tasks [2]. Nearly 40% of workers in the United States have reported experiencing significant stress and fatigue, which can have a negative effect on workers' safety, health status, and productivity [3,4]. Workplaces with hot and humid conditions, long hours, and heavy workloads have been shown to exacerbate the negative consequences of stress and fatigue [5-7], resulting in more accidents and mishaps [7]. Stress and fatigue may lead to the development of musculoskeletal problems or increase in the risk of fall injuries at work [8-10].

The term "fatigue" refers to a person's inability to perform at their best [11]. According to Boksem and Tops [12] and Boksem et al. [13], mental fatigue is the result of a prolonged and intense cognitive workload, whereas physical fatigue is the result of a prolonged and intense physical workload [14,15]. Occupational fatigue has widely been recognized as one of the top five health risks due to its detrimental effects on workers' health, safety, and productivity [16,17]. Concerns regarding workers' safety and health have prompted an increased focus to monitor stress and fatigue to avoid injuries and accidents in physically demanding workplaces [18]. For this reason, workers in several industries need regular examinations and early identification of fatigue [19-21].

Many factors contribute to the development of fatigue, including sleep deprivation, constant mental activity with a high workload, and long periods of physical exertion [22]. Physical exertion that lasts for a long duration can lead to fatigue, which can be felt in the peripheral muscles and the central nervous system (CNS) [23]. Michael et al. [22] found that when glycogen storage goes down and metabolites build up, the ionic balance of myocytes is changed. Even though the exact way this happens is still up for debate, it is known that cytokines and/or neurotransmitters like interleukin (IL) 1, IL-6, tumour necrosis factor (TNF), serotonin, dopamine, and tyrosine are changed when the CNS is involved in the experience of exhaustion [24,25]. Long-term physical activity has an impact on the autonomic nervous system (ANS), which causes the sympathetic nervous system (SNS) to activate and the parasympathetic nervous system (PNS) to withdraw simultaneously [26]. Therefore, all these physiological changes might be used as potential indicators for accurately detecting fatigue levels.

Historically, questionnaires have been widely regarded as the preferred method for assessing fatigue due to their ease of use, cost-effectiveness, and convenience [8]. While questionnaires were useful for understanding fatigue across different construction trades, they were not practical for proactive real-time fatigue management because they were intrusive (i.e., they interrupted the ongoing work) and could not be used to monitor the fatigue levels of multiple workers at once [8]. Additionally, continuous monitoring of the level of fatigue in an accurate and unobtrusive manner is important for the early detection and management of fatigue. Therefore, researchers have employed more objective, accurate, and non-invasive procedures because of the limitations of existing methods. At present, wearable sensing technologies are employed to detect early indications of fatigue through the analysis of changes in individuals' physiological responses [27,28]. Electroencephalogram (EEG), heart rate (HR), and electromyogram (EMG) measurements are used to measure activity in the brain, heart, and muscles, respectively [27,28]. The application of physiological signals as markers of fatigue enables the objective and immediate assessment of fatigue on an individual basis [29-31]. However, the identification of unconventional conditions is a complex task due to the fluctuation of physiological markers in reaction to fatigue and stressful situations, which can vary among individuals or even within individuals [32]. While humans possess a limited degree of control over their physiological signals, several factors such as environmental settings, emotions, and pathophysiological illnesses might influence these signals. The existing knowledge about the accuracy and reliability of fatigue detection and prediction based on physiological signals, especially in real-world situations, lacks conclusive findings [33].

More recently, chemical biomarkers have been considered as the gold standard for fatigue monitoring among the various approaches because of their precision and objectivity [34]. Construction workers, on the one hand, are frequently exposed to unique work environments that necessitate physically demanding and significant mental effort to complete work tasks, while on the other hand, athletes and sports people are involved in task-specific physical loads. It is possible that in this case, the underlying metabolic changes are rather distinct. In the past, the utilization of chemical biomarkers in real-time fatigue monitoring applications was limited due to the necessity of obtaining blood samples and conducting laboratory analysis [35]. Technological advancements have made non-invasive tests such as saliva and sweat analysis possible [36]. These measurements can also assess changes in biochemical profiles over time. Numerous chemical biomarkers, such as lactate, cortisol, pH, potassium, sodium, and blood glucose concentrations in sweat, could be investigated to determine the development of fatigue [37]. For instance, lactate was utilized in a prior study to demonstrate that continuous physical work results in a rise in the body's lactic acid content, which may contribute to feelings of fatigue [38]. Similarly, it has been discovered that mental fatigue is directly related to cortisol levels [39]. Furthermore, pH, potassium, sodium, and glucose levels are associated with a rise in lactic acid [34], hyper/hypokalemia, energy loss [40], drowsiness, irritability, and muscle cramps [41]. Despite the considerable advancements made in wearable biosensor technology in recent years, understanding the potential applications of these technologies to assess sweat-based biomarkers for monitoring fatigue and stress are still in its infancy. Additionally, systematic investigation of sweat biomarkers by using wearable biosensors to evaluate stress and fatigue is scarce. Furthermore, it is imperative to examine sweat-based biomarkers using wearable biosensors to monitor stress and fatigue. This approach is crucial due to its non-intrusive characteristics, ability to provide real-time monitoring, objective evaluation, comprehensive understanding, potential for tailored interventions, and early identification and prevention of stress-related illness. Therefore, this systematic review aims to fill these knowledge gaps by summarizing the findings of an evaluation of wearable biosensors for real-time monitoring of stress and fatigue by utilizing sweat biomarkers. This review makes an important contribution to the advancement of research, healthcare, and methods for effectively managing well-being among individuals who are experiencing fatigue and stress. This review identified three research questions. First, what are the sweat-based biomarkers that can be used to measure stress and fatigue? Secondly, what is the status of sweat-based biosensors for detecting stress and fatigue-related biomarkers? Third, how are biomarkers being measured in wearable biosensors?

2. METHODS

The current review methods comprise of three major steps: literature search, literature selection, and literature coding. A similar review of how to use wearable sensing technology to improve safety management in the construction industry led to the three-step method [8].

2.1. Literature Search

This review conducted a systematic search for relevant articles, critically appraised the applications and features of several wearable biosensors and summarized the properties of several sweat biomarkers for stress and fatigue measurement. Three electronic databases were searched from their origin until June 15, 2022. The search was conducted using the primary keywords (biomarkers, sweat, wearable biosensors, fatigue, and stress) as well as their derivatives. This systematic review was conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol [42]. The search strategies employed in this review are summarized in Table 1. The Web of Science was searched across all the subscription resources using the same set of search fields (e.g., topic search) to obtain the most comprehensive possible results. The primary search terms were put together using the AND operator so that a combined search could be done.

2.2. Literature selection

At this stage, we assess the titles and abstracts of the available publications. Articles that may be eligible must have been published prior to June 15, 2022. Additionally, the articles must be geared towards identifying fatigue or stress biomarkers in sweat. A full description of the sensors, their characteristics, and their suitability for use with human sweat must be provided. Finally, only journal articles written in English were included. Following that, we analyzed the full texts of all potentially relevant articles.

2.3. Literature coding and data extraction

The title, keywords, and abstract were the primary sources for coding an article in this review. Additionally, the full-text articles were examined for additional coding and data extraction. The coding of the literature was mostly concentrated on the parts of research methodology and conclusions. Each of the collected articles were coded to examine the research questions. During the coding process, the following key data points were extracted from each article and formatted in our database: citations, publishers, biomarkers, subject characteristics, types of sensors, types of wearables, and time taken to begin recording. The total citations of all included articles were also calculated based on their citations. The Web of Science Core Collection search tool and the Google Scholar search engine were used to determine the number of citations.

3. RESULTS

A preliminary search of electronic databases yielded 131 bibliometric records. Thirty-three documents were eliminated due to duplicates, bringing the total to 98. Another 17 articles were omitted because they were not related to human research, and two more articles were omitted because they were not written in English. The remaining 79 articles were further analyzed, and 32 unrelated articles were removed. A total of 47 articles remained for full-text examination. Another 30 articles were omitted from this review because they had no relevance to the primary goal of this study. As a result, the current review comprises a total of 17 journal articles. The complete selection algorithm is illustrated in **Figure 1**.

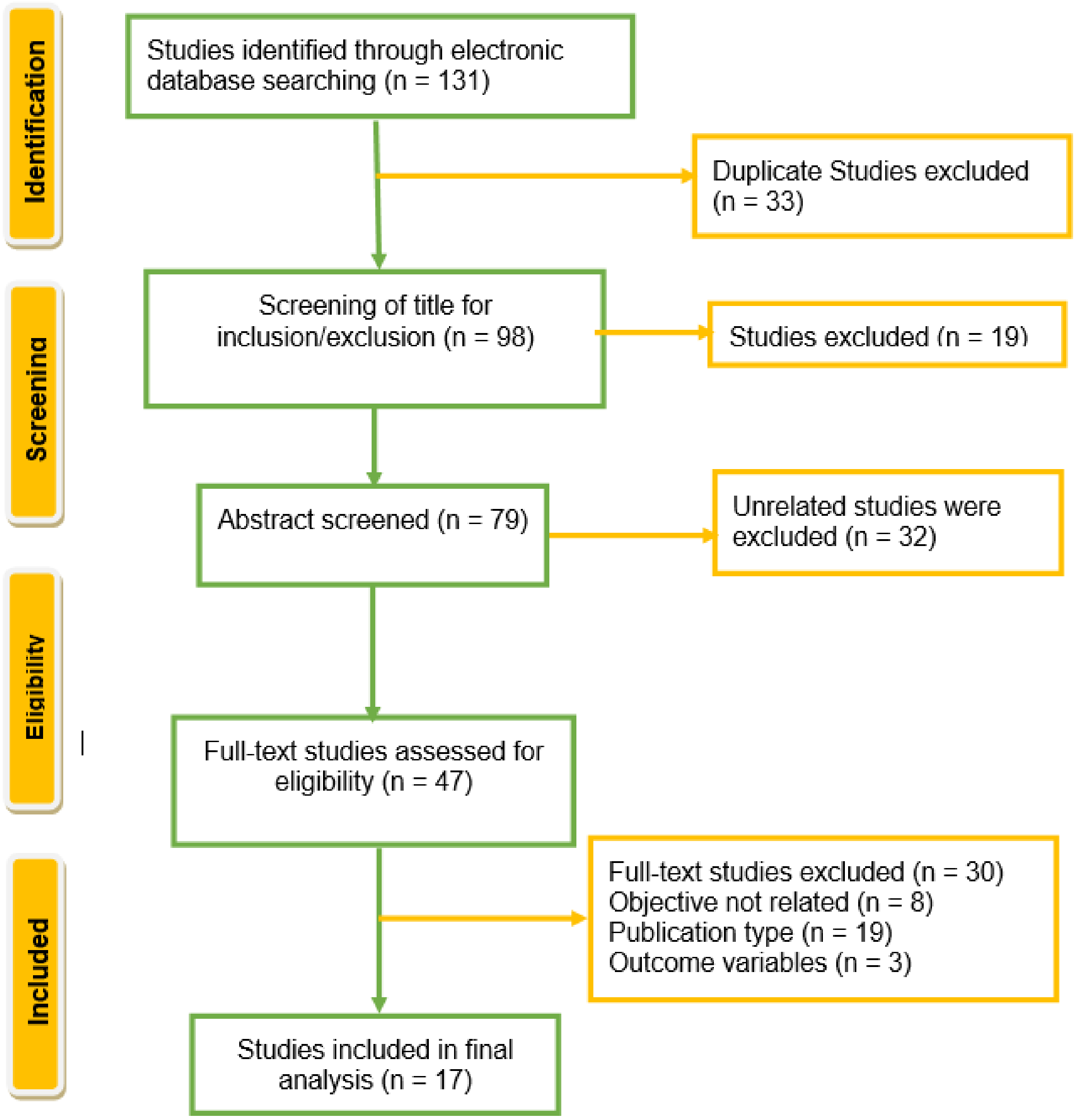

Figure 1. Study selection process and results of the literature search (PRISMA flow chart) [Note: n = number of articles]

Detailed information about the final selected articles is provided in **Table 2**, including the names of the authors and the names of the publishers, as well as information about the biomarkers evaluated, the participants and their demographics, the types of sensors and wearables used, the time it took for the sensor to begin recording, and the number of citations.

Table 3 has a detailed list of all eligible articles, which includes the validation techniques, experiments, findings, and conclusions of each article. Most of the included article used laboratory trials for the validation of wearable biosensors for monitoring sweat-based biomarkers. Most of the included articles in this review looked at the levels of sweat biomarkers under different physiological conditions using a stationary cycling programme.

Sweat biomarkers such as lactate, cortisol, glucose, and electrolytes are commonly used for monitoring stress and fatigue (**Figure 2**). Potentiometric and amperometric biosensors are widely used to detect sweat-based biomarkers in real-time. Wearable biosensors, such as an epidermal patch or a sweatband, have received a great deal of validation in scientific publications. The bio-signals collected by these wearable sensors could take anywhere from 1 to 20 minutes to begin recording.

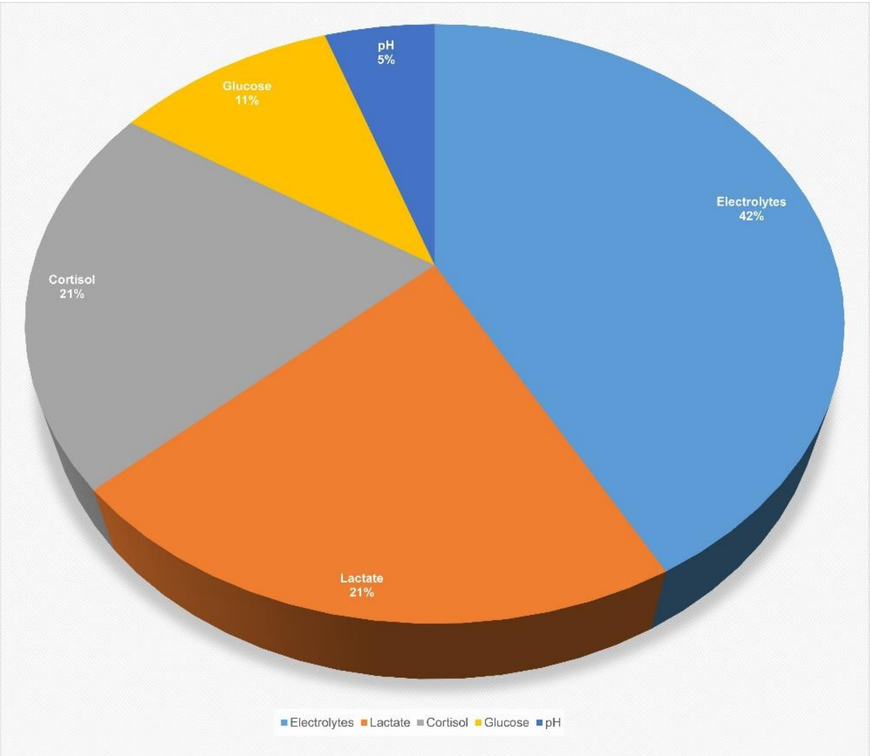

Figure 2. The identified sweat-based biomarkers

4. DISCUSSION

Sweat is a better alternative for biosensing than other potential biomarkers since it is readily available and contains a variety of essential electrolytes, metabolites, amino acids, proteins, and hormones. Sweat-based biomarkers have been discovered to have considerable promise for stress and fatigue evaluation in the current review. This review also found that sweat-based biosensors have become more popular in recent years to measure stress and fatigue.

4.1. Sweat biomarkers of stress and fatigue

Earlier research has concentrated on the detection of fatigue by using physiological signs, visual tasks, and biomarkers [43]. Changes in electroencephalogram (EEG) theta (θ) waves, high-frequency (HF) EEG, pulse signals, and the ratio of low- and high-frequency components (LF/HF ratio) are used to detect fatigue [44]. Additionally, numerous chemical biomarkers such as creatine kinase [45], blood interleukin (IL)-8 [46], α-amylase [47], and cortisol [48] can be used to detect fatigue. While some of these metrics have been used in clinical practice to quantify fatigue, the majority are invasive diagnostic tests that require blood samples, and hence, cannot be utilized for rapid, on-site, and accurate fatigue identification. When compared to blood and urine, which can be influenced by kidneys and other causes, sweat biofluid is more stable and easier to sample [49]. There were several research interests in sweat component analysis for fatigue detection in China and other nations [50,51]. Using sweat as an analysis fluid allows for non-invasive samples to be taken for both early and continuing diagnosis [52]. Depending on the analytical techniques, sweat samples, and preparation may be easier and faster than other biological fluids, such as blood [50,51]. Raiszadeh et al. [53] reported that sweat is a great source of chemical biomarkers because it is not very invasive and has a lot of proteins and peptides.

4.1.1. Sweat Cortisol

Cortisol has historically been known as the "stress biomarker" in the evaluation of stress-related conditions and is secreted primarily by the adrenal glands in the stress response [54]. Chronically increased levels of cortisol can cause cognitive impairment, hyperglycemia, sleep disturbance, hypertension, decreased immunological response, obesity, and fatigue [55]. Cortisol in sweat is thought to represent the free, unbound portion of cortisol in the blood as well as free cortisol in the urine [56]. It has also been suggested that sweat cortisol may represent activity in the hypothalamus, pituitary, and adrenal glands [57]. It was an enzyme-linked immunosorbent assay (ELISA) that was the first method to be reported for analyzing sweat cortisol [58], and since then several other methods have been reported, including high-performance liquid chromatography coupled to mass spectrometry (HPLC-MS) [59], thin-layer chromatography (TLC) [60], and immunosensor [61]. In another research study, liquid chromatography with detection by tandem mass spectrometry (LC-MSMS) was used to investigate the identification of stress biomarkers [62]. Obtaining a screening profile of stress biomarkers in sweat samples after exercise was the goal, so that researchers could figure out which biomarkers were most prevalent [52]. They found that the LC-MSMS in MRM-MS mode screening profile can be used to detect or identify sweat stress biomarkers linked to physical exercise. For instance, the concentration of cortisol in sweat increases nearly ten times after two hours of high-intensity exercise than it does after the same amount of time spent doing low-intensity exercise [63]. Consequently, the cortisol concentration in sweat was found to be 10.47 mol/cm^3, which is within the ideal range for cortisol concentration in sweat [64]. Furthermore, Torrente-Rodriguez et al. [65] discovered significantly higher sweat cortisol levels after 50 minutes of physical activity compared to those after 10 minutes of physical activity in response to a physiological stressor.

Practical implications of these findings may include physical workloads, where it is still important to have biomarkers for assessment and measurements of workload-induced stress, which may result in injuries. For example, in the construction sector, stress can have a negative impact on the health and performance of the workers. However, the composition of sweat samples collected during rest and exercise should be compared to identify the biomarkers that should be used in the context of exercise-induced stress [52]. Therefore, to ensure a proper sweat analysis, procedures and analytical instruments must be selected in accordance with the biomarkers to be determined [52]. One of the most significant advantages of employing MSMS is the ability to detect several biomarkers in a single run [52]. However, from a clinical perspective, it is still a time-consuming and expensive approach to use. Therefore, sweat-based wearable biosensors may be a viable option for overcoming these drawbacks.

The importance of sweat cortisol is found in its possible application for the management of stress and fatigue. For instance, cortisol can serve as a biomarker in relation to stress [66]. By monitoring the amounts of cortisol present in sweat, significant insights can be gained regarding an individual's response to stress. Through the analysis of variations in cortisol levels, individuals can get a more thorough understanding of their stress patterns and discover the factors that lead to stress [67]. This information has the potential to facilitate the development of individualized stress management methods and interventions. Moreover, there exists a correlation between cortisol levels and the regulation of fatigue and energy [68]. Abnormal cortisol levels, whether excessively high or insufficiently low, can potentially lead to the development of fatigue and burnout [69]. The monitoring of sweat cortisol levels has the potential to offer a non-invasive and easy approach for evaluating fatigue levels and detecting fatigue patterns over the course of a day [70]. This information can be utilized to enhance strategies for rest and rehabilitation, enhance productivity, and mitigate the risk of chronic fatigue. In a similar vein, the monitoring of cortisol levels in sweat has promised to facilitate individualized treatments aimed at managing stress and fatigue [71]. Through the monitoring of cortisol levels, individuals could ascertain the efficacy of various stress reduction approaches, including exercise, meditation, and relaxation strategies [72]. The presence of this feedback loop enables individuals to make informed decisions regarding the most effective interventions for their specific needs and subsequently adapt their methods accordingly [72]. Moreover, the monitoring of cortisol levels in sweat could potentially have substantial ramifications for the field of occupational health and safety [70]. Real-time monitoring of cortisol levels could be advantageous for individuals employed in high-stress occupations, such as construction workers, since it may aid in stress management and fatigue prevention [73]. This information can be utilized by construction managers to effectively execute remedies and establish work conditions that promote improved health and well-being. Notwithstanding the prospective applications, it is imperative to acknowledge that the measurement of cortisol in sweat is still a developing area, necessitating additional research to ascertain its reliability, precision, and standardization. Ongoing studies and developments in technology will play a crucial role in fully utilizing sweat cortisol monitoring to enhance well-being and overall health.

4.1.2. Sweat Lactate (sLa)

Several studies have explored the elements of sweat to determine if they can reflect the physiological state of individuals [74,75]. The determination of lactate in sweat has several clinical uses that are currently being explored [76]. One early notion was that because lactate is a result of anaerobic metabolism, it may be utilized to monitor parameters such as physical performance or limit oxygen levels [77]. It was stated that the assessment of sweat lactate would provide a non-invasive alternative to blood lactate measurements [74]. However, it appears that there is a very poor association between blood and sweat lactate levels due to a lack of physical exertion [78]. There are also certain advantages to using sweat lactate (sLa) measurement over other methods, such as its ease of use, non-invasiveness, and ability to measure continuously. New information can be gained from continuous monitoring of sweat gland activity by using an algorithm known as the sLa curve [79], even though some researchers have concluded that it only provides information about sweat gland metabolism and does not provide insight into the clinical use of sLa [74,80]. Several studies have demonstrated that sLa output decreases in participants when they become acclimated to heat, as well as that sLa output increases in arm sweat after the arm has been occluded [81,82]. It was discovered that sweat and blood lactate were unrelated during physical exercise when the authors compared the content of arm-bag sweat to the composition of whole-body sweat [81,82]. They also explored how sweat lactate is formed and its relationship to skin temperature, sweat rate, and sweat duration [81,82]. It has been previously discovered that when sweating begins, lactate is liberated from the epidermis [83]. As the resistance to cycling exercise increases, the sweat-lactate concentration increases as well, demonstrating a relationship between physical exertion, heart rate, and, after a physiologic time delay, lactate formation during the experiment [83]. When exercising at moderate intensity, the concentration of lactate was shown to be substantially higher than when resting ($p < 0.05$) [78]. This is because (a) exercise produces anaerobic metabolism, which results in the formation of lactate in sweat, and (b) activity generates a larger sweat release, which generates more lactate [78]. More recently, Huang et al. [84], on the other hand, found that as sweat rate increased, lactate levels fell progressively during exercise due to the dilution effect [40, 85]. As a result, sweat seems to be the best biofluid for assessing lactate.

The assessment of sweat lactate, which refers to the quantification of lactate concentrations in sweat, has garnered significant interest in recent years as a prospective means of monitoring and addressing stress and fatigue [86]. There exists a positive correlation between sweat lactate levels and bodily responses that are commonly linked with stress and fatigue [87]. During instances characterized by heightened stress or fatigue, the body's energy requirements are elevated, resulting in an augmented production of lactate [88]. Monitoring of sweat lactate levels can yield empirical data regarding the physiological response of the body to certain conditions [89,90]. This enables individuals to recognize situations characterized by increased stress or fatigue and afterwards adopt optimal techniques to address these circumstances [89,90]. For instance, in cases where individuals routinely exhibit heightened lactate levels during activities or at specific times of the day, they may consider adjusting their routines or employing stress-reduction approaches to effectively regulate their energy levels. The study of lactate levels in sweat can also provide significant insights for people engaged in physical performance, including those in occupations such as the construction industry [89,90]. Lactate has been found to be closely related to the initiation of fatigue during intense physical activity, and the monitoring of lactate levels in sweat can be utilized to enhance the efficiency of work intensity and mitigate the risk of excessive fatigue [91]. By comprehending the dynamics of lactate during physically strenuous construction jobs, workers could modify the intensity and duration of their workload to optimize performance and mitigate the likelihood of injuries or excessive fatigue. Given the possible applications mentioned, it is crucial to acknowledge that the analysis of sweat lactate remains an expanding field of study, necessitating further research to comprehensively explain its clinical usefulness and build widely accepted procedures.

4.1.3. Sweat Glucose

Controlling fatigue levels requires constant monitoring of glucose levels [92]. The amount of glucose in human sweat ranges from 10 to 200 µM [93], and studies have investigated the association between sweat glucose and blood glucose levels [94,95]. It was revealed that the transit of sweat glucose and critical electrolyte concentrations were like those in the blood [96]. Sweat obtained using iontophoresis has also been proven to contain glucose levels that are comparable to those found in the blood [97]. According to a more recent study, Huang et al. [84] discovered that when perspiration rate rose, glucose levels decreased gradually during exercise because of the diluting effect [40,85]. Developing biosensors that can reliably measure analytes like glucose, which alter health status when exercising, require knowledge of lag periods and transport kinetics [34].

The importance of sweat glucose monitoring relies on its prospective applications for the management of stress and fatigue. The influence of stress on glucose metabolism is substantial [98]. In instances of heightened stress, the human body initiates the release of stress hormones such as cortisol, thereby potentially elevating the levels of glucose in the bloodstream [99]. The monitoring of sweat glucose levels has the potential to yield significant insights into the physiological reaction to stress, thereby empowering individuals to enhance their stress identification and management strategies. By monitoring sweat glucose levels, individuals can enhance their comprehension of the relationship between stress and glucose levels, enabling them to adopt proactive strategies to alleviate its influence [100]. Furthermore, fatigue can serve as both a precipitating factor and a manifestation of abnormal glucose levels [101]. Variations in blood glucose levels can result in diminished levels of energy and heightened fatigue [88]. Through the monitoring of sweat glucose levels, individuals could acquire valuable insights into their glucose patterns, enabling them to detect potential causes of fatigue [100]. Effective management of stress and fatigue plays a pivotal role in enhancing the productivity of construction workers. The utilization of sweat glucose monitoring has the potential to offer immediate and continuous input regarding glucose levels in the context of construction tasks. This information can facilitate workers' comprehension of the physiological responses of their bodies to various task intensities, durations, and rest-break techniques. By adjusting their task schedule according to sweat glucose data, workers would have the potential to improve their productivity and reduce the risk of overexertion or injuries.

4.1.4. Other Sweat Biomarkers

In sweat, electrolytes such as sodium (Na), chloride (Cl), potassium (K^+), and ammonia (NH_4^+) are abundant. Maintaining electrolyte balance necessitates replenishing Na^+ and Cl^-

levels following a period of high-intensity exercise [102, 103]. Sweating rate and concentration (Na+) influence total Na+ loss from sweat [102]. Hence, calculating sweat Na+ loss is critical for speeding up fatigue recovery and reducing soft tissue damage caused by dehydration [104]. Sweating rate and total body sweating loss can be calculated using the equations published elsewhere [102]. Additionally, Baker and colleagues [105] devised a methodology to quantify the Na+ content in sweat from the forearm using absorbent patches taken from the forearm. Based on their findings, Matzeu et al. [106] hypothesized that athletes' "over time sodium profiles" could be generated by monitoring changes in Na+ levels as sweat made its way into contact with the sensor.

Given that ammonium is formed in the blood because of the breakdown of proteins [107], measuring plasma ammonium levels can provide extremely valuable physiological information [108]. For example, during exercise, the concentration of ammonium changes when the body transitions from aerobic to an anaerobic state [109]. However, ammonium in plasma can only be monitored by taking blood samples, which is a major drawback when exercising or engaging in other physical activity [108]. Several studies have shown that ammonium concentrations in sweat can be strongly associated with ammonium levels in plasma [110, 111], which is why sweating is a good way to monitor ammonium levels. Czarnowski and colleagues [111] investigated the association between ammonia levels in plasma and ammonium concentrations in sweat. They believe that ammonia in plasma is the primary source of ammonium in sweat. Ammonium production via sweating during physical activity such as jogging has been studied, and the researchers concluded that the difference in nitrogen loss between the two mechanisms was negligible [112]. It has been shown that ammonium is secreted through sweat after short-term activity at the commencement of sweating [111]. A study by Yuan and colleagues [113] found that a one-year training programme had a unique effect on the ammonia threshold, which was associated with endurance time. Also, research on rugby players found that ammonium levels in their sweat rose significantly while they were playing the game [114]. This was also linked to an increase in blood ammonia levels that was roughly three times greater than before. Another study found that when a participant increases the workload after beginning to sweat, the levels of ammonium in the sweat rise [108]. Because of this, the amount of ammonium in sweat can be used as a biomarker. This gives very useful information in a wide range of situations, such as when a person is switching from aerobic to anaerobic exercise or when they are measuring their physical performance.

Likewise, muscle activity is predicted by potassium (K+) concentrations in plasma, which can be used as a biomarker to detect muscle fatigue [115]. The electrical activity of the muscles involved in exercise can explain the increase in K+ concentration during exercise [115]. The rate at which K+ is excreted is directly related to the intensity of activity. To remove K+ from the circulation, this proportional regulator, which may be a sodium-potassium pump in the exercising muscle, is responsible [115]. The rate of absorption of extracellular K+ is related to the pump stimulus, and the rate of extracellular accumulation in the extracellular space is related to the rate of absorption [115]. A correlation between sweat K+ loss and the rate of sweat flow has been established, but its underlying mechanism is still unknown and needs additional investigation [116]. Despite this, final sweat often has a K+ that is like, albeit with a slightly greater range (~ 2–8 mmol/L), that of blood plasma, which has been recorded [102]. To quantify and assess the intensity of the workload and the level of fatigue, the measurement of K+ levels could be quite beneficial [34].

4.2. Sweat-based wearable biosensors

The general population is becoming interested in smartwatches [117], wearable fitness trackers [118], and smart, at-home health services [119,120]. Photoplethysmography is one of the most widely used techniques for measuring real-time stress and fatigue [121]. Other techniques include heart rate variability [122], as well as respiratory signal and ECG data [123].

These signals are linked to a stress response, but they do not generate it; rather, they represent the physiological impact of stress and fatigue biomarkers released in the body. As a result, biomarker detection could be a more precise means of detecting stress and fatigue. People are working on making devices that can measure stress and fatigue more accurately by detecting specific biomarkers of stress and fatigue. These devices will be able to provide useful, concrete data by detecting specific stress and fatigue biomarkers accurately.

Innovative, non-invasive, sweat-based sensors for stress and fatigue biomarker monitoring have been developed. Wearable sweat sensors have seen a tenfold rise in development and research in the last few years [124]. Medical researchers are still attempting to find out how biomarkers in sweat may be used to monitor our health, but their potential is undeniable [125]. The amount of several molecular markers in sweat was found comparable to the amount seen in human blood plasma [126].

4.2.1. Biosensors for sweat cortisol

Biosensors have previously been used to assess a wide range of biomarkers such as cortisol, dopamine, neuropeptide Y, and interleukin-6 in stress and cognition [127-129]. For the non-invasive detection of cortisol, Parlak et al. [130] developed a multi-layered organic electrochemical sensor. Cortisol may be detected using a combination of biomimetic polymeric membranes and an electrochemical transistor [63,65131,132]. Cortisol levels may be monitored by spraying artificial sweat on the forearms, and real-time testing of the device during exercise proved its efficacy [131,132]. Using wearable sensors to examine stress and fatigue biomarkers could provide a way to keep tabs on these issues [133]. For instance, skin patch sensors based on porous Ultra-High Molecular Weight Polyethylene (UHMWPE) nanomembranes have recently been introduced by Oktavius et al. [63] to detect muscle fatigue by measuring sweat biomarkers, mainly cortisol hormone. The patch was able to detect sweat cortisol, which is a reliable predictor of sports fatigue based on their experimental results, which showed that the cortisol level increases with increasing exercise intensity. In another work, Torrente-Rodriguez et al. [65] used an integrated wireless sensing device to explore the dynamics of the stress hormone cortisol in human sweat. Their findings showed that there is a high link between sweat and circulating cortisol, as well as a rapid reaction to acute stress events. From the commencement of sweat (10 minutes) through the end of the activity (50 minutes), cortisol levels in pre- and post-exercise serum samples show a strong association [65]. The sweat hormone profiles of untrained individuals were like those reported following high-intensity exercise [134]. The trained subject, on the other hand, shows a reduced cortisol response because of exercise-induced adaptation [65]. According to prior research, trained individuals may perceive the given workload as a lesser stressor and display decreased activation in response to physical [135] and psychosocial stimuli [136]. Therefore, Torrente-Rodriguez et al. [65] concluded that a flexible sensor array that takes advantage of laser-induced graphene's outstanding electrochemical sensing capability allowed for highly sensitive, selective, and efficient cortisol sensing. More recently, a flexible and wearable cortisol aptasensor for real-time monitoring of cortisol was presented by An et al. [131]. The sensor was found to have stable and consistent electrical features such as ohmic behavior, a transition curve, and a signal intensity that was proportionate to the concentration. The sensitivity (10 pM) and selectivity (> 90%) of the electrode-type sensor were the most notable advantages. A saliva-sweat association is critical for future sweat-based wearable application research because it allows researchers to use already existing salivary biomarker knowledge [137, 138]. Consequently, saliva and sweat were compared by Wang et al. [132]. The correlation between salivary and sweat cortisol levels was 0.73, which supports the idea that salivary and sweat cortisol levels are related.

In contrast, most devices described in the commercial and scientific literature for real-time stress and fatigue detection have not yet been tested in clinical trials [139]. It is important to make multi-modal sensors that include physiological parameters (like heart rate, sleep, and/or skin conductivity), biochemical markers, and clinical validation in non-stationary conditions so that stress levels can be measured accurately. This will help people get the most out of their performance, recovery, and health. The distinction between physical and mental stress remains an unmet medical need, as does a better understanding of the physical and mental demands placed on individuals.

4.2.2. Biosensors for sweat lactate

Likewise, lactate concentrations in the blood closely resemble those in the sweat, which indicates the level of physical exertion and the intensity of the exercise [140]. For example, screen-printed lactate biosensors with three electrodes and two electrodes for ECG were used to make a hybrid epidermal wearable device that could simultaneously monitor lactate and heart activity at the same time [83]. A hydrophobic coating was used to improve the impedance between the amperometric electrodes and the ECG, preventing sensor crosstalk. Physicochemical and electrophysiological measurements were made possible with this wearable gadget thanks to the inclusion of both types of sensors on the same piece of equipment. The simultaneous lactate detection of the ECG had no effect, according to real-time monitoring as compared to current wearable technologies. As the intensity of the activity grew, so did the lactate levels record by the biosensor, which matched the estimated sweat-lactate profile. Continuous monitoring of stress and fatigue may be substantially enhanced by converting this device into a wearable. In another investigation, lactate was measured using a flexible and wearable patch [79]. Sweat was transported using a microfluidic tube equipped with an array of microneedle-type sensors (50 μm in diameter). For the amperometric-based lactate sensor, enzymes were doped and placed on top of a semipermeable copolymer membrane with an outer polyurethane layer on top. The 180 μm thick patch was attached to the skin of six healthy volunteers before cycling and running using a double-layered adhesive. As a result of thermoregulation, sweating began 10–15 minutes into the warm-up phase. Exercise-induced rises in lactate show a shift towards anaerobic metabolism. Recently, Saha et al. [78] created an innovative sweat sampling patch that uses hydrogel discs and paper microfluidic channels to extract sweat over an extended period. During periods of inactivity, the hydrogel disc can collect moisture from the skin by osmosis and transmit it to the paper. Even without the hydrogel patch, the paper can collect sweat during active sweating (e.g., exercise). Colorimetric assays are used to measure lactate in the collected fluid. The sweat rate was connected to the amount of lactate excreted in the sweat. High-intensity exercise improves the correlation between sweat and blood lactate concentrations. In addition, the in-situ detection of lactate content in human sweat was accomplished by Huang et al. [84] using a newly invented epidermal, stretchable, self-powered biosensor. Stretchable electronics, a microfluidic system, and biosensors work together in harmony to give the self-powered sweat sensing instrument remarkable sweat collection and sensing accuracy even when stretched to its limits. Measuring lactate levels in people shows that the proposed biosensor could be used for wearable sweat sensing and healthcare monitoring, indicating the potential of the sensor.

4.2.3. Biosensors for sweat glucose

It is critical to keep an eye on blood glucose levels when exercising or doing physical work to avoid becoming overly fatigued [92]. Abellan Llobregat et al. [141] described the development of a sweat glucose-detecting sensor based on printable and highly stretchy platinum (Pt)-decorated graphite. Glucose oxidase immobilized on Pt-decorated graphite was used to monitor the reduction of hydrogen peroxide using chronoamperometry. Based on results obtained with commercial glucose meters, this sensor worked well with human sweat samples to show a high link between sweat glucose concentrations and blood glucose concentrations. Sensors for glucose monitoring were printed using flexible, tattoo-based sensors [142]. Interstitial glucose was extracted through reverse iontophoretic extraction, and an enzyme-based amperometric biosensor was used. Glucose and lactate can be detected using a microfluidic epidermal device developed by Martin et al. [143]. Adhesives on both sides of the double-sided polydimethylsiloxane layers make up the structure of the biosensor. Microfluidic passages (inlets and outlets), as well as a reservoir for the detection process, were contained in both layers of polydimethylsiloxane. As the wearer repeatedly deformed the biosensor, the sweat was sent to the electrochemical sensor, and the biosensor remained attached to the sweat pores of the skin. During a 20-minute bout of indoor cycling, the sweat glucose levels of two healthy human individuals were monitored in real-time on their bodies. During the continuous monitoring of the amperometric sweat glucose response from the subjects, a rise in the current signal was seen when a sample of sweat went into and filled the reservoir of the glucose oxidase-modified flow detector. In another study, Emaminejad et al. [144] tested a wearable device for noninvasive glucose monitoring and real-time sweat stimulation on a group of participants who participated in both fasting and post-glucose intake trials. According to the wearable, oral glucose ingestion increased glucose levels in both sweat and blood in subjects who were fasting. In addition, Huang et al. [84] used a newly designed epidermal, stretchable, self-powered biosensor to measure glucose concentration in human sweat in situ. In combination with stretchable electronics and a microfluidic system, biosensors enable self-powered sweat sensing equipment to gather sweat with astonishing precision, regardless of how far it is stretched. Based on how people measure their glucose levels, the proposed biosensor can be used for wearable sweat sensing and healthcare monitoring.

4.2.4. Biosensors for other sweat biomarkers

Furthermore, epidermal sensors have been used to detect several electrolytes in the literature. Bandodkar et al. [145] successfully developed and tested an epidermal tattoo potentiometric sodium sensor for uninterrupted, noninvasive monitoring of sodium excreted in sweat. There was no interference in analyte detection or wireless transmission using screen-printed devices, indicating their potential for use during physical activity [145]. The Na+ electrochemical amperometric sensor was developed by researchers in another study, and it is characterized as being flexible and wearable [146]. The sensor was built using a nylon-6 mat made from multiwall carbon nanotubes (MWCNTs). To produce supramolecular complexes with sodium ions, the MWCNTs were functionalized with cyclo-oligomeric calixarene. After the complex was formed, the charge carriers moved out of the layer to stop the flow of electricity. In this way, sodium ions might be detected at the correct level in the body. Additionally, a solid-contact ion-selective electrode and a liquid-junction-free reference electrode were used to detect sodium in sweat [106]. To collect sweat samples, the potentiometric strips were coupled to a passive pump via a microfluidic chip (PotMicroChip). The system was attached to a 3D-printed enclosure that contained a miniature wireless communication system. During stationary cycling sessions, the sodium concentrations of healthy volunteers were continuously monitored using the gadget. It is possible to compare these results to those of current analytical procedures using techniques like ion chromatography, atomic absorption, and commercial sodium meters (e.g., AquaTwinTM) [106]. Similarly, it has also been designed and tested as a completely integrated and wearable platform for the collection and analysis of sweat sodium concentration in real-time during exercise [147]. The platform was fabricated in significant part utilizing 3D-printing, which greatly simplifies the process of construction and operation. Because of the 3D-printed platform, the sample storage reservoir has been increased from 0.6 to 1.3 mL, assembly time has been reduced, and alignment and contact of the integrated solid-state ion-selective and reference electrodes with the sorbent material have been made simple. The platform was tested in the lab and during exercise trials, which lasted around 60 minutes with continuous monitoring and recording. According to the findings, the sodium content in sweat increased first to roughly 17 mM and then decreased progressively throughout the trial to approximately 11–12 mM. Also recently created by Alizadeh and colleagues [148], a wireless sweat monitoring device provides a unique combination of user comfort, good accuracy, and continuous, non-obtrusive sweat electrolyte monitoring over an extended period of time. This system is composed of two modules: a disposable sensor/microfluidics module that is extremely flexible and a reusable electronics module that is durable. This makes it extremely adaptable and suitable for continuous Na^+ and K^+ measurement in sports or other physiological applications. Researchers have also used a fluorometric technique to detect Na^+ and Cl^- from excrine sweat collected in a wearable microfluidic system with an imaging module for smartphones [149]. A smartphone equipped with an optics module observed variations in fluorescence excitation intensity as a result of the interaction of the microreservoir probes with the specific ions. For human participants engaged in physical activity, the ion concentrations measured with this platform were identical to those obtained using more standard laboratory procedures like ion chromatography for Cl^- and atomic absorption for Na^+. It is possible that microfluidics, rather than the current sweat patches, could provide significant advantages in measuring sweat rate and hydration levels. Additionally, a wearable sweat analysis platform was developed by Emaminejad et al. [144], which included an electrochemically improved iontophoresis interface that was integrated with the platform. A variety of secretion profiles, including Na^+ and Cl^-, can be programmed into this interface to generate sweat for real-time study. Human-subject studies were conducted in the context of cystic fibrosis diagnosis in order to establish the clinical utility of this platform. Using this technology, they were able to detect the increased electrolyte content in the sweat of cystic fibrosis patients as compared to healthy control individuals.

Guinovart et al. [108] made and tested a new potentiometric cell that could be used to monitor ammonium levels in sweat. This skin-worn sensor can be made using a screen-printed design and all-solid-state potentiometric sensors for both the working and reference electrodes. It also has a polymer membrane that is ammonium-selective because it is made of the nonactin ionophore. The tattooed potentiometric sensor has a working range of between 104 M and 0.1 M, which is close to the amount of ammonium in sweat that is normal. Using screen-printed technology, epidermal integration, and potentiometric sensing is a good way to keep track of a wide range of electrolytes in human sweat without having to be invasive. Also, Renner et al. [150] conducted ammonium measurements in blood and sweat during a stepwise incremental cycle ergometer test on 40 participants under controlled conditions in order to evaluate the relationship between ammonium concentrations in blood and sweat. Aside from that, blood lactate and heart rate were monitored to guarantee that the recorded quantities could be categorized appropriately. It was shown that while the blood ammonium concentration corresponded to the commonly acknowledged levels of physical fatigue, the sweat ammonium concentration appeared to decrease with physical exertion. This may be due to the dilution effects, which occur as the rate of sweat rises [40,85]. As a result, they suggested that wearable technologies will greatly benefit from this research since it sheds light on the relationship between blood and sweat parameters.

4.3. Sweat sensing approach

Understanding the complex chemical composition and physical properties of sweat can provide valuable insights into human health issues in a variety of situations, including stress and fatigue. Chemically related devices are commonly used in the majority of sweat biosensing. Numerous research studies have investigated the relationship between the quantities of chemical components in the environment and human health states in depth. For example, during activity, the salt and chloride concentrations in sweat can represent the amount of water lost by the human body through the skin [151,152]. It has been extensively researched to determine the concentration of cortisol, popularly known as the "stress" hormone, in sweat in order to continuously monitor the mental condition of subjects [65,153]. It has been created using electrochemical, colorimetric, and hybrid chemical sensing approaches to measure the amounts of these chemical components in sweat. This subsection primarily discusses new technologies and how they can be used in chemical sensing.

4.3.1. Electrochemical sweat sensors

It has been proven that biomarkers in sweat alter dynamically in response to factors such as health, stress, and food [154]. The monitoring of sweat biomarkers in real-time is critical. Electrochemical sensors connected to the skin that use conductometric, amperometric [79,83], potentiometric [93,106,108,144,155], and voltimetric measurement techniques can be used to constantly monitor analytes in sweat [151,156]. It is possible to establish a proportionate link between analyte concentrations and electrical signals with high specificity and rapid response times while using only a small amount of power. Thus, tiny sensor designs that are suitable for wearable platforms can be developed, which can communicate data to an external personal device assistant (such as a smartphone or smartwatch) for real-time sweat analysis. For example, a new solid-state tattoo potentiometric cell was developed by Guinovart et al. [108] using screen-printed technology on a temporary transfer tattoo to detect ammonium (NH4+) in sweat. Polyvinyl butyral (PVB) solid-state reference membranes are improved in this cell design, which is employed during the wearable device's rest period. Similar to potentiometric electrodes, their sensor was able to detect NH4+ in sweat at physiological levels with comparable performance. Additionally, Bariya et al. [93] developed an electrode with roll-to-roll gravure printing that can handle a variety of electrochemical sensing tasks. They print devices with homogeneous redox kinetics on 150-meter-long flexible substrate rolls using inks and electrode morphologies designed for electrochemical and mechanical durability. Using these electrodes, the researchers showed that they can be used to make sensors that consistently do a good job of detecting ions, metabolites, heavy metals, and other small molecules in biofluids that can be accessed without harming the body.

4.3.2. Colorimetric sweat sensors

Elastomeric substrates with microfluidic channels placed in them can be used to collect and store sweat, which can then be used for various purposes. Combining colorimetric [157,158] and fluorescence [149,159] tests allow for the quantitative analysis of interest sweat constituents. When sweat is routed to discrete chambers, sweat components interact with specific chemical reagents to produce a distinct optical signal corresponding to a target analyte concentration. By utilizing the natural pressure that sweat glands produce, it is possible to quantify sweat rate. This sort of instrument is used to determine the concentration of a target analyte in a sample. A smartphone-based image capture and color-based processing method have recently been shown to be useful for measuring sweat chloride, pH, lactate, glucose, urea, and creatinine, among other substances [142,149,158-160].

4.3.3. Hybrid sweat sensors

Wearable sensors that combine optical and electrochemical sensing technologies in a single analytical platform [161] can now measure biomarkers like cortisol, ascorbic acid, glucose, and sweat rate wirelessly and without batteries. This can be done continuously or as a one-time check. Colorimetric lateral flow immunoassays for cortisol, fluorescence assays for ascorbic acid and glucose, and impedance-based sensors for sweat rate and galvanic skin reactions are used in this dual sensing technique. Field testing shows that these features may be used to track physiological parameters related to physical and mental stress over many days in the real world. This type of hybrid technique has the potential to provide long-term continuous and intermittent monitoring of physiological indicators and situations. For instance, Imani et al. [83] developed a wearable device that can assess chemical and electrophysiological data at the same time using a single epidermal patch. There are two electrocardiogram (ECG) electrodes, and a three-electrode amperometric lactate biosensor are combined in a hybrid wearable, allowing for simultaneous real-time readings of lactate and ECG. The ECG measures can be used in physical exertion monitoring to monitor heart health and function, while sweat lactate measurements can be utilized to assess an individual's performance and exertion level. Due to its dual-sensor design, the hybrid wearable patch can monitor a person's electrophysiology as well as their physicochemical state. This gives them a more complete picture of their overall health than current wearable fitness monitors can provide on their own.

4.4. Challenges and limitations of wearable biosensors for monitoring sweat biomarkers

Sweat-based biomarker monitoring via wearable biosensors presents several challenges and limitations. First, the task of establishing an accurate correlation between biomarkers found in sweat and certain health problems or physiological parameters poses a considerable challenge. The investigation into the correlation between specific biomarkers and health outcomes is still ongoing, and the analysis of sweat biomarker information is frequently complex and inconsistent [148]. Second, the task of attaining a high level of accuracy and sensitivity in the measurement of sweat biomarkers presents significant challenges. The concentrations of sweat biomarkers exhibit significant inter-individual variability and can also demonstrate intra-individual variation over time [162]. One of the challenges in the field of wearable biosensors is ensuring the correct detection and quantification of biomarkers throughout a broad spectrum of concentrations [163]. Third, the process of calibrating wearable biosensors for each individual and defining personalized thresholds might present a significant level of complexity. The need for personalized calibration and adaptation of algorithms arises from the variability in sweat composition, flow rate, and other relevant parameters [164]. This process can be labor-intensive and necessitates regular recalibration. Fourth, the process of collecting and preserving perspiration for study poses many difficulties. Environmental factors that affect sweat generation and evaporation rates might have an impact on the accuracy and consistency of readings [79]. It is imperative to establish optimal contact between the sensor and the skin to promote the collection of perspiration without any disruption [165]. Fifth, the analysis and interpretation of the substantial volume of data produced by wearable biosensors pose a multifaceted challenge. The development of efficient algorithms and machine learning models for data processing and the extraction of significant insights necessitate the utilization of sophisticated computational methodologies and specialized knowledge [166]. Lastly, the success of wearable biosensors heavily relies on users' acceptability and compliance [8]. Various factors, including the level of comfort, user-friendliness, and perceived value of the health information offered, can significantly impact the extent to which users embrace and continue to use a particular product or service. Considering the issues of users and developing gadgets that are easy to use are crucial factors to consider. The limitations and obstacles underscore the complex nature of sweat-based biomarker monitoring through the utilization of wearable biosensors. To overcome these challenges, it is imperative to engage in continuous research, foster technical progress, and promote multidisciplinary cooperation among specialists in the fields of sensor development, data analysis, and healthcare.

5. LIMITATIONS AND FUTURE RESEARCH DIRECTIONS

There are certain limitations to the current review. It is important to note that most of the articles included in this review used extremely small samples. Only a few of the reviewed studies include demographic information on the participants. Studies included in this review, for example, only looked at healthy young individuals, so it is unclear if these metrics are still valid for stress and fatigue detection with sweat biosensors in healthy older adults. While nine of the included articles said that the current sweat sensors would take between 1 and 20 minutes to begin recording data, other studies did not provide any information on how long it would take for the data to be collected. Lastly, most of the articles included in this review primarily utilized laboratory methods to demonstrate that sweat biosensors could measure stress and fatigue in real-time.

Despite these limitations, the current review provides essential information for future relevant research projects that will involve the design and implementation of wearable biosensors for monitoring stress and fatigue by using sweat biomarkers. It is necessary to do additional research to validate the use of biosensors that analyze sweat biofluids to identify stress and fatigue. To do so, an investigation must be carried out in greater depth. If the presented data were interpreted and utilized appropriately, it would be possible to construct more advanced biosensors capable of detecting a variety of biomarkers, such as lactate, cortisol, glucose, and electrolytes. This will make it possible to build more advanced biosensors capable of detecting a variety of biomarkers. Also, the results of this review could provide a substantial basis for developing a good method for using sweat biomarkers to monitor stress and fatigue in real-time.

6. CONCLUSION

The current review summarizes the findings of an evaluation of wearable biosensors for real-time monitoring of stress and fatigue using sweat biomarkers. For this review, systematic search strategies were utilized to gather relevant data and critically evaluate the use of different sweat biomarkers in the measurement of stress and fatigue. Sweat biomarkers such as lactate, cortisol, glucose, and electrolytes were commonly used to assess stress and fatigue. Potentiometric and amperometric biosensors are frequently used to detect sweat-based biomarkers in real-time. Biosensors that are worn on the skin, such as an epidermal patch or a sweatband, have been validated in scientific literature.

The use of sweat as a non-invasive method of acquiring individualized biological information is becoming more popular. It is becoming increasingly common to use biosensors to measure a wide range of sweat biomarkers to detect and prevent fatigue during high-intensity industries, such as construction. Although wearable biosensors have been validated for monitoring several sweat biomarkers, direct evaluation of stress and fatigue using such biomarkers is still limited. Therefore, further research and testing are required before any firm conclusions can be drawn. Additionally, sample integrity must be ensured during a monitoring period, and this is a major challenge. Movement artefacts can cause a great deal of noise, especially if the sensor platform moves or lifts temporarily from the skin and air enters the fluidic system. The high number of biomarkers that can be reliably detected in sweat biofluid is expected to grow in the future as technology advances. Therefore, this could improve the clinical usability of the tool as well as provide reliable diagnostic or screening tools for stress and fatigue assessment, ultimately improving the health and safety of workers on the job site. In short, this review study may provide opportunities for academics and practitioners to expand the use of wearable biosensors for monitoring sweat-based chemical biomarkers for the real-time assessment of stress and fatigue.

References

1. Watanabe N, Stewart R, Jenkins R, Bhugra DK, Furukawa TA. The epidemiology of chronic fatigue, physical illness, and symptoms of common mental disorders: a cross-sectional survey from the second British National Survey of Psychiatric Morbidity. Journal of psychosomatic research. 2008 Apr 1;64(4):357-62.
2. Ng ST, Tang Z. Labour-intensive construction sub-contractors: Their critical success factors. International journal of project management. 2010 Oct 1;28(7):732-40.

3. Ricci JA, Chee E, Lorandeau AL, Berger J. Fatigue in the US workforce: prevalence and implications for lost productive work time. Journal of occupational and environmental medicine. 2007 Jan 1:1-0.
4. Rosa RR. Long work hours, fatigue, safety, and health. InThe Handbook of Operator Fatigue 2017 Nov 1 (pp. 335-348). CRC Press.
5. Abdelhamid TS, Everett JG. Physiological demands during construction work. Journal of construction engineering and management. 2002 Oct;128(5):427-37.
6. Hallowell MR. Worker fatigue: Managing concerns in rapid renewal highway construction projects. Professional safety. 2010 Dec 1;55(12):18-26.
7. Sluiter JK. High-demand jobs: age-related diversity in work ability? Applied ergonomics. 2006 Jul 1;37(4):429-40.
8. Anwer S, Li H, Antwi-Afari MF, Umer W, Wong AY. Evaluation of physiological metrics as real-time measurement of physical fatigue in construction workers: state-of-the-art review. Journal of Construction Engineering and Management. 2021 May 1;147(5):03121001.
9. Yu Y, Umer W, Yang X, Antwi-Afari MF. Posture-related data collection methods for construction workers: A review. Automation in Construction. 2021 Apr 1;124:103538.
10. Umer W, Antwi-Afari MF, Li H, Szeto GP, Wong AY. The prevalence of musculoskeletal symptoms in the construction industry: a systematic review and meta-analysis. International archives of occupational and environmental health. 2018 Feb;91:125-44.
11. Edwards R. Human Muscle Function and Fatigue Human Muscle Fatigue. Physiological Mechanisms, London. 1981;8.

12. Boksem MA, Tops M. Mental fatigue: costs and benefits. Brain research reviews. 2008 Nov 1;59(1):125-39.
13. Boksem MA, Meijman TF, Lorist MM. Effects of mental fatigue on attention: an ERP study. Cognitive brain research. 2005 Sep 1;25(1):107-16.
14. Gawron VJ, French J, Funke D. An overview of fatigue. Stress, workload, and fatigue. 2000 Nov 1:581-95.
15. Frone MR, Tidwell MC. The meaning and measurement of work fatigue: Development and evaluation of the Three-Dimensional Work Fatigue Inventory (3D-WFI). Journal of occupational health psychology. 2015 Jul;20(3):273.
16. Shortz AE, Mehta RK, Peres SC, Benden ME, Zheng Q. Development of the fatigue risk assessment and management in high-risk environments (FRAME) survey: A participatory approach. International journal of environmental research and public health. 2019 Feb;16(4):522.
17. Lerman SE, Eskin E, Flower DJ, George EC, Gerson B, Hartenbaum N, Hursh SR, Moore-Ede M. Fatigue risk management in the workplace. Journal of Occupational and Environmental Medicine. 2012 Feb 1;54(2):231-58.
18. Hwang S, Seo J, Jebelli H, Lee S. Feasibility analysis of heart rate monitoring of construction workers using a photoplethysmography (PPG) sensor embedded in a wristband-type activity tracker. Automation in construction. 2016 Nov 1;71:372-81.
19. Umer W, Li H, Szeto GP, Wong AY. Identification of biomechanical risk factors for the development of lower-back disorders during manual rebar tying. Journal of Construction Engineering and Management. 2017 Jan 1;143(1):04016080.
20. Anwer S, Li H, Antwi-Afari MF, Umer W, Mehmood I, Al-Hussein M, Wong AY. Test-retest reliability, validity, and responsiveness of a textile-based wearable sensor

for real-time assessment of physical fatigue in construction bar-benders. Journal of Building Engineering. 2021 Dec 1;44:103348.

21. Antwi-Afari MF, Anwer S, Umer W, Mi HY, Yu Y, Moon S, Hossain MU. Machine learning-based identification and classification of physical fatigue levels: A novel method based on a wearable insole device. International Journal of Industrial Ergonomics. 2023 Jan 1;93:103404.
22. Michael DJ, Daugherty S, Santos A, Ruby BC, Kalns JE. Fatigue biomarker index: An objective salivary measure of fatigue level. Accident Analysis & Prevention. 2012 Mar 1;45:68-73.
23. Ament W, Verkerke GJ. Exercise and fatigue. Sports medicine. 2009 May;39:389-422.
24. Cannon JG, Fielding RA, Fiatarone MA, Orencole SF, Dinarello CA, Evans WJ. Increased interleukin 1 beta in human skeletal muscle after exercise. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 1989 Aug 1;257(2):R451-5.
25. Cannon JG, Kluger MJ. Endogenous pyrogen activity in human plasma after exercise. Science. 1983 May 6;220(4597):617-9.
26. Klein LC, Corwin EJ. Seeing the unexpected: how sex differences in stress responses may provide a new perspective on the manifestation of psychiatric disorders. Current psychiatry reports. 2002 Nov;4(6):441-8.
27. Zhang X, Li J, Liu Y, Zhang Z, Wang Z, Luo D, Zhou X, Zhu M, Salman W, Hu G, Wang C. Design of a fatigue detection system for high-speed trains based on driver vigilance using a wireless wearable EEG. Sensors. 2017 Mar 1;17(3):486.
28. Zhou X, Yao D, Zhu M, Zhang X, Qi L, Pan H, Zhu X, Wang Y, Zhang Z. Vigilance detection method for high-speed rail using wireless wearable EEG collection

technology based on low-rank matrix decomposition. IET Intelligent Transport Systems. 2018 Oct;12(8):819-25.

29. Hu S, Zheng G, Peters B. Driver fatigue detection from electroencephalogram spectrum after electrooculography artefact removal. IET Intelligent Transport Systems. 2013 Mar;7(1):105-13.
30. Sikander G, Anwar S. Driver fatigue detection systems: A review. IEEE Transactions on Intelligent Transportation Systems. 2018 Oct 5;20(6):2339-52.
31. Hu X, Lodewijks G. Detecting fatigue in car drivers and aircraft pilots by using non-invasive measures: The value of differentiation of sleepiness and mental fatigue. Journal of safety research. 2020 Feb 1;72:173-87.
32. Adão Martins NR, Annaheim S, Spengler CM, Rossi RM. Fatigue monitoring through wearables: A state-of-the-art review. Frontiers in physiology. 2021 Dec 15;12:2285.
33. Balkin TJ, Horrey WJ, Graeber RC, Czeisler CA, Dinges DF. The challenges and opportunities of technological approaches to fatigue management. Accident Analysis & Prevention. 2011 Mar 1;43(2):565-72.
34. Seshadri DR, Li RT, Voos JE, Rowbottom JR, Alfes CM, Zorman CA, Drummond CK. Wearable sensors for monitoring the physiological and biochemical profile of the athlete. NPJ digital medicine. 2019 Jul 22;2(1):72.
35. Mohan AV, Rajendran V, Mishra RK, Jayaraman M. Recent advances and perspectives in sweat based wearable electrochemical sensors. TrAC Trends in Analytical Chemistry. 2020 Oct 1;131:116024.
36. Xu J, Fang Y, Chen J. Wearable biosensors for non-invasive sweat diagnostics. Biosensors. 2021 Jul 23;11(8):245.
37. Qiao Y, Qiao L, Chen Z, Liu B, Gao L, Zhang L. Wearable sensor for continuous sweat biomarker monitoring. Chemosensors. 2022 Jul 12;10(7):273.

38. Wickens CD, Gordon SE, Liu Y, Lee J. An introduction to human factors engineering. Upper Saddle River, NJ: Pearson Prentice Hall; 2004.
39. Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology. 2009 Feb 1;34(2):163-71.
40. Gao W, Emaminejad S, Nyein HY, Challa S, Chen K, Peck A, Fahad HM, Ota H, Shiraki H, Kiriya D, Lien DH. Fully integrated wearable sensor arrays for multiplexed in situ perspiration analysis. Nature. 2016 Jan 28;529(7587):509-14.
41. Hargreaves M, Spriet LL. Skeletal muscle energy metabolism during exercise. Nature metabolism. 2020 Sep;2(9):817-28.
42. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Moher D. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. Journal of clinical epidemiology. 2021 Jun 1;134:103-12.
43. Xu YL, ZHAO CX, XI AP, DING M, LI Y, JIANJUN H, SU XH, LIU FL, WANG JZ, LIU ZJ, GONG YN. Discovery and identification of fatigue-related biomarkers in human saliva. European Review for Medical & Pharmacological Sciences. 2018 Dec 1;22(23).
44. Li R, Su W, Lu Z. Physiological signal analysis for fatigue level of experienced and inexperienced drivers. Traffic injury prevention. 2017 Feb 17;18(2):139-44.
45. Hecksteden A, Skorski S, Schwindling S, Hammes D, Pfeiffer M, Kellmann M, Ferrauti A, Meyer T. Blood-borne markers of fatigue in competitive athletes–results from simulated training camps. PloS one. 2016 Feb 18;11(2):e0148810.
46. Dutheil F, Trousselard M, Perrier C, Lac G, Chamoux A, Duclos M, Naughton G, Mnatzaganian G, Schmidt J. Urinary interleukin-8 is a biomarker of stress in

emergency physicians, especially with advancing age—The JOBSTRESS* randomized trial. PloS one. 2013 Aug 19;8(8):e71658.

47. Yamaguchi M, Deguchi M, Wakasugi J, Ono S, Takai N, Higashi T, Mizuno Y. Hand-held monitor of sympathetic nervous system using salivary amylase activity and its validation by driver fatigue assessment. Biosensors and Bioelectronics. 2006 Jan 15;21(7):1007-14.
48. Adam EK, Hawkley LC, Kudielka BM, Cacioppo JT. Day-to-day dynamics of experience–cortisol associations in a population-based sample of older adults. Proceedings of the National Academy of Sciences. 2006 Nov 7;103(45):17058-63.
49. Xu Y, Xiao D, Zhang H, He L, Gu Y, Peng X, Gao X, Liu Z, Zhang J. A prospective study on peptide mapping of human fatigue saliva markers based on magnetic beads. Experimental and Therapeutic Medicine. 2019 Apr 1;17(4):2995-3002.
50. Zhang G. Neurotransmitter biomarkers. Targeted Biomarker Quantitation by LC–MS. 2017 Aug 4:357-70.
51. Calderón-Santiago M, Priego-Capote F, Jurado-Gámez B, de Castro ML. Optimization study for metabolomics analysis of human sweat by liquid chromatography–tandem mass spectrometry in high resolution mode. Journal of chromatography A. 2014 Mar 14;1333:70-8.
52. Nunes MJ, Cordas CM, Moura JJ, Noronha JP, Branco LC. Screening of potential stress biomarkers in sweat associated with sports training. Sports medicine-open. 2021 Dec;7(1):1-9.
53. Raiszadeh MM, Ross MM, Russo PS, Schaepper MA, Zhou W, Deng J, Ng D, Dickson A, Dickson C, Strom M, Osorio C. Proteomic analysis of eccrine sweat: implications for the discovery of schizophrenia biomarker proteins. Journal of proteome research. 2012 Apr 6;11(4):2127-39.

54. Sato KE, Leidal RE, Sato F. Morphology and development of an apoeccrine sweat gland in human axillae. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 1987 Jan 1;252(1):R166-80.
55. Sternberg EM, Jia M, inventors; Arizona Board of Regents of University of Arizona, assignee. Stress biomarkers and related non-invasive detection methods. United States patent US 10,996,205. 2021 May 4.
56. Jessop DS, Turner-Cobb JM. Measurement and meaning of salivary cortisol: a focus on health and disease in children. Stress. 2008 Jan 1;11(1):1-4.
57. Kudielka BM, Hellhammer DH, Wüst S. Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. Psychoneuroendocrinology. 2009 Jan 1;34(1):2-18.
58. Russell E, Koren G, Rieder M, Van Uum SH. The detection of cortisol in human sweat: implications for measurement of cortisol in hair. Therapeutic drug monitoring. 2014 Feb 1;36(1):30-4.
59. Jia M, Chew WM, Feinstein Y, Skeath P, Sternberg EM. Quantification of cortisol in human eccrine sweat by liquid chromatography–tandem mass spectrometry. Analyst. 2016;141(6):2053-60.
60. Isaac A, Ibrahim Y, Andrew A, Edward D, Solomon A. The cortisol steroid levels as a determinant of health status in animals. J Proteomics Bioinform. 2017;10:277-83.
61. Kinnamon D, Ghanta R, Lin KC, Muthukumar S, Prasad S. Portable biosensor for monitoring cortisol in low-volume perspired human sweat. Scientific reports. 2017 Oct 17;7(1):13312.
62. Hooton K, Han W, Li L. Comprehensive and quantitative profiling of the human sweat submetabolome using high-performance chemical isotope labeling LC–MS. Analytical chemistry. 2016 Jul 19;88(14):7378-86.

63. Oktavius AK, Gu Q, Wihardjo N, Winata O, Sunanto SW, Li J, Gao P. Fully-conformable porous polyethylene nanofilm sweat sensor for sports fatigue. IEEE Sensors Journal. 2021 Jan 27;21(7):8861-7.
64. Parlak O, Keene ST, Marais A, Curto VF, Salleo A. Molecularly selective nanoporous membrane-based wearable organic electrochemical device for noninvasive cortisol sensing. Science advances. 2018 Jul 20;4(7):eaar2904.
65. Torrente-Rodríguez RM, Tu J, Yang Y, Min J, Wang M, Song Y, Yu Y, Xu C, Ye C, IsHak WW, Gao W. Investigation of cortisol dynamics in human sweat using a graphene-based wireless mHealth system. Matter. 2020 Apr 1;2(4):921-37.
66. Steckl AJ, Ray P. Stress biomarkers in biological fluids and their point-of-use detection. ACS sensors. 2018 Sep 28;3(10):2025-44.
67. Lee DY, Kim E, Choi MH. Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. BMB reports. 2015 Apr;48(4):209.
68. Doerr JM, Fischer S, Nater UM, Strahler J. Influence of stress systems and physical activity on different dimensions of fatigue in female fibromyalgia patients. Journal of Psychosomatic Research. 2017 Feb 1;93:55-61.
69. Wingenfeld K, Schulz M, Damkroeger A, Rose M, Driessen M. Elevated diurnal salivary cortisol in nurses is associated with burnout but not with vital exhaustion. Psychoneuroendocrinology. 2009 Sep 1;34(8):1144-51.
70. Sekar M, Sriramprabha R, Sekhar PK, Bhansali S, Ponpandian N, Pandiaraj M, Viswanathan C. Towards wearable sensor platforms for the electrochemical detection of cortisol. Journal of The Electrochemical Society. 2020 Mar 20;167(6):067508.
71. Parrilla M, De Wael K. Wearable self‐powered electrochemical devices for continuous health management. Advanced Functional Materials. 2021 Dec;31(50):2107042.

72. Smyth N, Rossi E, Wood C. Effectiveness of stress-relieving strategies in regulating patterns of cortisol secretion and promoting brain health. International review of neurobiology. 2020 Jan 1;150:219-46.
73. Gerding T, Wang J. Stressed at work: investigating the relationship between occupational stress and salivary cortisol fluctuations. International Journal of Environmental Research and Public Health. 2022 Sep 28;19(19):12311.
74. Derbyshire PJ, Barr H, Davis F, Higson SP. Lactate in human sweat: a critical review of research to the present day. The journal of physiological sciences. 2012 Nov;62(6):429-40.
75. Taylor NA, Machado-Moreira CA. Regional variations in transepidermal water loss, eccrine sweat gland density, sweat secretion rates and electrolyte composition in resting and exercising humans. Extreme physiology & medicine. 2013 Dec;2(1):1-30.
76. Onor M, Gufoni S, Lomonaco T, Ghimenti S, Salvo P, Sorrentino F, Bramanti E. Potentiometric sensor for non invasive lactate determination in human sweat. Analytica chimica acta. 2017 Oct 9;989:80-7.
77. Spurway NC. Aerobic exercise, anaerobic exercise and the lactate threshold. British Medical Bulletin. 1992 Jan 1;48(3):569-91.
78. Saha T, Fang J, Mukherjee S, Knisely CT, Dickey MD, Velev OD. Osmotically enabled wearable patch for sweat harvesting and lactate quantification. Micromachines. 2021 Dec 4;12(12):1513.
79. Seki Y, Nakashima D, Shiraishi Y, Ryuzaki T, Ikura H, Miura K, Suzuki M, Watanabe T, Nagura T, Matsumato M, Nakamura M. A novel device for detecting anaerobic threshold using sweat lactate during exercise. Scientific reports. 2021 Mar 2;11(1):4929.

80. Baker LB, Wolfe AS. Physiological mechanisms determining eccrine sweat composition. European journal of applied physiology. 2020 Apr;120:719-52.
81. Weiner JS, van Heyningen R. Lactic acid and sweat gland function. Nature. 1949 Aug 27;164(4165):351-2.
82. van Heyningen R, Weiner JS. A comparison of arm-bag sweat and body sweat. The Journal of Physiology. 1952 Apr 4;116(4):395.
83. Imani S, Bandodkar AJ, Mohan AV, Kumar R, Yu S, Wang J, Mercier PP. A wearable chemical–electrophysiological hybrid biosensing system for real-time health and fitness monitoring. Nature communications. 2016 May 23;7(1):11650.
84. Huang X, Li J, Liu Y, Wong T, Su J, Yao K, Zhou J, Huang Y, Li H, Li D, Wu M. Epidermal self-powered sweat sensors for glucose and lactate monitoring. Bio-Design and Manufacturing. 2022 Jan 1:1-9.
85. Sonner Z, Wilder E, Heikenfeld J, Kasting G, Beyette F, Swaile D, Sherman F, Joyce J, Hagen J, Kelley-Loughnane N, Naik R. The microfluidics of the eccrine sweat gland, including biomarker partitioning, transport, and biosensing implications. Biomicrofluidics. 2015 May 1;9(3).
86. Gao F, Liu C, Zhang L, Liu T, Wang Z, Song Z, Cai H, Fang Z, Chen J, Wang J, Han M. Wearable and flexible electrochemical sensors for sweat analysis: A review. Microsystems & Nanoengineering. 2023 Jan 1;9(1):1.
87. Okawara H, Sawada T, Nakashima D, Maeda Y, Minoji S, Morisue T, Katsumata Y, Matsumoto M, Nakamura M, Nagura T. Kinetic changes in sweat lactate following fatigue during constant workload exercise. Physiological Reports. 2022 Jan;10(2):e15169.
88. Finsterer J. Biomarkers of peripheral muscle fatigue during exercise. BMC musculoskeletal disorders. 2012 Dec;13:1-3.

89. Ma J, Li H, Huang X, Fang B, Zhao Z, Mehmood I, Liu Y, Zhang G, Fang X, Arashpour M, Anwer S. Fatigue assessment of construction equipment operators using a sweat lactate biosensor. International Journal of Industrial Ergonomics. 2023 Jul 1;96:103472.
90. Ma J, Li H, Yu X, Fang X, Fang B, Zhao Z, Huang X, Anwer S, Xing X. Sweat Analysis-Based Fatigue Monitoring during Construction Rebar Bending Tasks. Journal of Construction Engineering and Management. 2023 Sep 1;149(9):04023072.
91. Ferguson BS, Rogatzki MJ, Goodwin ML, Kane DA, Rightmire Z, Gladden LB. Lactate metabolism: historical context, prior misinterpretations, and current understanding. European journal of applied physiology. 2018 Apr;118:691-728.
92. Seshadri DR, Rowbottom JR, Drummond C, Voos JE, Craker J. A review of wearable technology: Moving beyond the hype: From need through sensor implementation. In2016 8th Cairo International Biomedical Engineering Conference (CIBEC) 2016 Dec 15 (pp. 52-55). IEEE.
93. Bariya M, Shahpar Z, Park H, Sun J, Jung Y, Gao W, Nyein HY, Liaw TS, Tai LC, Ngo QP, Chao M. Roll-to-roll gravure printed electrochemical sensors for wearable and medical devices. ACS nano. 2018 Jun 20;12(7):6978-87.
94. Olarte O, Chilo J, Pelegri-Sebastia J, Barbé K, Van Moer W. Glucose detection in human sweat using an electronic nose. In2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) 2013 Jul 3 (pp. 1462-1465). IEEE.
95. Wang J. Electrochemical glucose biosensors. Chemical reviews. 2008 Feb 13;108(2):814-25.

96. La Count TD, Jajack A, Heikenfeld J, Kasting GB. Modeling glucose transport from systemic circulation to sweat. Journal of pharmaceutical sciences. 2019 Jan 1;108(1):364-71.

97. Moyer J, Wilson D, Finkelshtein I, Wong B, Potts R. Correlation between sweat glucose and blood glucose in subjects with diabetes. Diabetes technology & therapeutics. 2012 May 1;14(5):398-402.

98. Williams ED, Magliano DJ, Tapp RJ, Oldenburg BF, Shaw JE. Psychosocial stress predicts abnormal glucose metabolism: the Australian Diabetes, Obesity and Lifestyle (AusDiab) study. Annals of Behavioral Medicine. 2013 Aug 1;46(1):62-72.

99. Noushad S, Ahmed S, Ansari B, Mustafa UH, Saleem Y, Hazrat H. Physiological biomarkers of chronic stress: A systematic review. International journal of health sciences. 2021 Sep;15(5):46.

100. Zafar H, Channa A, Jeoti V, Stojanović GM. Comprehensive review on wearable sweat-glucose sensors for continuous glucose monitoring. Sensors. 2022 Jan 14;22(2):638.

101. Lock AM, Bonetti DL, Campbell AD. The psychological and physiological health effects of fatigue. Occupational medicine. 2018 Nov 16;68(8):502-11.

102. Baker LB. Sweating rate and sweat sodium concentration in athletes: a review of methodology and intra/interindividual variability. Sports Medicine. 2017 Mar;47:111-28.

103. Baker LB, Barnes KA, Anderson ML, Passe DH, Stofan JR. Normative data for regional sweat sodium concentration and whole-body sweating rate in athletes. Journal of sports sciences. 2016 Feb 16;34(4):358-68.

104. Allan JR, Wilson CG. Influence of acclimatization on sweat sodium concentration. Journal of Applied Physiology. 1971 May;30(5):708-12.

105. Baker LB, Stofan JR, Hamilton AA, Horswill CA. Comparison of regional patch collection vs. whole body washdown for measuring sweat sodium and potassium loss during exercise. Journal of Applied Physiology. 2009 Sep 1.

106. Matzeu G, O'Quigley C, McNamara E, Zuliani C, Fay C, Glennon T, Diamond D. An integrated sensing and wireless communications platform for sensing sodium in sweat. Analytical Methods. 2016;8(1):64-71.

107. Sato K, Kang WH, Saga K, Sato KT. Biology of sweat glands and their disorders. I. Normal sweat gland function. Journal of the American Academy of Dermatology. 1989 Apr 1;20(4):537-63.

108. Guinovart T, Bandodkar AJ, Windmiller JR, Andrade FJ, Wang J. A potentiometric tattoo sensor for monitoring ammonium in sweat. Analyst. 2013;138(22):7031-8.

109. Ravier G, Dugue B, Grappe F, Rouillon JD. Maximal accumulated oxygen deficit and blood responses of ammonia, lactate and pH after anaerobic test: a comparison between international and national elite karate athletes. International journal of sports medicine. 2006 Feb 1:810-7.

110. Brusilow SW, Gordes EH. Ammonia secretion in sweat. American Journal of Physiology-Legacy Content. 1968 Mar 1;214(3):513-7.

111. Czarnowski DA, Górski J. Sweat ammonia excretion during submaximal cycling exercise. Journal of Applied Physiology. 1991 Jan 1;70(1):371-4.

112. Colombani P, Späti S, Spleiss C, Frey-Rindova P, Wenk C. Exercise-induced sweat nitrogen excretion: evaluation of a regional collection method using gauze padsBelastungsbedingte Stickstoffverluste über den Schweiss: Auswertung einer lokalen Sammelmethode mit Gazen. Zeitschrift für Ernährungswissenschaft. 1997;36(3):237-43.

113. Yuan Y, Chan KM. A longitudinal study on the ammonia threshold in junior cyclists. British journal of sports medicine. 2004 Apr 1;38(2):115-9.

114. Alvear-Ordenes I, García-López D, De Paz JA, González-Gallego J. Sweat lactate, ammonia, and urea in rugby players. International journal of sports medicine. 2005 Oct;26(08):632-7.

115. Medbø JI, Sejersted OM. Plasma potassium changes with high intensity exercise. The Journal of physiology. 1990 Feb 1;421(1):105-22.

116. Adrian RH, Helmreich E, Holzer H, Jung R, Kramer K, Krayer O, Linden RJ, Lynen F, Miescher PA, Piiper J, Rasmussen H. The physiology, pharmacology, and biochemistry of the eccrine sweat gland. Reviews of Physiology, Biochemistry and Pharmacology, Volume 79. 1977:51-131.

117. Hsiao KL, Chen CC. What drives smartwatch purchase intention? Perspectives from hardware, software, design, and value. Telematics and Informatics. 2018 Apr 1;35(1):103-13.

118. Lee SY, Lee K. Factors that influence an individual's intention to adopt a wearable healthcare device: The case of a wearable fitness tracker. Technological Forecasting and Social Change. 2018 Apr 1;129:154-63.

119. Wiegard RB, Breitner MH. Smart services in healthcare: A risk-benefit-analysis of pay-as-you-live services from customer perspective in Germany. Electronic Markets. 2019 Mar 12;29:107-23.

120. Kim JS, Yun D, Kim HJ, Ryu HY, Oh J, Kang SM. Need assessment for smartphone-based cardiac telerehabilitation. Healthcare Informatics Research. 2018 Oct 31;24(4):283-91.

121. Park J, Kim J, Kim SP. Prediction of daily mental stress levels using a wearable photoplethysmography sensor. InTENCON 2018-2018 IEEE Region 10 Conference 2018 Oct 28 (pp. 1899-1902). IEEE.

122. Mohan PM, Nagarajan V, Das SR. Stress measurement from wearable photoplethysmographic sensor using heart rate variability data. In2016 International Conference on Communication and Signal Processing (ICCSP) 2016 Apr 6 (pp. 1141-1144). IEEE.

123. Chen L, Zhang X, Wang H. An obstructive sleep apnea detection approach using kernel density classification based on single-lead electrocardiogram. Journal of medical systems. 2015 May;39:1-1.

124. Ibrahim NF, Sabani N, Johari S, Manaf AA, Wahab AA, Zakaria Z, Noor AM. A comprehensive review of the recent developments in wearable sweat-sensing devices. Sensors. 2022 Oct 10;22(19):7670.

125. Cuartero M, Parrilla M, Crespo GA. Wearable potentiometric sensors for medical applications. Sensors. 2019 Jan 17;19(2):363.

126. Marques-Deak A, Cizza G, Eskandari F, Torvik S, Christie IC, Sternberg EM, Phillips TM, the POWER F, Group S. Measurement of cytokines in sweat patches and plasma in healthy women: validation in a controlled study. Journal of immunological methods. 2006 Aug 31;315(1-2):99-109.

127. Venugopal M, Arya SK, Chornokur G, Bhansali S. A realtime and continuous assessment of cortisol in ISF using electrochemical impedance spectroscopy. Sensors and Actuators A: Physical. 2011 Dec 1;172(1):154-60.

128. Roychoudhury A, Basu S, Jha SK. Dopamine biosensor based on surface functionalized nanostructured nickel oxide platform. Biosensors and Bioelectronics. 2016 Oct 15;84:72-81.

129. Kumar LS, Wang X, Hagen J, Naik R, Papautsky I, Heikenfeld J. Label free nano-aptasensor for interleukin-6 in protein-dilute bio fluids such as sweat. Analytical Methods. 2016;8(17):3440-4.

130. Parlak O, Keene ST, Marais A, Curto VF, Salleo A. Molecularly selective nanoporous membrane-based wearable organic electrochemical device for noninvasive cortisol sensing. Science advances. 2018 Jul 20;4(7):eaar2904

131. An JE, Kim KH, Park SJ, Seo SE, Kim J, Ha S, Bae J, Kwon OS. Wearable cortisol aptasensor for simple and rapid real-time monitoring. ACS sensors. 2022 Jan 7;7(1):99-108.

132. Wang B, Zhao C, Wang Z, Yang KA, Cheng X, Liu W, Yu W, Lin S, Zhao Y, Cheung KM, Lin H. Wearable aptamer-field-effect transistor sensing system for noninvasive cortisol monitoring. Science advances. 2022 Jan 5;8(1):eabk0967.

133. Yarrow K, Brown P, Krakauer JW. Inside the brain of an elite athlete: the neural processes that support high achievement in sports. Nature Reviews Neuroscience. 2009 Aug;10(8):585-96.

134. Weise M, Drinkard B, Mehlinger SL, Holzer SM, Eisenhofer G, Charmandari E, Chrousos GP, Merke DP. Stress dose of hydrocortisone is not beneficial in patients with classic congenital adrenal hyperplasia undergoing short-term, high-intensity exercise. The Journal of Clinical Endocrinology & Metabolism. 2004 Aug 1;89(8):3679-84.

135. Luger A, Deuster PA, Kyle SB, Gallucci WT, Montgomery LC, Gold PW, Loriaux DL, Chrousos GP. Acute hypothalamic–pituitary–adrenal responses to the stress of treadmill exercise. New England Journal of Medicine. 1987 May 21;316(21):1309-15.

136. Rimmele U, Zellweger BC, Marti B, Seiler R, Mohiyeddini C, Ehlert U, Heinrichs M. Trained men show lower cortisol, heart rate and psychological responses to psychosocial stress compared with untrained men. Psychoneuroendocrinology. 2007 Jul 1;32(6):627-35.

137. Yoshizawa JM, Schafer CA, Schafer JJ, Farrell JJ, Paster BJ, Wong DT. Salivary biomarkers: toward future clinical and diagnostic utilities. Clinical microbiology reviews. 2013 Oct;26(4):781-91.

138. Ngamchuea K, Chaisiwamongkhol K, Batchelor-McAuley C, Compton RG. Chemical analysis in saliva and the search for salivary biomarkers–a tutorial review. Analyst. 2018;143(1):81-99.

139. He C, Chen YY, Phang CR, Stevenson C, Chen IP, Jung TP, Ko LW. Diversity and Suitability of the State-of-the-Art Wearable and Wireless EEG Systems Review. IEEE Journal of Biomedical and Health Informatics. 2023 Jan 24.

140. Jia W, Bandodkar AJ, Valdés-Ramírez G, Windmiller JR, Yang Z, Ramírez J, Chan G, Wang J. Electrochemical tattoo biosensors for real-time noninvasive lactate monitoring in human perspiration. Analytical chemistry. 2013 Jul 16;85(14):6553-60.

141. Abellán-Llobregat A, Jeerapan I, Bandodkar A, Vidal L, Canals A, Wang J, Morallon E. A stretchable and screen-printed electrochemical sensor for glucose determination in human perspiration. Biosensors and Bioelectronics. 2017 May 15;91:885-91.

142. Bandodkar AJ, Jia W, Yardımcı C, Wang X, Ramirez J, Wang J. Tattoo-based noninvasive glucose monitoring: a proof-of-concept study. Analytical chemistry. 2015 Jan 6;87(1):394-8.

143. Martín A, Kim J, Kurniawan JF, Sempionatto JR, Moreto JR, Tang G, Campbell AS, Shin A, Lee MY, Liu X, Wang J. Epidermal microfluidic

electrochemical detection system: Enhanced sweat sampling and metabolite detection. ACS sensors. 2017 Dec 22;2(12):1860-8.

144. Emaminejad S, Gao W, Wu E, Davies ZA, Yin Yin Nyein H, Challa S, Ryan SP, Fahad HM, Chen K, Shahpar Z, Talebi S. Autonomous sweat extraction and analysis applied to cystic fibrosis and glucose monitoring using a fully integrated wearable platform. Proceedings of the National Academy of sciences. 2017 May 2;114(18):4625-30.

145. Bandodkar AJ, Molinnus D, Mirza O, Guinovart T, Windmiller JR, Valdés-Ramírez G, Andrade FJ, Schöning MJ, Wang J. Epidermal tattoo potentiometric sodium sensors with wireless signal transduction for continuous non-invasive sweat monitoring. Biosensors and bioelectronics. 2014 Apr 15;54:603-9.

146. Wujcik EK, Blasdel NJ, Trowbridge D, Monty CN. Ion sensor for the quantification of sodium in sweat samples. IEEE Sensors Journal. 2013 Apr 5;13(9):3430-6.

147. McCaul M, Porter A, Barrett R, White P, Stroiescu F, Wallace G, Diamond D. Wearable platform for real‐time monitoring of sodium in sweat. ChemPhysChem. 2018 Jun 19;19(12):1531-6.

148. Alizadeh A, Burns A, Lenigk R, Gettings R, Ashe J, Porter A, McCaul M, Barrett R, Diamond D, White P, Skeath P. A wearable patch for continuous monitoring of sweat electrolytes during exertion. Lab on a Chip. 2018;18(17):2632-41.

149. Sekine Y, Kim SB, Zhang Y, Bandodkar AJ, Xu S, Choi J, Irie M, Ray TR, Kohli P, Kozai N, Sugita T. A fluorometric skin-interfaced microfluidic device and smartphone imaging module for in situ quantitative analysis of sweat chemistry. Lab on a Chip. 2018;18(15):2178-86.

150. Renner E, Lang N, Langenstein B, Struck M, Bertsch T. Validating sweat ammonia as physiological parameter for wearable devices in sports science. In2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC) 2020 Jul 20 (pp. 4644-4647). IEEE.

151. Zhao Z, Li Q, Chen L, Zhao Y, Gong J, Li Z, Zhang J. A thread/fabric-based band as a flexible and wearable microfluidic device for sweat sensing and monitoring. Lab on a Chip. 2021;21(5):916-32.

152. Kim SB, Lee K, Raj MS, Lee B, Reeder JT, Koo J, Hourlier-Fargette A, Bandodkar AJ, Won SM, Sekine Y, Choi J. Soft, skin-interfaced microfluidic systems with wireless, battery-free electronics for digital, real-time tracking of sweat loss and electrolyte composition. Small. 2018 Nov;14(45):1802876.

153. Madhu S, Anthuuvan AJ, Ramasamy S, Manickam P, Bhansali S, Nagamony P, Chinnuswamy V. ZnO nanorod integrated flexible carbon fibers for sweat cortisol detection. ACS Applied Electronic Materials. 2020 Jan 30;2(2):499-509.

154. Kaya T, Liu G, Ho J, Yelamarthi K, Miller K, Edwards J, Stannard A. Wearable sweat sensors: background and current trends. Electroanalysis. 2019 Mar;31(3):411-21.

155. Rose DP, Ratterman ME, Griffin DK, Hou L, Kelley-Loughnane N, Naik RR, Hagen JA, Papautsky I, Heikenfeld JC. Adhesive RFID sensor patch for monitoring of sweat electrolytes. IEEE Transactions on Biomedical Engineering. 2014 Nov 11;62(6):1457-65.

156. Francis J, Stamper I, Heikenfeld J, Gomez EF. Digital nanoliter to milliliter flow rate sensor with in vivo demonstration for continuous sweat rate measurement. Lab on a Chip. 2019;19(1):178-85.

157. Choi J, Ghaffari R, Baker LB, Rogers JA. Skin-interfaced systems for sweat collection and analytics. Science advances. 2018 Feb 16;4(2):eaar3921.

158. Choi J, Bandodkar AJ, Reeder JT, Ray TR, Turnquist A, Kim SB, Nyberg N, Hourlier-Fargette A, Model JB, Aranyosi AJ, Xu S. Soft, skin-integrated multifunctional microfluidic systems for accurate colorimetric analysis of sweat biomarkers and temperature. ACS sensors. 2019 Feb 1;4(2):379-88.

159. Cui Y, Duan W, Jin Y, Wo F, Xi F, Wu J. Ratiometric fluorescent nanohybrid for noninvasive and visual monitoring of sweat glucose. ACS sensors. 2020 May 26;5(7):2096-105.

160. Kim S, Lee B, Reeder JT, Seo SH, Lee SU, Hourlier-Fargette A, Shin J, Sekine Y, Jeong H, Oh YS, Aranyosi AJ. Soft, skin-interfaced microfluidic systems with integrated immunoassays, fluorometric sensors, and impedance measurement capabilities. Proceedings of the National Academy of Sciences. 2020 Nov 10;117(45):27906-15.

161. Kim SB, Koo J, Yoon J, Hourlier-Fargette A, Lee B, Chen S, Jo S, Choi J, Oh YS, Lee G, Won SM. Soft, skin-interfaced microfluidic systems with integrated enzymatic assays for measuring the concentration of ammonia and ethanol in sweat. Lab on a Chip. 2020;20(1):84-92.

162. Kaur S, Gupta N, Malhotra BD. Recent developments in wearable & non-wearable point-of-care biosensors for cortisol detection. Expert Review of Molecular Diagnostics. 2023 Mar 4;23(3):217-30.

163. Chung M, Fortunato G, Radacsi N. Wearable flexible sweat sensors for healthcare monitoring: a review. Journal of the Royal Society Interface. 2019 Oct 31;16(159):20190217.

164. Ghaffari R, Rogers JA, Ray TR. Recent progress, challenges, and opportunities for wearable biochemical sensors for sweat analysis. Sensors and Actuators B: Chemical. 2021 Apr 1;332:129447.

165. Kim DH, Ghaffari R, Lu N, Rogers JA. Flexible and stretchable electronics for biointegrated devices. Annual review of biomedical engineering. 2012 Aug 15;14:113-28.

166. McDermott JE, Wang J, Mitchell H, Webb-Robertson BJ, Hafen R, Ramey J, Rodland KD. Challenges in biomarker discovery: combining expert insights with statistical analysis of complex omics data. Expert opinion on medical diagnostics. 2013 Jan 1;7(1):37-51.

Table 1. Search strategies

Keyword	**PubMed**	**Web of Science (all databases)**	**IEEE Explorer**
Sweat biomarkers OR Chemical biomarkers OR Sweat Cortisol OR Sweat electrolytes OR Sweat ammonia OR Sweat glucose OR Sweat Lactate	66,388	81,709	145
Wearable biosensors OR Wearable sensors OR Wearable biosensing technology OR Wearable electrochemical sensors OR Wearable biochemical Sensors OR Wearable Chemical Sensors	10,937	37,734	3,616
Fatigue OR Stress OR Burnout OR Exertion OR Exhaustion	1,388,941	2,520,421	32,940
Combined (Operator ‘AND’)	42	82	7
Total after duplicates removed		**98**	

Table 2. Overview of wearable biosensors for monitoring sweat-based biomarkers

Author (Year)	**Publisher**	**Biomarker**	**Subject**	**Demographic**	**Types of sensors**	**Types of wearables**	**Time taken to start recording**	**Cited by**
Oktavius et al. [63]	IEEE	Cortisol	Not reported	Not reported	Skin patch sensor based on porous Ultra-High Molecular-Weight Polyethylene (UHMWPE) nanomembrane	Epidermal patch	Not reported	2
Torrente-Rodrıguez et al. [65]	Elsevier	Cortisol	12 healthy subjects,	age range 18–65 years	Graphene-Based Wireless mHealth System	Graphene sensor patch	10 min	117
Saha et al. [78]	MDPI	Lactate	Eight healthy subjects	5 females and 3 males, aged 20–28	Polydimethylsiloxane (PDMS)-based hydrogels	Wearable patch	Not reported	1
Seki et al. [79]	Nature	Lactate	23 healthy 42 patients (CVDs)	Age 20 Y (healthy) 63 Y (patients) Male 21 (healthy), 32 (patients) Height 171 cm (healthy), 165 cm (patients) BMI 22 (healthy), 23 (patients)	Amperometric lactate biosensor	Sensor chips	Not reported	5
Imani et al. [83]	Nature	Lactate	3 healthy males	Not reported	Amperometric lactate biosensor	Epidermal patch	Not reported	546
Huang et al. [84]	Springer	Glucose Lactate	Not reported	Not reported	Polydimethylsiloxane (PDMS)-based enzymatic biofuel cells	Epidermal patch	1 min	5

Bariya et al. [93]	American Chemical Society	pH	Not reported	Not reported	Potentiometric electrolyte sensors	Wristband	14 min	166
Matzeu et al. [106]	The Royal Society of Chemistry	Electrolytes ($Na+$)	Four Healthy active male athletes	Not reported	Potentiometric electrolyte sensors	Sweatband	20 min	64
Guinovart et al. [108]	The Royal Society of Chemistry	Electrolytes (Ammonia)	Not reported	Not reported	Potentiometric sensor	Tattooed sensor	Not reported	231
An et al. [131]	American Chemical Society	Cortisol	5 subjects	Not reported	Silk substrate-based cortisol aptasensor	Electrode-type sensor	Not reported	1
Wang et al. [132]	Science Advances	Cortisol	71 healthy participants	Not reported	A flexible field-effect transistor (FET) biosensor	Smart watch	5 – 15 min	nil
Emaminejad et al. [144]	National Academy Sciences	Electrolytes ($Na+/Cl^{-}$) Glucose	Six healthy volunteers and three Cystic Fibrosis patients	Not reported	Potentiometric electrolyte sensors Amperometric glucose sensors	Sweatband	20 min	435
McCaul et al. [147]	Wiley	Electrolytes ($Na+$)	One healthy male	26 Y	Potentiometric electrolyte sensors	Wristband	8 min	32
Alizadeh et al. [148]	The Royal Society of Chemistry	Electrolytes ($Na+$ and $K+$)	One healthy male	Not reported	Potentiometric electrolyte sensors	Epidermal patch	Not reported	92
Renner et al. [150]	IEEE	Electrolytes (Ammonia)	35 male and 5 female	Age 39.9 ± 12.5 years Height 180.3 ± 7.9 cm, Weight 80.9 ± 12.7 kg	A screen-printed electrolyte sensor	Polystyrene tubes	Not reported	4
Rose et al. [155]	IEEE	Electrolytes ($Na+$)	Seven healthy volunteers	Not reported	Potentiometric electrolyte sensors	Epidermal patch	4 min	364
Choi et al. [157]	Elsevier	Electrolytes (Cl^{-})	10 individuals with Cystic Fibrosis (CF) and 10 healthy subjects	CF: male = 4, female = 6, age = 28.9 ± 7.4 years; healthy individuals: male = 1, female = 9, age = 35.0 ± 12.1 years	Colorimetric sensors	Epidermal patch	15 min	41

Table 3. Validation experiment for continuous monitoring of sweat-based biomarkers using wearable biosensors

Author (Year)	**Sweat Biomarker**	**Validation method**	**Experiment**	**Finding**	**Conclusion**
Oktavius et al. [63]	Cortisol	Blood cortisol	The healthy volunteers had a 15-minute workout that began at a low intensity (100 revolutions per minute (RPM)) and gradually rose in intensity (140 RPM until voluntarily stopped). Participants sweated while wearing two membranes that were detached once the low and high intensity levels had been completed, respectively. Similar to the sweat samples, each subject's finger was poked after completing each of the activity levels at the same intensity. Easy removal of the sweat sensor for laboratory Raman analysis was achieved using a paper frame attached with double-sided adhesive.	After the participant did the high-intensity exercise, the sweat sample exhibits a strong cortisol peak on Raman shifts of 1610 cm^{-1}, whereas this peak is absent from the control sample. The Raman peaks of sweat follow a similar pattern to those of blood, with Cortisol detected in an area of 1600cm^{-1} despite the substantial intensity difference. Additionally, it was discovered that the estimated cortisol content in blood is approximately 7.48 times that in perspiration. After almost two hours of high-intensity activity, the Area Under the Curve (AUC) ratio of sweat cortisol increased nearly tenfold compared to the concentration during low-intensity exercise, resulting in a cortisol concentration of 10.47 µmol/cm3.	Using a flexible, breathable membrane, this work can detect sports fatigue by measuring cortisol levels. Other methods, such as Raman spectrometry and quantitative analysis, can capture biomarkers from human sweat, particularly cortisol. This work could lead to a less invasive and more convenient way to track fatigue than blood tests.
Torrente-Rodríguez et al. [65]	Cortisol	ELISA (Cortisol levels in serum)	A 50-minute stationary cycle workout with a constant workload was used to determine the sweat cortisol concentration in this study. For the 50-minute workout, the GS4 was used to collect and analyze sweat samples from the	Sweat cortisol levels grow gradually in all persons studied and reach a maximum after 40 minutes of continuous riding. Near the end of the activity, a modest reduction in cortisol levels is noticed in all individuals. Cortisol levels in pre- and post-	This pilot study found a strong correlation between the amount of cortisol in the blood and the amount of cortisol in the sweat. This shows that sweat analysis has a lot of potential for noninvasive dynamic stress monitoring using wearable and portable sensing devices.

			three physically untrained subjects and one trained (athletic) subject on a cycling ergometer at 10-minute intervals. Additionally, cortisol levels in the blood were examined before and shortly after the cyclic activity to see if the sweat cortisol fluctuation correlated to circulating cortisol levels. An exploratory cold pressor test (CPT) was performed on four healthy volunteers by the research team in order to discover how quickly sweat cortisol reacts to acute stress. Before beginning, participants were told to immerse their non-dominant hand in ice water for three minutes. Samples of sweat were obtained every eight minutes with iontophoretic sweat stimulation.	exercise serum samples correlate well with the change in cortisol levels from the start of perspiration (10 minutes) to the end of the activity (50 minutes). At 50 minutes, sweat cortisol levels were significantly higher than at 10 minutes, in response to the physiological stressor. Cortisol levels were higher in the morning than in the evening for both groups; the evening exercise results in a greater relative percentage change in cortisol. Cortisol levels increased following CPT completion, reaching a mean high between 8 and 16 minutes after CPT.	
Saha et al. [78]	Lactate	Blood lactate	Using a lactate paper sample, researchers were able to determine the amount of lactate in the blood under five different physiological conditions: rest, moderate exercise (60–70% of maximal heart rate), post-medium-intensity exercise, and post-high intensity exercise. All of the experiments were	The hydrogel disc can take fluid from the skin and transmit it to the paper via osmosis while the user is sleeping or otherwise resting. Even without the hydrogel patch, the paper can still collect perspiration during periods of intense sweating (for example, exercise). Inversely proportional to sweating rate is the total	This wearable osmotic sweat sampling patch looks to have significant potential in permitting continuous sweat collection for hours at a time. It provides valuable health information regarding human lactate patterns under a variety of physiological circumstances. In addition to the skin tests, this patch needs additional post-processing steps to get a reliable estimate of the amount of lactate in sweat.

			conducted at 22 degrees Celsius and 45 percent RH (relative humidity).	amount of lactate moles measured in the experiments. High-intensity exercise has the best association between perspiration and blood lactate concentrations.	
Seki et al. [79]	Lactate	Blood lactate, and ventilatory threshold	The RAMP protocol ergometer was used to conduct exercise testing on healthy volunteers, while a wearable lactate sensor measured changes in sweat lactate. Lactate levels in the blood were monitored every two minutes using a sensor attached to the upper arm of healthy individuals. The subjects performed the test in an upright position on an electrically braked ergometer. Subjects began by pedaling for 2 minutes at 50 W for healthy males and 0 W for healthy females, then increased the intensity of their exercise until they were no longer able to maintain the pedaling rate (volitional exhaustion). Every minute, the intensity was stepped up by 20 W. (RAMP protocol). At 60 rotations per minute, the pedaling speed was set. According to the subject's exercise capacity, the incremental exercise testing lasted between 10 and 20 minutes. Individuals were	At the start of the cycling activity, the lactate biosensor registered a negligible current response due to a lack of sweat. As the riding continued to volitional exhaustion, a dramatic increase in sweat lactate levels was noticed. After the workout period, sweat lactate readings continued to decline slowly in comparison to the heart rate decrease. The correlations between sweat lactate and blood lactate were excellent ($r=0.92$, $P<0.001$). The least-product regression analysis revealed no evidence of a fixed bias or a proportionate bias (95 percent confidence intervals (CIs) for the y-intercept ranged from 9.16 to 19.1; CIs for the slope ranged from 0.854 to 1.020). Similarly, a strong association between the sweat lactate and ventilatory threshold was seen ($r=0.71$, $P<0.001$). Between each threshold, least-product regression analysis revealed a fixed bias (y-intercept, 22.7) and a proportionate bias (slope, 0.57).	It was the first study to monitor sweat lactate in real time during progressive exercise in healthy and cardiovascular disease (CVD) patients. Monitoring the amount of lactate in sweat could help find the ventilatory threshold, which is important because it is hard to find.

			instructed to stop cycling immediately and remain on the ergometer for three minutes after the exercise tests were completed.		
Imani et al. [83]	Lactate	enzyme-free amperometric sensor	The Chem–Phys hybrid patch was created and applied to the fourth intercostal area of three healthy male volunteers in order to evaluate performance under realistic conditions. Sweat-lactate levels and ECG signals were regularly measured during 15–30 minutes of intense cycling exertion. While pedaling difficulty was increased intermittently, participants were instructed to maintain a steady riding cadence on a stationary cycle.	Heart rate (HR) was 60 to 120 beats per minute and low current response was recorded by the lactate biosensor at the start of the cycling activity HR and sweat production increased as individuals increased amount of effort. LOx-based biosensor recorded lactate from the epidermis at the commencement of perspiration. Perspiration rate, HR, lactate levels increased as riding intensity increased. The HR returned to a level close to normal resting HR after cooldown session. Simultaneously, the lactate concentration decreased.	This is the first time that researchers have been able to monitor both physiochemistry and electrophysiology at the same time with little interference. This opens the door for a new class of hybrid sensing devices.
Huang et al. [84]	Glucose Lactate	Laboratory trials	The lactate and glucose concentrations of a cyclist were monitored in real time as he or she cycled at a steady load. Sensors implanted in the subject's back measured glucose and lactate concentrations during a period of 1200 seconds of activity. The lactate and glucose concentrations in three	Throughout the exercise, the glucose and lactate concentrations gradually reduced due to the dilution impact of the increased sweat rate. Lactate and glucose concentrations were nearly same across all test locations, and a significant drop was observed after 0.5 hours of perspiration.	A stretchable, self-powered biosensor could be used to track the levels of lactate and glucose in human sweat in real time. Biofuel cells functioning as precise sensing components can work without the use of external power supplies. The suggested biosensor could be used to measure sweat and keep an eye on the health of people.

			independent body regions were also measured after 0.5 hours of continuous activity. After that, the sensors were attached to the backs of three volunteers and the changes in lactate and glucose levels in sweat were measured.	A determination coefficient (R2) of 0.98 and a sensitivity of 2.48 mV/mM were noted for lactate detection, and a determination coefficient (R2) of 0.96 and a sensitivity of 0.11 mV/mM for glucose detection.	
Choi et al. [93]	Electrolytes (Cl^-)	Standard laboratory test	Pilocarpine iontophoresis was used to generate sweat on both forearms of ten people with Cystic Fibrosis and ten healthy volunteers. On one arm, a Macroduct sweat collection device was mounted, and perspiration was collected for 30 minutes before being transported to the laboratory for analysis. In the other arm, a sensor was attached, and the concentration of chloride ions was monitored in real time for 30 minutes.	The wearable sensor was able to collect steady sweat chloride levels within 15 minutes of starting to sweat. The sensor measured a sweat volume of 13.1 ± 11.4 L (SD) at detection time (5 minutes), which was typically less than the minimum sweat volume of 15 L required for conventional testing. Chloride concentration differences between the sensor and typical laboratory practice were 6.2 ± 9.5 mEq/L (SD), which was compared to the arm-to-arm variability of roughly 3 mEq/L. It was discovered that the two measurements had a Pearson correlation coefficient of 0.97.	When utilized in conjunction with a wearable sensor, real-time measurements of sweat chloride can be obtained within 15 minutes of sweat induction. This method requires only a small quantity of sweat volume and provides excellent agreement with standard methods in the process.
Matzeu et al. [106]	Electrolytes (Na+)	Laboratory trials	Using stationary bikes and a cycle ergometer at an effort level that elicited sweating, a group of healthy, active male athletes was tested in an indoor environment. The PotMicroChip was attached to the upper left arm using a Velcro® strap (after cleaning	Linear relationship between the sensors and a PEDOT solid-contact layer (R2 > 0.98), with an average slope and offset of 55.5 mV/log Na+ and 474.8 mV, respectively. The slope and offset standard deviations = 4.9 mV/log Na+ and 23.1 mV.	After a series of high-energy workouts, the results show that the sensor can make different sodium profiles for each athlete over a long period of time.

			the sampling region with alcohol swabs and deionised water). The external forearm was selected as the primary sampling location. When the athlete was unable to keep up with the set intensity load, the trials were halted.	Sensors with a PEDOT/PB film as the SC layer demonstrated excellent linear calibration ($R2 > 0.98$). The slope and offset values = 53.4 ± 3.0 mV/log Na+ and 524.1 ± 14.4 mV. When the PotMicroChips began harvesting perspiration, Na+ levels increased for 2 and 5 minutes, respectively. Na+ levels then stabilized at an average of 10.3 ± 0.2 mM and 24.2 ± 2.7 mM. The average interpolated sodium concentration at the end of cycling sessions was found to be 18.2 ± 8.9 mM.	
Guinovart et al. [108]	Electrolytes (Ammonia)	Laboratory trials	A 30-minute stationary cycling regimen with three-minute cool-down periods and another three-minute rest period was employed in the study. To achieve an anaerobic state, each volunteer drank mineral water the entire time and cycled and ran alternately every five minutes.	High Noise signal at the beginning. Low Noise signal (< 0.5 mV) when sweat begins. Amount of NH4+ = 0.1 to 1 mM (range). NH4+ levels increased with the increased load of cycling without sprinting. Sensor signals increased with the increased speed of cycling.	Solid-state tattoo potentiometric cells that can detect ammonium (NH4 +) in sweat have been developed and are currently being tested. It combines screen-printed technology with a temporary tattoo. Preliminary findings indicate this tattoo can sense the transition of subjects doing intense exercise.
An et al. [131]	Cortisol	ELISA (Cortisol levels in serum)	After a period of intense exercise (cycling), the actual sweat cortisol level was measured. Sweat samples were utilized to conduct an ELISA test, which helped researchers calculate the concentration	Real-time monitoring was carried out when the subject was cycling aggressively to increase the amount of stress. The no sweat portion of the real-time response corresponds to the time when stress was administered, but not	Using a PEDOT-PAN NF layer on a silk substrate, a flexible and wearable aptasensor was created to detect cortisol, a stress hormone. Electrical experiments revealed the sensor's ohmic behavior, transition curve, and proportional signal intensity to substance concentration. Electrode-type sensors were more

			level needed for real-time monitoring.	recognized by the aptasensor since no cortisol was administered to the aptasensor, and the perspiration portion corresponds to the time when the aptasensor began to detect cortisol. The comparison of the intensity between the subjects demonstrates that this cortisol aptasensor is capable of demonstrating the difference in cortisol levels between various people. The absorbance measurement revealed that the actual sample concentration was around 1 nM. Taking these facts into consideration, the cortisol aptasensor has the potential to be used as a flexible and wearable device.	sensitive (10 pM) and selective. This study will benefit research on ultralight, disposable gadgets with low environmental impact, such as medical devices. Ultralight silk-surfaced wearable sensors need more testing before production.
Wang et al. [132]	Cortisol	ELISA (Saliva Cortisol)	A gold standard laboratory technique, the Trier Social Stress Test (TSST), was used to evaluate stress-induced cortisol spikes in salivary and sweat cortisol. 71 healthy volunteers were studied over four hours, collecting saliva and perspiration samples at each stop (i.e., prestress and 15, 25, and 90 min after stress). It was done using a cortisol-aptamer-FET device to analyze saliva and sweat samples from one of the study participants.	After 15 minutes of stress, salivary cortisol concentrations peaked and then proceeded to decline for the next 75 minutes. In addition, cortisol levels peaked 15 minutes after stress, then returned to baseline levels 90 minutes later, which was consistent with the cumulative trend indicated by the conventional lab assays. Cortisol levels in saliva and sweat were found to be greater in the mornings of most participants than in the afternoons. A moderate connection between	Sweat cortisol monitoring has the potential to be employed in translational applications, especially when considering the huge body of knowledge presently available on salivary cortisol levels. The translation of this technology into health and performance monitoring and optimization and other uses necessitates the coordination of both engineering and clinical initiatives.

			Researchers measured the levels of the stress hormone cortisol in saliva using a standard laboratory technique (such as ELISA).	salivary and sweat cortisol levels (r = 0.73) could not rule out the idea that salivary and sweat cortisol levels were linked. Cortisol levels in saliva and sweat samples were greater in the morning and decreased in the afternoon, consistent with findings from an ELISA analysis of the same samples.	
Bariya et al. [147]	pH	Laboratory trials	As they pedaled stationary bikes, researchers monitored the pH of their sweat. The printed array-based pH sensor is held in place on the subject's arm by an adjustable bracelet. A thin PDMS wall surrounds the sensing electrodes, producing a well for perspiration to condense and preventing the sensing layer from abrasion against the skin. Sweat pH is determined throughout an exercise session that includes six minutes of warm-up and 45 minutes of cycling at a power output of 120 W.	No meaningful pH reading within the first 14 minutes because of insufficient sweat. Sensor readings commence once the well has been properly filled, and initially show a slow rise in pH suggesting a fall in the quantity of lactate in the bloodstream. While riding a bike, the pH of sweat remains constant during the entire workout. For continuous, real-time physiological indicator monitoring in mechanically demanding environments, the printed array-based sensors' on-body data closely matches the readings from a commercial pH meter.	This work is a big step forward in the field of translational research because it makes it possible to make a large number of low-cost, disposable wearable sensors for individual health monitoring applications that can be used on a large scale and are very flexible.
Alizadeh et al. [148]	Electrolytes (Na+ and K+)	Laboratory trials	A healthy male volunteer underwent on-body testing of the fully integrated sweat sensors while undergoing high intensity activity on a bicycle on a roller trainer and treadmill running trials. The patches	The sensitivity of the Na+ and K+ = 55.7 mV per log a Na+ and 53.9 mV per log a K+ per decade. The results in the Na+ concentration demonstrate the expected rise in voltage associated with the introduction	A wireless sweat monitoring device that provides good accuracy while also providing continuous and unobtrusive sweat electrolyte monitoring over a prolonged period of time. The device learned by this device could be applicable to a wide variety of analytes even

			were applied to the back of the individual, around the latissimus dorsi muscle and/or the thoracolumbar fascia in the upper lumbar vertebrae region. Averaging 26 to 29 mph, the bike's top speed during the session, which typically lasts 30 to 60 minutes, caused the person being tested to perspire profusely.	of eutonic sweat to the ISE (from a dry baseline), with minor noise aberrations.	though it was designed for electrolyte analysis during vigorous perspiration only.
Emaminejad et al. [149]	Electrolytes ($Na+/Cl^-$) Glucose	Blood glucose	To assess the wearable platform's efficacy for noninvasive glucose monitoring, they performed real-time sweat stimulation and glucose sensing measurements of a group of subjects participating in fasting and post-glucose ingestion experiments. A commercially accessible glucometer was used to conduct the blood glucose analysis.	The results of this experiment demonstrate that the sweat and blood glucose levels before and after 30 g oral glucose consumption follow a similar pattern. The off-body measurements obtained from the sweat sample created by the wearable device reveal that oral glucose consumption in fasting people typically leads to a rise in both sweat and blood glucose levels.	The technology detects an increased electrolyte content in the perspiration of patients with the disease compared to healthy control volunteers and a correlation between sweat and blood sugar levels.
Renner et al. [150]	Electrolytes (Ammonia)	Blood ammonia, blood lactate, and heart rate	An electromagnetically braked cycle ergometer was used to test the subjects' maximum load capacity. It was constantly monitored for changes in heart rate and breathing gas levels. The subjects were at rest when the baseline data was obtained. A 25 W increase in exertion was made every three minutes after the first three minutes. If a	The data indicate that the HR increases approximately linearly as the effort increases. Lactate concentrations were measured throughout the program, ranging from 0.5 mmol/l at the start to 16.3 mmol/l at the conclusion. Blood ammonium concentrations have been measured to range between 15 and 193 µmol/l.	The rate of ammonium production must be taken into account in order to make sweat ammonium practical to use and meaningful to understand data collected in sweat. In this study, we used a screen-printed electrolyte sensor that is suited for application in wearable electronic devices.

			participant felt they had expended all of their energy, they were allowed to stop the activity. 375 W was the maximum load that could be applied. At the end of each procedure step, 5 ml round-bottom clear polystyrene tubes were used to collect sweat samples from the upper body. The upper arms, shoulders, and back were the preferred locations to gather sweat because they are hairless.	In comparison, following a modest plateau between 150 and 200 W, the sweat ammonium concentration decreases with effort. The content of ammonium in sweat was found to range between 0.12 and 2.17 mmol/l. Sweat ammonium concentration is decreasing, contradicting the other three values. Similar to the other observed characteristics, the sweat ammonium curve exhibits a shift in concentration at 300 W.	
Rose et al. [155]	Electrolytes (Na+)	Laboratory trials	To determine the radio-frequency ID (RFID) Na+ sensor's accuracy, they repeatedly measured 50mM NaCl, which should provide 185mV according to the calibration curve. To further investigate the possibility of continuous monitoring in sweat, the concentration of NaCl was adjusted every 4 minutes for 45 minutes, ranging from 20mM to 70mM.	The sensor output *rose* as the analyte concentration *increased*. The sensor responded fast to each concentration change, with a response time of around *30 seconds*. The correlation coefficient = *0.99.* Sensor sensitivity = *0.3 mV/mM. Sensor accuracy = 96%. Sensor precision = 28%. Average value for high concentration = 255mV.* CV = 0.1%. *Average value for low concentration = 237mV.* CV = 0.8%.	The current patch works well and accurately but would perform even better with a higher sampling frequency, improved power management, sensor signal conditioning, and analog sensor input conversion efficiency. When it comes to collecting real-time data on people's health, wearable and wireless gadgets fill a huge gap in the technology needed.
McCaul et al. [157]	Electrolytes (Na+)	Laboratory trials	A watch-type sweat sampling and analysis platform was used during on-body trials using exercise-induced perspiration. VO2Max (absolute oxygen consumption per minute) and	Within 8 minutes, the signal at the electrodes begins to rapidly grow as the perspiration replaces the conditioning fluid (0.13 mM NaCl).	The findings demonstrate that there was no statistically significant change in the response characteristics of the system. The trial data seem to be pretty accurate, since there was only a five-minute delay between when sweat appeared on the skin and when the electrodes picked it up.

	relative oxygen consumption per kilogram of body weight (relative oxygen consumption per kilogram of body weight) were measured before the volunteer participated in the trial. In this experiment, the sweat sensor was attached to the volunteer's wrist. A 10-minute warm-up was followed by a 5-minute ramp-up before the subject completed a 50-minute cycling period at 120 W followed by a 10-minute cool-down period.	After 12 minutes, the signal began to settle and remained stable until 50 minutes had passed. The concentration of sweat NaCl increases to a high of 17.0 to 17.5 mM (11–13 minutes) and then progressively declines to 11.0 to 11.5% (30–50 minutes). Following that, the Na+ concentration appears to decrease at a faster rate, eventually falling below 6.0 mM near the end of the trial.	