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Portable and wearable real-time stress monitoring: A critical review

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ABSTRACT

This review aims to summarize the rapidly emerging field of real-time stress monitoring by focusing on early breakthroughs and critical developments in portable and wearable cortisol sensors. Here, brief, albeit comprehensive, information on technological advances and current state-of-the-art concepts on real-time cortisol sensing are provided. Specific examples where materials include up-to-date information related to complex sensing conditions, and methodologies, are pieced together. Examples of electrochemical cortisol sensing are categorized by sample types, focusing on sensing from body fluids in vitro and wearable sensors, which have attracted significant interest due to their integration with everyday life activity. The overall progress made to date in building such conceptualized efforts for real-time, continuous monitoring of cortisol and the future of the field is discussed.

1. Introduction to stress monitoring

Since the very first report on "diverse nocuous agents" defined in Hans Selye's legendary article in 1936, [38] where he described the most stereotypical manifestations of the "general alarm reaction of the organism," including gastric ulcer, lipid discharge from the adrenal, and thymicolymphatic involution, the research on "general-adaptation syndrome," or "stress syndrome" inspired many researchers around the world to work on still growing medical research particularly physiology, clinical medicine, and medical diagnostics. [37,46]

Among these research fields, medical diagnostics that target quantification of stress by assessing the body's endocrine response to stressors has recently attracted considerable attention due to the exponential increase in the pace of life that requires intense mental and physical efforts from individuals. [59] Stress is broadly defined as any situation that tends to disturb the equilibrium or homeostasis between living organisms and their surroundings. [12,36] It can be either acute and chronic. Chronic stress starts when individuals are exposed to the stress for an extended period of time, which causes a breakdown of the body's defense mechanism. [24] Continuous exposure to stress has many diverse effects on metabolism and can result in long-term or permanent changes in the emotional, physiological, and behavioral responses and increase susceptibility to many diseases. [21] Stress has a strong influence on regulating immune and inflammatory systems and potentially induces cardiovascular, autoimmune diseases, cancer, and mental disorders. [12]

Despite a serious impact, the current screening and diagnosis approach for stress is not well established. [47,48] The current system to measure an individual's stress includes either self-reporting using a questionnaire or laboratory-based specific biomarker analysis based on blood and urine tests. [41] However, these methods require a long and complicated analysis procedure, skilled personnel to analyze the results, and thus do not provide real-time information due to infrequent short measurement periods or lack of adequate health care access. These challenges make it difficult to ascertain if a significant health change has occurred in a patient. [59]

Recent years witnessed many reports on stress monitoring devices by mainly focusing on physical parameters. [39] In some of these studies, stress monitoring devices integrated with various skin temperature sensors, skin conductance, and pulse-wave using flexible and very thin electronics have been developed. [27] These devices successfully measured skin conductance with high sensitivity and concise response time. However, even though most of these studies show success on real-time measurements of physical parameters, it is currently not possible to test these devices under a stressor. They cannot differentiate normal conditions from stress conditions. Many similar studies and products show poor performance on real stress-induced conditions and always require external complementary measures to precisely diagnose stress. [58] Therefore, recent clinical studies and research show that there is an obvious need to go further beyond physical parameters and track chemical footprints of stress in the human body. [10,59]

Besides physical responses to stressors, the human body responds to the stressor by releasing certain chemicals, including hormones via the endocrine system and neurotransmitter released by the nervous system, to maintain a stable equilibrium, so-called homeostasis, with the help of the mutual interaction of both endocrine and nervous system by

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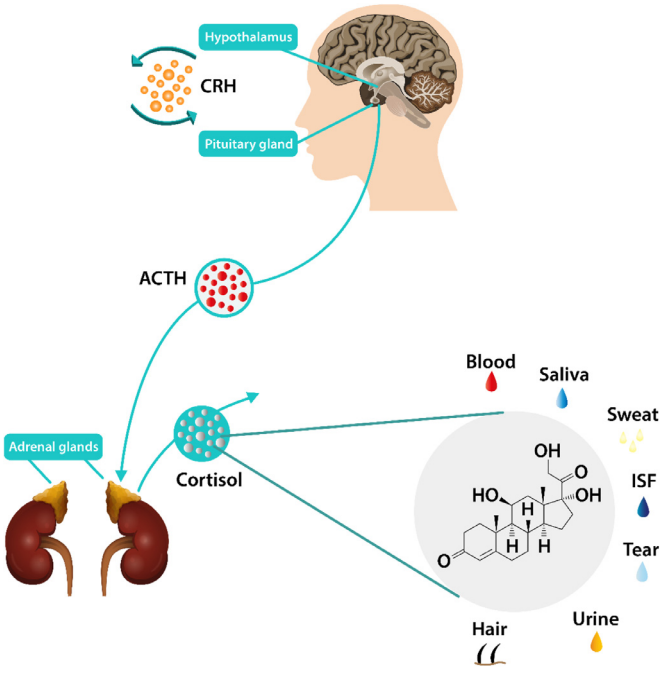
controlling and regulating the multiple glands that play a crucial role for the body. [25] For instance, when the body faces a stressful situation, the body responds to it with a fight-or-flight response that is mainly regulated by adrenal and thyroid glands. [59] These two glands orchestrate the responses, resulting in the generation of certain hormones to provide communication between glands and target cells in the selected tissues or organs. [8] These hormones are usually released in the bloodstream and trigger different mechanisms based on their biochemical features. [25] In addition to hormones, various neurotransmitters also contribute to this general response system by controlling involuntary body movements, such as those of the heart, lungs, and stomach via neurotransmission process that eventually affect mood and response to stress. [35] All of these hormones and neurotransmitters ranging from small molecules to large proteins and other biomolecules that are not categorized as either hormone or neurotransmitter can also be associated with stress (i.e., α-amylase), are considered as essential biomarkers for the quantification of stress. [7]

Among many different hormones, neurotransmitter, and other associated biomolecules, cortisol is one of the most commonly studied biomarkers for the assessment of stress due to its ability to give a direct indication of a stressful situation and well-defined working mechanisms in the body as well as its accessibility from different body-fluids with relatively higher concentrations compared to similar biomarkers. [41] Human cortisol is one of the significant glucocorticoids secreted from the adrenal cortex, and its secretion is regulated by the hypothalamic-pituitary-adrenal (HPA) axis, as schematically illustrated in Scheme 1. [59]. The mechanism shows that almost 90% of circulating cortisol is bound to cortisol-binding globulin and albumin, and only a small amount of cortisol is free to bind glucocorticoid receptors to initiate physiological events. [13] This mechanism ends when cortisol is secreted into the bloodstream and passively diffuses through different parts of the body. [43]

In the absence of pathological conditions, cortisol level in the bloodstream fluctuates during the day parallel with circadian rhythm. [18] For example, cortisol levels are at a minimum at midnight and start increasing in the early morning, reach a peak just after awakening, and gradually decrease during the day. [1] Cortisol is a critical hormone for quantifying stress because it involved several metabolic pathways such as activation of anti-inflammatory and anti-stress pathways via regulating blood glucose level. [45] However, cortisol can have deleterious effects on the immune system by affecting T-cell multiplication, reduces bone formation, which causes osteoporosis in the long-term, and potentially causes many other chronic diseases. [26] Among different body fluids, salivary cortisol correlates very well with the free cortisol in the blood following the same passive diffusion through cells of the salivary gland independent from flow rate. Similarly, sweat shows similar characteristics to salivary cortisol. [28] Moreover, the strong correlation between sweat and saliva suggests that both are the results of acute HPA activity. [10] Recently, it has been shown that cortisol can be detected in interstitial fluids, hair, and urine, as well as tears in different concentrations. [42,51,59]



Scheme 1. Schematic illustration of human cortisol generation path and diffusion into the bloodstream and other body fluids via passive diffusion. (CRH: corticotropin-releasing hormone ACTH: adrenocorticotropic hormone).

Considering the importance of real-time cortisol monitoring, recent investigations on electrochemical cortisol sensor shows that there have been many important challenges and technical hurdles in the research and development of cortisol monitoring devices. [41,53] For example, the correlation of stress biomarkers' level in various body fluids with blood, the stability of biorecognition units for specific biomarkers, and continuous and precise sample handling strategies still await improved solutions. A few interesting and focused discussions, reviews, and thoughts have been published, and researchers around the world have strived to overcome many existing problems, but these issues deserve separate discussion and fall out of the scope of the current review. [13,43,53]

Here, this review aims to piece together early breakthrough and important applications on point-of-care cortisol sensing using novel concepts range from portable devices to wearable electronics, and highlight and discuss the future of non-invasive stress monitoring by giving a particular focus to electrochemical cortisol detection. But first, the review aims to ponder the question: "why do we need real-time stress monitoring?"

1.1. *Why do we need real-time stress monitoring?*

Even though the definition of stress is frequently used in a wide variety of contexts in daily life, it has been shown that people under continuous stress experience unbalanced physical and mental functioning, and this results in loss of workdays, increased impairment at work, and frequent use of healthcare services. [18] Another important aspect is that disabilities caused by stress are rising continuously and are expected to reach disability caused by workplace accidents and many other medical conditions, including hypertension or diabetes. [39] The global economic burden of stress-related mental illness is also likely to rise in the coming decade. The World Health Organization [55] Global Burden of Disease Survey estimates that *'by the year 2020, depression and anxiety disorders, including stress-related mental health conditions, will be highly prevalent and will be second only to ischemic heart disease in the scope of disabilities experienced by sufferers*. Since the socioeconomic demand for the management of chronic stress is increasing continuously, it is necessary to adopt a preventive approach to the problem by establishing a predictive model. [9] With this approach, early diagnosis is essential for timely identification and treatment of patients at risk.

Continuous stress monitoring via detection of specific biomarkers, especially cortisol hormone, plays a critical role in preventing many diseases. [2] Therefore, this review aims to highlight the recent advances in stress monitoring by specializing in cortisol detection. The electrochemical cortisol sensing systems covered in this review are categorized into two groups stimulated by either: ex-situ, portable device-based approach, or wearable sensing approach. The former method includes various methodologies and concepts designed for single or periodical measurements that use different biological fluids, and the latter involves particular examples of wearable devices that follow non-invasive, real-time sensing of cortisol. Each section concludes with a discussion of

practical aspects such as methodology, device preparations, and sensing performances, including sensitivity and selectivity.

2. Point-of-care diagnostic tools for stress monitoring

Commonly used methods for sensing and monitoring stress biomarkers are mainly based on spectroscopic and chromatographic techniques. [47,59] Even though the majority of these techniques are very precise for identification of individual biomarkers and provide essential pieces of information on molecular structure, interactions, and concentrations in various body fluids, they often require trained users, time-consuming complementary steps as well as high operation cost, and they can only be performed in well-equipped laboratories. [13]

Therefore, there has been continuous growth in the development of various point-of-care diagnostic devices for stress monitoring. Most of these devices are used for biosensing applications to quantitatively detect stress biomarkers, particularly cortisol. Among many different techniques, electrochemical methods show considerable success compared to other methods in terms of selectivity, practicality, and measurement sensitivity. [30,31] Recently, many signs of progress have been achieved in the development of highly sensitive and selective electrochemical biosensing of cortisol in various biological fluids but particularly saliva and sweat, in addition to the blood, where detection specificity is a key factor. Fig. 1a describes the number of published papers and citations on electrochemical cortisol sensors regardless of materials, biorecognition units, and biological fluids in use. The results show a continuous and growing interest in developing practical biosensing approaches for cortisol sensing and quantifications. In the following sections, some of these key publications are highlighted and discussed in detail.

One of the first electrochemical cortisol biosensors was developed by Xu et al. using an immunosensing approach. [57] In this early study, the Authors co-immobilized horseradish peroxidase (POD) and cortisol antibody on a membrane inserted into the tip of an oxygen electrode. In this peroxide-based sensing system, the first chemically activated the hydrophilic microporous membrane that cortisol antibody was immobilized, then they monitored enzymatic activity upon combining with the antigen and measured generated oxygen with decreasing POD activity. This method made it possible to detect cortisol by measuring the relative inhibition of the activity and catalytic response without using any secondary antibody or enzyme-labeling. The sensor also showed good reusability by simply washing with a dilute hydrochloric acid solution and

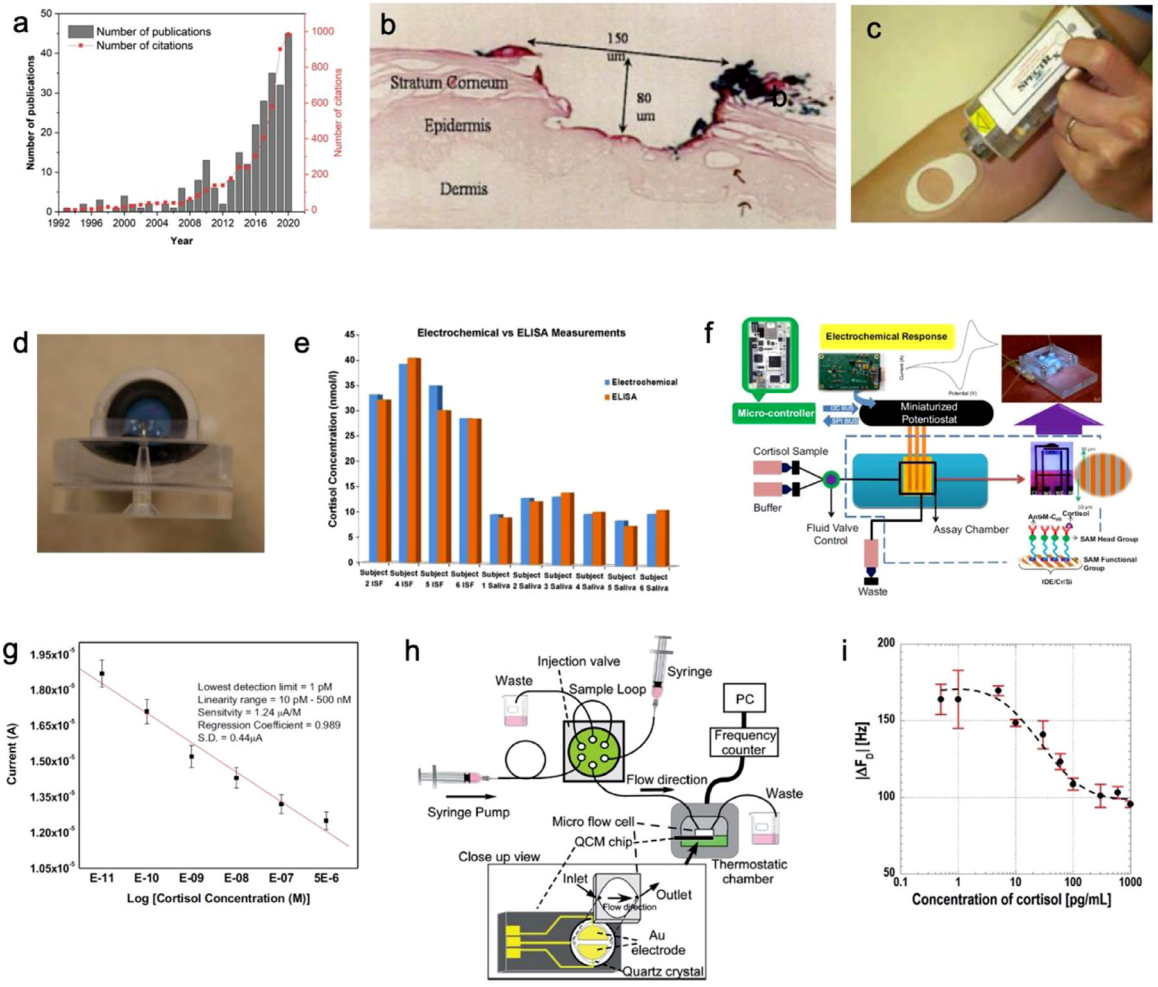


Fig. 1. (a) Graphical demonstration of a number of publications and citations based on the keyword ''cortisol sensor'', using the Web of Knowledge. (b) Cross-section image of a micropore on the skin and (c) the usage of a handheld laser device applied on the skin through black. (d) Photographic image of sample collection compartment. (e) Comparison of biosensor performance with ELISA measurements for saliva and ISF samples. (f) Schematic diagram of miniaturized potentiostat controlled by microcontroller unit and demonstration of sensing mechanisms for a surface-functionalized gold electrode. (g) Calibration curve and sensing parameters obtained by miniaturized potentiostat illustrated in (h) for cortisol sensing. (h) A schematic illustration of QCM bases twin sensing chip for cortisol sensing in the flow system. (i) Calibration curve of the cortisol sensing inflow system described in panel h. Panels b-g are reprinted with permission from Ref. [54] and Ref. [4] Copyright 2015, Elsevier B.V, and panels h-i are reprinted with permission from Ref. [11] Copyright 2014, The Royal Society of Chemistry.

high-selectivity and sensitivity with a linear response in the range between 0.1−10 μM.

Similar approaches were developed in the following years, especially the Bhansali group for salivary cortisol measurements. [22,23,41,44] In one of these studies, Sun et al. developed an immunoelectrochemical sensor based on alkaline phosphate (AP) enzyme for the salivary cortisol. [44] This study developed microfabricated gold electrodes that were integrated with a microfluidic chamber and immobilized with cortisol capture antibodies. The principal sensing mechanism of the designed sensor was based on monitoring of oxidation of reaction of p-nitrophenol generated by the reaction between the AP enzyme attached to the cortisol antigen via detector antibodies with the p-nitrophenyl phosphate solution. The sensor showed a quite accurate detection in the collected saliva achieved to a concentration of 0.76 nM with 10 min of incubation time. In a follow-up study, the same group developed a real-time and continuous measurement platform for impedimetric cortisol sensing in interstitial fluids of the human subject. [54] In this interesting study, the authors developed a tool that helps to generate micropores on the stratum corneum layer by means of vacuum-pressure following near-infrared laser irradiation on a layer of black dye material attached to the skin for the extraction of ISF, as shown in Fig. 1c,d. Besides its interesting device architecture, the Authors also developed a gold microelectrode array functionalized with a self-assembled monolayer of succinimidyl propionate to bind anti-cortisol (Mab) to fabricate cortisol immunosensor. Additionally, the sensing surface was modified with ethanolamine to block the non-specific binding site, and cortisol quantification was conducted using electrochemical impedance spectroscopy. The biosensor was successfully used for in-vitro detection of cortisol in ISF as well as saliva with a linear response in the range 1 pM to 100 nM, and results were correlated with the enzyme-linked immunoassay (ELISA) method, as described in Fig. 1e. Even though the proposed device design required invasive sampling methodology, it was one of the first studies that showed the feasibility of a wearable electrochemical cortisol sensor. The same group also applied the same immunosensing method for cortisol sensing using low-cost, miniaturized, and portable potentiostat capable of performing cyclic voltammetry, as shown in Fig. 1f. [4] Using an open-source microcontroller unit together with a micro-power electrochemical sensing integrated circuit was developed. The sensing principle involves three-electrode system-based electrochemical measurements in which the potential is scanned in a wide range of potential at a fixed sweep rate for both oxidation and reduction reactions of surface-modified with succinimidyl propionate to bind the anti-cortisol antibody. The miniaturized biosensor showed the capability to detect cortisol at 1 pM with linearity of 10 pM to 500 nM and with a sensitivity of 1.24 μM. (Fig. 1g) This study was particularly important since it showed that obtained results are comparable to conventional analyzers and suggested that this electrochemical immunosensing concept can be integrated with a miniaturized system for cortisol sensing.

As an alternative electrochemical method, Ito et al. combine flow injection analysis and quartz crystal microbalance (QCM) technique for rapid and sensitive cortisol detection. [11] In this study, the authors demonstrated a successful detection system consists of a twin sensor chip, as described in Fig. 1h. In this design, one sensor was used to detect antigen-antibody interaction, together with the other sensor surface, as a reference to remove environmental influences. The QCM-based sensor device consisted of a competitive assay since the molecular weight of cortisol is so small to detect directly, and other alternative methods such as sandwich assays are costly and require a long detection time. This study was particularly suitable for clinical laboratory use since the proposed design is integrated with flow injection analysis that allows sequential analysis and regenerations of the sensor surface. Overall, the biosensor showed high sensitivity and high throughput with repeatability in situ surface generation with a linear response range from 5 to 100 pg/mL with a correction factor of 0.94, and a detecting limit of 11 pg/mL ($S/N = 3$) (Fig. 1i).

Besides classical approaches on developing solid-state materials-based sensors such as metals or semiconductors as a principal component of transaction mechanisms, different approaches such as polymer substrates, membranes, or papers were also studied alternatively. [41] In one of these studies, Khan et al. reported a label-free paper-based electrical biosensor that operates in-real time fashion wirelessly to quantify salivary cortisol. [14] In this study, the authors integrate the sensor chip with a handheld miniaturized electronics printed circuit board and performed cortisol analysis directly incubating the saliva samples on-chip surface without additional processing. The device architecture was built on filter paper coated by poly(styrene)-block-poly(acrylic acid) (PS67-b-PAA27) polymer and graphene nanoplatelets (GP) suspension, as shown in Fig. 2a. Then this surface was conjugated with an anti-cortisol antibody (anti-CAB) on top of gold microelectrodes using 3,3′-dithiodipropionic acid di(N-hydroxysuccinimide ester (DTSP) as a self-assembled monolayer (SAM) agent. The biosensor demonstrated a wide cortisol-detection range from 3 pg/mL to 10 μg/mL, with a sensitivity of 50 Ω/(pg/mL), and results were correlated with the ELISA method with a regression value of 0.9951. (Fig. 2b,c)

Following the similar antibody-based sensing principle with different transaction methods, Yo-Han et al. developed chemiresistor sensing for direct measurement of the cortisol. [16] In this study, the authors designed an electrode by conjugating a monoclonal antibody with reduced graphene oxide (rGO) as a direct sensing element to drive change of resistance or conductance between two planar electrodes, as shown in Fig. 2d,e. Upon the cortisol binding, the current signal changed between 2 and 4 μm channels due to the charged rGO sheet exhibiting resistance variations, achieving the limit of detection of 27 pM using real saliva samples (Fig. 2f).

Among many electrochemical cortisol biosensors, an immunosensing strategy based on the reaction of cortisol with cortisol antibody or enzyme-assisted immunoassays is the most commonly employed methodology. [59] However, a few alternative approaches have been recently developed by different research groups, focusing on either aptamer or molecularly-imprinted polymers (MIPs) as major biorecognition elements. [5,6,33] In one of these examples, Fernandez et al. developed a hybrid approach based on the ink-jet printed sensor on a paper substrate with macrocyclic catalyst, metalloporphyrin, that electrochemically reduce the cortisol and captured by the aptamer functionalized magnetic nanoparticles, as illustrated in Fig. 2g. [6] In addition to these two-step sensing mechanisms, the biosensor also consists of a thin magnetic disc positioned at the back of the electrode to enrich the magnetic nanoparticle-bound cortisol at the electrode surface. Biosensors were also tested in real human saliva samples with low limits of detection (10 pM) with a linear response range between 100 pM to 50 nM, and the results were correlated with standard ELISA testing with high accuracy.

In another interesting study, Xu et al. developed a simpler aptamer-based approach that doesn't require any enrichment steps or additional sample processing. [56] In this report, the Authors fabricated a reconfigurable and solution processible nanoscale biosensor with multiplexed sensing capability by modifying aptamer functionalized single-walled carbon nanotube onto the pre-patterned electrode, prepared by dielectrophoresis, as shown in Fig. 2h. Authors successfully showed real-time detection of cortisol in serum in the range from 50 nM to 1 μM together with other biomarkers, including neuropeptide Y and dehydroepiandrosterone-sulfate.

There are, of course, many other interesting research articles that have been published over the years, and researchers developed many alternative and successful approaches for the electrochemical sensing of cortisol. [10,41,59] However, this review only focuses on some of the key developments that direct the readers through wearable electrochemical cortisol sensors.

3. Wearable stress monitoring

3.1. Can wearable biosensors be a solution for real-time stress monitoring?

Wearable health monitoring tools, but especially wearable biosensors, have recently shown significant progress in biomedical applications

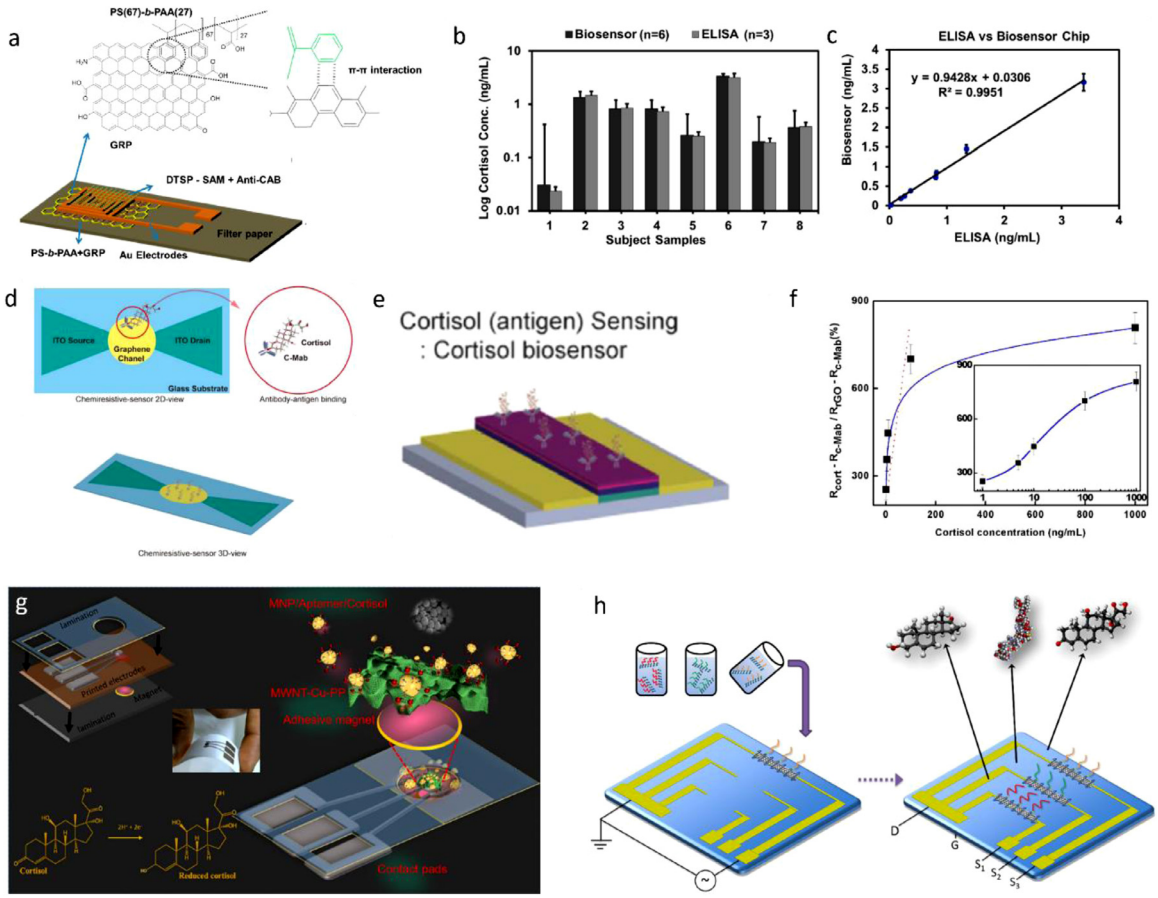


Fig. 2. (a) Schematic illustration of paper-based electrical cortisol sensors prepared by graphene nanoplatelet and poly(styrene)-block poly(acrylic acid) (b,c) Comparison of device performance on six different subjects and validation with standard ELISA method. (d,e) Graphical illustration of device fabrication and coating graphene-modified channel with cortisol antibody. (f) The resistance calibration curve of the biosensor with increasing cortisol concentrations. (g) Schematic illustration of device architecture, sensing mechanisms, and surface modification for the magnetic nanoparticle enriched aptamer-based cortisol sensor. (h) Schematic diagram of the direct aptamer-based sensing on SWCNT-coated device channel. Panels a-c are reprinted with permission from Ref. [14] Copyright 2017, American Chemical Society. Panels d–f are reprinted with permission from Ref. [16]Copyright 2020, Elsevier B.V. Panel g is reprinted with permission from Ref. [6] Copyright 2017 AAS. Panel h is reprinted with permission from Ref. [56] Copyright 2018, American Chemical Society.

due to their ability to detect many physical and chemical signals and help to sustain an optimal health status. [15,32,40,52] In general, wearable biosensors have been recently considered as a key player to revolutionize centralized healthcare care systems with home-based personal diagnostics to reduce not only healthcare costs but also time-to-diagnosis by providing real-time biological information. [33] In this respect, wearable biosensors have recently emerged as an alternative to provide vital signs monitoring of patients, athletes, premature infants, children, psychiatric patients, people who need long-term care, and people in impassable regions far from health and medical services, and they are significantly effective in the prevention, timely diagnosis, control, and treatment of diseases. [15,49]

Most of the recent wearable stress sensors have mainly focused on addressing the demand for physical sensing, which helps to measure skin perspiration or conductivity, heart rate, and temperature. [27] However, these methods cannot provide sufficient information about a person's physiological conditions and may cause serious misleading information due to possible alteration of bodily parameters, which can be induced by non-stress related natural conditions such as weather conditions or fever. This has resulted in an increasing interest in developing wearable diagnostic tools to detect various biomarkers for chronic stress disorders and stress-induced diseases.

Moreover, it is believed that real-time cortisol monitoring using wearable devices will be particularly beneficial for those who involve stressful occupations, including armed forces personnel, police, and firefighters or other types of occupations such as professional athletes or individuals with certain medical need as well as individuals who want to improve their overall health status regardless of any medical conditions. Therefore, wearable devices will potentially offer the enormous advantage of providing real-time and continuous data on the stress levels of individuals while they perform regular duties or activities at home or workplaces with the help of relatively simple, compact, and low-cost instruments.

In the following section, we highlight and discuss some of the most prominent, up-to-date examples of wearables, particularly focus on wearable electrochemical cortisol sensors chronologically, as illustrated in Fig. 3.

3.2. *Special focus: wearable electrochemical cortisol sensing*

Even though it is not in the wearable format, the first real-time electrochemical monitoring of cortisol was developed by Cook et al. in the study that cortisol detection was achieved by monitoring peroxidase activity on an electrode surface by following competitive binding of endogenous corticosteroid and a corticosteroid-peroxidase conjugate with antibodies. [3] In this study, in vivo cortisol measurement was achieved by implanting the small size probe into a tissue or circulatory system. This was achieved through the isolation of the working electrode from sampled fluids by encasing the electrode with a dialysate membrane. The sensor system also showed stability and durability for in

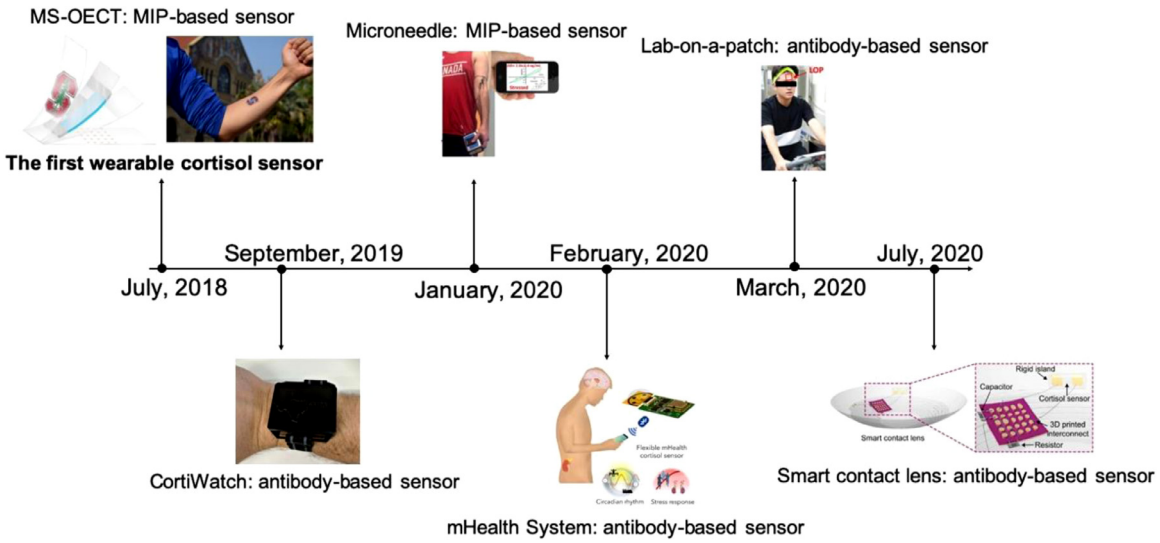


Fig. 3. Historical timeline and development of wearable electrochemical cortisol sensors. The photos in the Figure are reprinted with permission from Ref. [50] and Ref. [20] Copyright 2020, Elsevier B.V., Ref. [33] and Ref. [29] and Ref. [19] Copyright 2020 AAS.

vivo measurements for more than 48 h and 400 successive measurements as well as 0.2 μg/100 mL sensitivity. This research was one of the very early breakthroughs and open-up the discussion of implantable or wearable electrochemical cortisol sensor research.

In several other articles, the concept of wearable electrochemical cortisol sensors was discussed, but there was no direct on-body real-sample analysis in any of those studies [17], and yet the very first example of a wearable electrochemical cortisol sensor was published by Parlak et al. in 2018. [33] In this study, a novel skin-mounted patch-type molecularly selective organic electrochemical transistor device (MS-OECT) was developed to detect cortisol hormone directly from sweat during physical exercise. To implement this strategy, first, the MS-OECT device was built on flexible and stretchable styrene-ethylene-butylene-styrene (SEBS) elastomer by coating poly(ethylene dioxythiophene): poly(styrene sulfonate) (PEDOT: PSS) as a channel materials between two planar Ag/AgCl contacts on SEBS substrate. Then, as a biorecognition layer, a molecularly selective membrane was coated on top of the PEDOT: PSS channel. After building the transducing components, the device was combined with a laser-patterned microcapillary channel array for sample acquisition and a hydrophobic protection layer. In this study, molecularly selective membrane as a crucial part of the sensor device was synthesized by copolymerizing functional monomers together with cross-linking agents in the presence of template molecule cortisol. After testing several different polymerization conditions, the most selective and sensitive membrane was chosen to test in vitro cortisol sensing in artificial sweat. After obtaining a successful response over cortisol binding experiments, the biosensor device was tested using skin-like microfluidics to mimic real-sensing conditions on human skin; a skin-like microfluidic device based on poly(methyl methacrylate) (PMMA) was used, as shown in Fig. 4a. The laser-patterned skin-like flexible microfluidic device was fabricated using a multi-layered fabrication approach that mainly incorporated thick PMMA foil and skin-like pores that were defined on another PMAA layer using laser ablation. (Fig. 4b,c). This skin-like microfluidic system was used to perform real-sample analysis by collecting sweat samples from two human subjects using a sweat collector placed on the forearm. Then, approximately 50–100 μL of human sweat samples were delivered to the patch-type device through skin-like microfluidics using a syringe. The analysis was performed using the standard addition method, and results were correlated with standard cortisol ELISA methods. (Fig. 4d,e) Following in vitro sweat analysis, on-body measurements were performed by applying MS-OECT device on volunteer's forearm to assess cortisol concentration after 20-min intensive outdoor running (Figure f-i). The sensor response was monitored by following the change in the device's channel current based on cortisol binding to the membrane. Upon binding event, interfacial resistance increases, and pores on the molecularly selective membrane were blocked by the cortisol molecules, therefore reduced the channel current. To validate the cortisol sensing measurement, the channel current signal obtained by on-body measurement following outdoor running exercise was compared with the results with body prayed samples to determine the exact concentration of cortisol. The cortisol concentration was determined by interpolating the channel current values of the on-body calibration curve obtained by sprayed samples. To further validate the on-body results, the standard ELISA test was performed in parallel using the sweat sample collected during the exercise, and the biosensor device showed a strong correlation between in vitro and on-body measurement of cortisol, as shown in Fig. 4j. Overall, MS-OECT-based biosensor shows a wide range of log-linear responses for cortisol in the range of 0.01 to 10 μM with a sensitivity of 2.68 μA/dec (current per order of magnitude change in $C_{cortisol}$) and high selectivity towards possible interference hormones and molecules found in sweat.

After the implementation MS-OECT device as the first wearable cortisol sensor, a few other studies were published in the last two years. Similar to the molecularly-selective membrane approach developed previously, Mugo et al. developed another molecularly imprinted polymer-based device for the detection of cortisol in human sweat. [29] In this study, a wearable and flexible cortisol sensor was fabricated using a layer-by-layer approach using polydimethylsiloxane (PDMS) as a base layer together with carbon nanotube-cellulose composite as a conductive nanostructured film. On top of the conductive layer, the Authors imprinted poly(glycidyl methacrylate-co ethylene glycol dimethacrylate) as a capturing membrane for cortisol sensing directly from sweat. The biosensor showed rapid analysis time and a low limit of detection of 2.0 ng/mL ± 0.4 ng/mL with a dynamic sensing range of 10–66 ng/mL.

Following molecularly-imprinted polymer or membrane-based approaches, Rice et al. developed another interesting concept that Authors named CortiWatch, for tracking sweat cortisol in watch format. [34] The sensory part of CortiWatch was designed by depositing gold onto polyimide substrate using Cryo e-beam and successively treated by DTSP and cortisol antibody. This sensory part was then integrated with an electronic circuit to complete the watch design. The sensor device was first tested in artificial sweat then applied to the user's wrist for real sample analysis to track the circadian rise and fall of cortisol. The device was tested over four days on the human subject to test repeatability and also tested cortisol sensing hourly for 9 h. The device also showed a

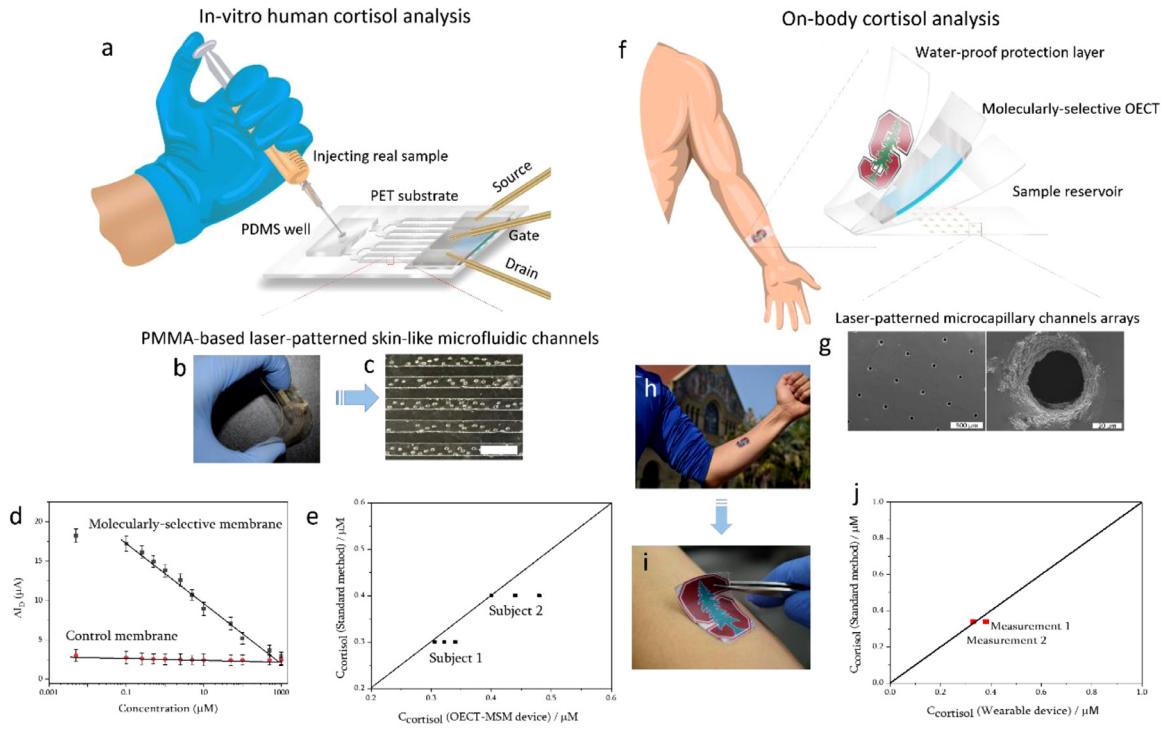


Fig. 4. (a) Schematic illustration of skin-like flexible microfluidic, while the device is flexed (b), and an optical micrograph of the device surface (c). Scale bar, 500 μm. (d,e) Real sample analysis with molecularly imprinted polymer-based and control device with different concentrations of cortisol and validation of sensor results with standard cortisol ELISA for two subjects for three repetitive measurements. (f) Schematic drawings of a multi-layered wearable device and (g) scanning electron microscopy images of laser-patterned microcapillary channel arrays (h,i) while the sensor was applied on the volunteer's forearm. (j) Correlation of real-sample analysis by a wearable device with a standard method. Reprinted with permission from Ref. [33] Copyright 2018 AAS.

good range of detection between 1 pg/mL to 150 ng/mL using chronoamperometric and impedimetric measurements.

Another significant breakthrough of wearable electrochemical sensing of cortisol was recently reported by Torrente-Rodríguez et al. [50]. In this study, the authors developed a fully integrated, flexible, and wireless device, called mHealth, by mainly using laser-induced graphene with an immunosensing approach for sensitive and non-invasive monitoring of cortisol hormone from human sweat. This study was particularly important because it revealed the strong correlation between sweat and circulating hormone for the first time. The authors investigated the dynamics of the sweat cortisol using an integrated wireless mHealth device via a graphene-based sweat sensing system. The graphene-based flexible electrode patch system was built on a polyimide substrate via laser engraving of five graphene-based electrodes. These five electrode-based sensor patches consisted of three graphene-based working electrodes, one Ag/AgCl reference electrode, and one graphene counter electrode. With the help of multi-step electrode modification, sweat analysis was achieved by competitive binding of sweat cortisol and horseradish peroxidase-labeled cortisol onto the antibody-modified graphene electrode, results in cathodic current mediated by hydroquinone. As a result, the amount of cortisol in the body fluids was calculated by measuring cathodic current on the electrode surface, as illustrated in Fig. 5a–e. The authors also showed that the sensor patch has excellent mechanical flexibility and can easily be laminated on the skin, as shown in Fig. 5f. More importantly, the Authors successfully implement their mHealth device to measure reproducible patterns obtained from the exploratory study by measuring the sweat cortisol and its variations for up to six days. (Fig. 5g) The authors also showed a positive correlation of sweat concentrations between sweat and serum samples (Fig. 5h) as well as between sweat and saliva samples (Fig. 5i). Although the number of measurements conducted in this study is still very low to conclude the strong correlations between sweat, saliva, and serum samples, this study dared to challenge many technical hurdles, including remote sensing, sample handling, and contributed significantly to the area of wearable cortisol sensing.

In another study, Lee et al. developed an interesting wearable lab-on-a-patch platform with a nanostructured device for non-invasive sensing of cortisol from human sweat using an antibody-based approach. [20] The authors demonstrated a fully stretchable sensing platform that combines impedance-based sensing methodology with a passive microfluidic device that collects and delivers a fixed volume of sweat sample via one-touch finger operation for both signal generation and washing processes, as shown in Fig. 6a. In this study, the electrode materials were built by using three-dimensional nanostructured gold combined with a redox mediator. This mediator-nanostructure platform was further used to conjugate with cortisol antibody that selectively binds to cortisol hormone in the range of 1 pg/mL to 1 μmL. After testing and correlating biosensor devices spiked with cortisol in artificial sweat (Fig. 6c-d), the Authors further evaluated the device performance for on-body cortisol testing by integrating the biosensor device with passive microfluidics. The devices were applied to the forehead of three human subjects, and measurements were performed during physical exercise, as demonstrated in Fig. 6e. The device performance was evaluated by measuring cortisol concentration in sweat two times a day (morning 9 am and evening at 6 pm) for each subject, and results were correlated with commercial ELISA assay. Overall, the lab-on-a-patch platform shows remarkable success for impedance-based signal read-out and wireless data transmission as well as passive microfluidic technology integrated with wearable electronic format.

Most of the existing wearable electrochemical cortisol sensors were developed using sweat as a body fluid for the assessment of cortisol; however, Ku et al. developed an alternative strategy and successfully expanded the concept of wearable cortisol sensor by applying the similar sensing principles that developed before to the human tear as a body fluid. [19] In this study, the authors fabricated a graphene-based field-effect transistor sensor by binding cortisol antibody to the surface of

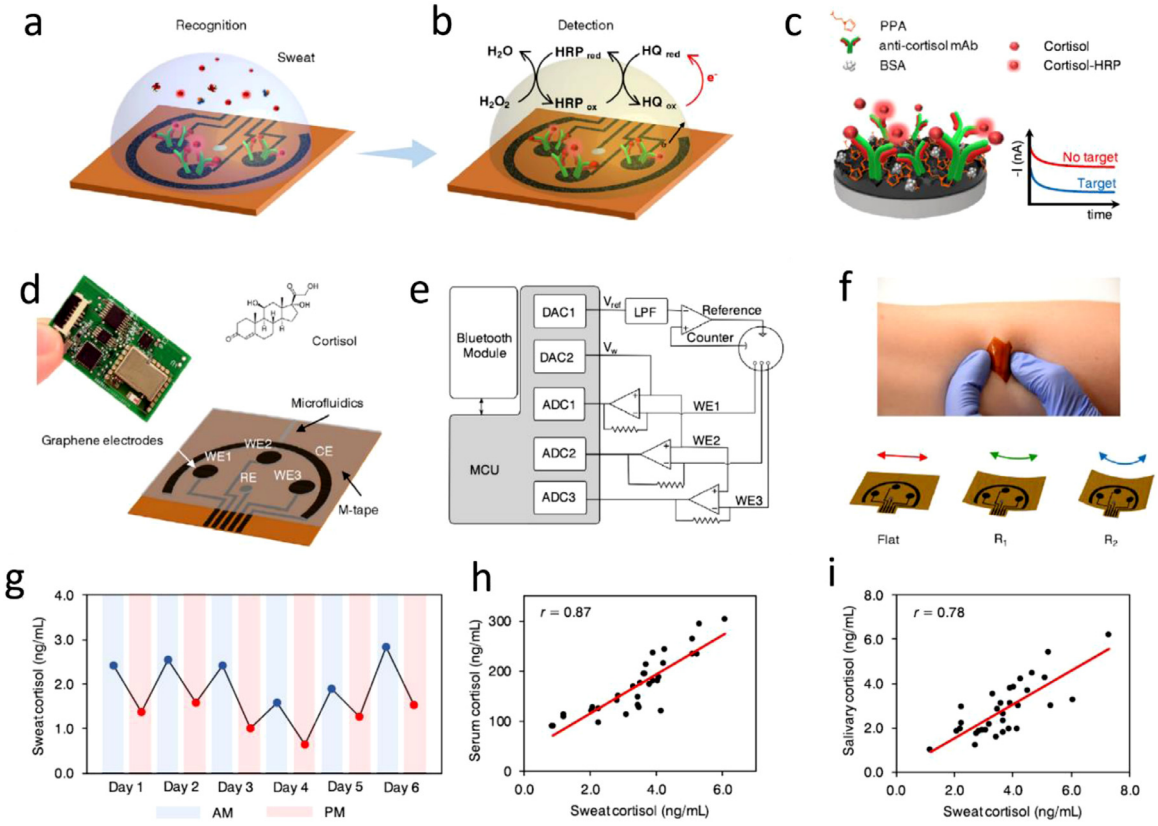


Fig. 5. (a,b) Schematics of cortisol sensing event in human sweat based on affinity-based electrochemical sensing and (c) demonstration of electrode surface modification and biorecognition elements with a hypothetical signal response. (d) The photograph of the printed circuit board with graphene-based patch type electrode for wearable cortisol detection and (e) block diagram of the sensing device in the board circuit. MCU, microcontroller unit; LPF, low-pass filter; DAC, digital-to-analog converter; ADC, analog-to-digital converter. (f) Photograph of the wearable sensor array while applied to the forearm and being flexed. (g) Measuring circadian rhythm by detecting sweat cortisol using a wearable device applied to a healthy human subject for six days. (h) Correlation of serum cortisol with sweat cortisol with 0.87 correlation number (i) correlation of saliva samples with sweat samples with 0.78 correlation number. Reprinted with permission from Ref. [50] Copyright 2020, Elsevier B.V.

graphene for electrochemical of cortisol. To build the sensing interface, the Authors first used graphene as a principal transducing element that converts the binding event between cortisol and cortisol antibody into the electrical signal. After initial in vitro testing, the biosensor was tested on the human subject with a fully integrated contact lens. The contact lens was designed for real-time wireless sensing of cortisol and interfaced with a mobile phone. Besides testing the biosensor on a human subject, the Authors also tested their device in vivo with live rabbits, and they verified the biocompatibility of the sensing system as a non-invasive methodology. As a result, the contact-lenses integrated sensor showed a low detection limit of 10 pg/mL in human tears.

Overall, all of this early progress on wearable electrochemical cortisol sensing shows that there is continuous development and solutions to technical hurdles faced in earlier publications in device design, transaction mechanism, and sample handling from the first example to the last and measurement methodologies.

4. Future perspective

Since the initial studies of Hans Selye, the research in the last eighty years demonstrate that physiological stress plays a very critical but also dual role by not only protecting but also damaging the body. These paradoxical aspects of stress, specifically stress biomarkers, challenged many researchers and therefore resulted in a diverse range of studies from clinical medicine to medical diagnostics. Today, there are still many questions that are waiting to be answered, such as what are the links between contradictory roles of stress biomarkers? How stress biomarkers play a role in disease progress? How stress biomarkers change and stay elevated long-term? And more importantly, from a diagnostic perspective, how can one perform real-time, continuous, and multiplexed monitoring of many stress biomarkers at the same time? What is the possibility of predicting the occurrence of many stress-related diseases? Many of these puzzles can be solved by developing practical, easy-to-use point-of-care devices that provide precise and real-time quantifications of stress biomarkers.

Apart from assessing an individual's stress level, another important aspect of stress monitoring is sensing the immune function and neuroendocrine biomarkers for fundamental studies such as animal experimentation that is particularly crucial to assess the effect of stress biomarkers on disease development by routinely following specific hormones. The current monitoring models, especially in animal models, are based on blood collection during the experiments; however, this intervention potentially creates additional external stress to the desired stressor on animals. Therefore, continuous and simultaneous monitoring of stress biomarkers in bodily fluids has great relevance to monitor stress and understand the effect of biomarker levels in stress-induced disease mechanisms.

Overall, wearable stress monitoring methods are still in development and require more testing to clearly see the route to manufacture robust devices based on these approaches. More importantly, most of the fundamental problems such as stability of biorecognition units, sample handling, and regeneration of sensor surfaces are often overlooked in many studies. Nevertheless, it is reasonable to believe that there is considerable potential for future progress in these fields, and further creative experimentation and approaches will reveal the true efficacy of this interdisciplinary research. Given the potential and the importance of the stress monitoring market, paradigm-changing technologies are quick to grab the headlines and turn into products. If all these recent trends reach

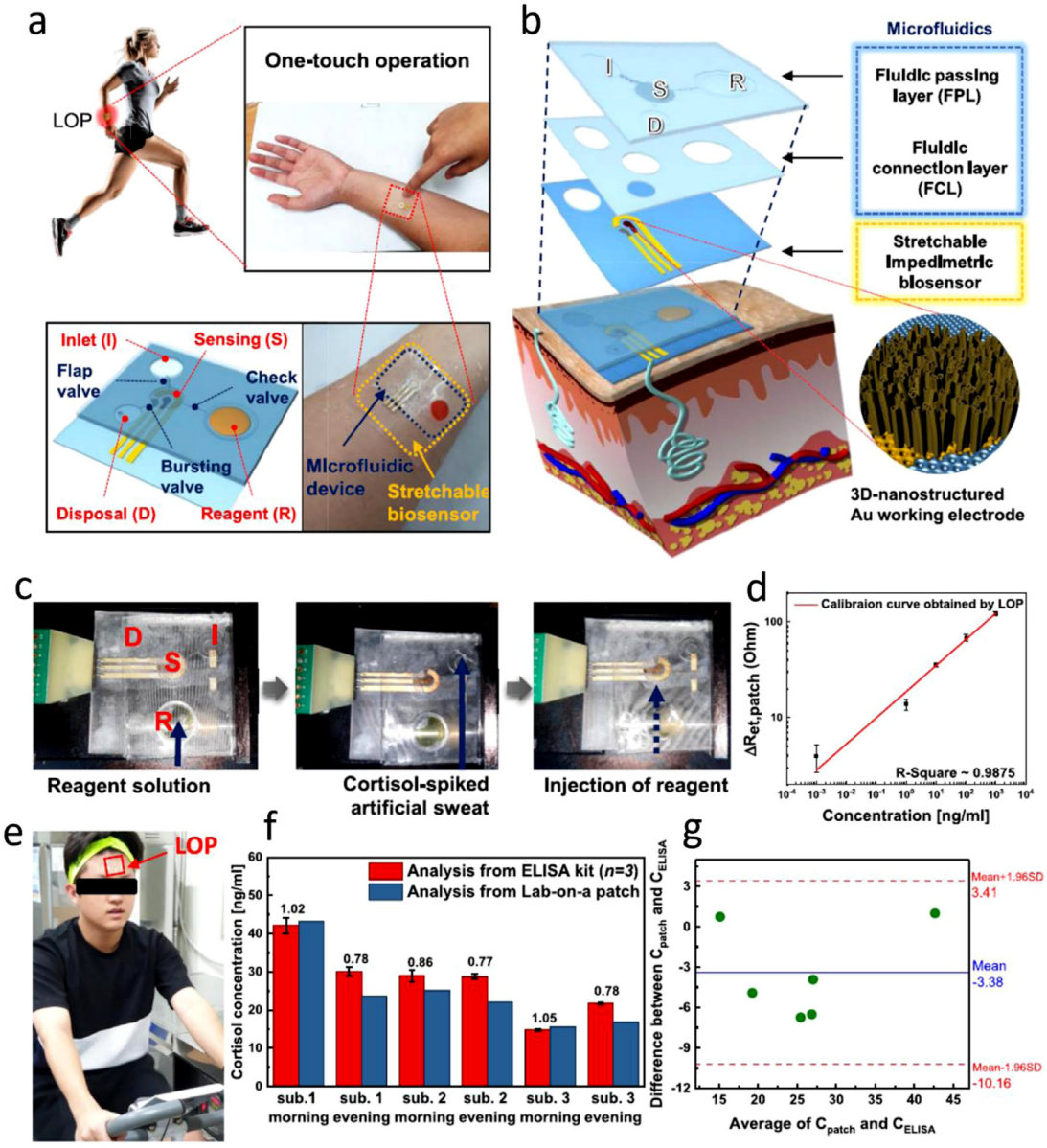


Fig. 6. (a) Schematic illustration lab-on-a-patch device applied on the skin and device structure integrated with a passive microfluidic system (b) The schematic drawing of device architecture and the 3D nanostructured electrode surface. (c) Picture of the lab-on-a-patch device with defined electrode area and (d) calibration curve based on device response with increasing concentration of cortisol. (e) Picture of the wearable device applied on volunteer's forehead and (f-g) device response for three different subjects for morning and evening measurements together with a correlation of sensor response by standard ELISA method. Reprinted with permission from Ref. [20] Copyright 2020, Elsevier B.V.

a reliable lab-scale success and then commercial applications, it will signal a major shift in the stress monitoring industry and patients' life.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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