Wearable and digital devices to monitor and treat metabolic diseases

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Leveraging wearable and digital devices to improve our knowledge and treatment of metabolic diseases

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Abstract

Metabolic diseases are a major public health concern due to their increasing prevalence. Obesity, Diabetes, the Metabolic Syndrome (MetS) and cardiovascular disease are only part of a larger set of diseases, whose prevalence is rising worldwide, with large economic costs to health care systems. Many of these are characterized by a high degree of inter-patient variability, with regard to symptoms, degree of severity, complications and responsiveness to treatments. Detailed characterization of the changes in physiological and pathological indicators during the early stage of disease is critical for timely diagnosis, interventions and in the future - prevention of deterioration. Recent surges in technological advances, and the growing availability of wearable and digital devices are now making it feasible to profile individuals in ever increasing depth. These include profiling multiple healthy aspects, including clinical, molecular and lifestyle changes. Wearable devices allowing for continuous and longitudinal health monitoring outside the clinic can be used to monitor health and metabolic status of large-scale cohorts - from healthy individuals to patients at different stages of disease. Data collected from wearable devices on such cohorts could be used to deepen our understanding of metabolic diseases, improve their diagnosis, identify early disease markers and contribute to individualization of treatment and prevention plans.

Introduction

The wearables revolution

Technological advances in the past decade have introduced improved wearable and digital devices, with various functionalities and decreasing costs. These allow continuous monitoring of individuals throughout their daily lives, from self logging of diet and sleep via various lifestyle apps, to monitoring heart rate using a smartwatch, and blood glucose levels using continuous glucose monitoring (CGM). With the rising availability, and the expanding adoption of wearable and digital devices by healthcare systems [1], more data is being collected from these devices - presenting new opportunities in clinical practice, disease understanding and management, and early marker identification. Several applications have proven the potential of using wearable and digital devices in the clinic: detection of falling and seizure onset to allow for fast reaction of medical teams [2,3]; Closed-loop control (CLC) devices were shown to improve management care in diabetic patients [4,5]; and monitoring and detection of atrial fibrillation using Photoplethysmogram (PPG) measures [6] [7,8]. The contribution of such devices has also proven useful for advancing basic and translational medical research. For example, glycemic profiles of individuals captured using CGMs were used to identify subtypes of type 2 diabetes [9], which varied in clinical measures such as HbA1C and insulin-sensitivity, suggesting a difference in clinical pathophysiology of the subgroups [10].

Wearable and digital devices allow for frequent characterization, independent of clinic visitations, and the common and widespread use of devices such as smartphones and smartwatches facilitate data collection of large cohorts of healthy and diseased individuals. Their mobile nature allows for prolonged measures outside the clinic, and throughout daily life. Data generated by wearables could be used to map the complex dynamics of metabolic diseases, from prodromal stages to monitoring progression and treatment. Utilizing data collected both on healthy individuals, and individuals in varying stages of metabolic diseases development could further our understanding of the composite relationship between metabolic diseases risk factors and causes, which could in turn aid in devising prevention and treatment strategies.

The complexity of metabolic diseases

Metabolic diseases, such as diabetes, cardiovascular diseases, hypertension, metabolic syndrome (MetS), dyslipidemia etc. have become major public health issues worldwide [11]. Diabetes has become the ninth major cause of death worldwide [12]. Hyperlipidemia has been firmly established as a primary risk factor for various cardiovascular diseases [13]. With modern lifestyle changes, affecting dietary habits and promoting sedentarism - MetS prevalence has increased worldwide, and in the US increased prevalence was observed regardless of age, sex and ethinicity from 2011 to 2016 [14].

Metabolic diseases share complex pathophysiology. For instance, despite many known risk factors for MetS, such as visceral obesity, systemic inflammation and insulin resistance - an underlying pathophysiological mechanism of the syndrome has yet to be discovered, which prevented the development of a treatment [15]. Previous works have explored the possible underlying causes of MetS. Insulin resistance, caused mainly by a high-fat, refined-carbohydrate diet and physical inactivity, was shown to have a critical role in initiating the manifestations of the MetS [16,17] . Other works focus on the role of the sympathetic nervous system as having a pivotal role in circulatory and metabolic control [18]. These diverse potential mechanisms emphasize the multifactorial nature of metabolic disorders. Moreover, they stress the need to deepen the characterization of healthy and diseased individuals, in various aspects including biological and physical measures along with lifestyle and diet habits, to further our understanding of metabolic diseases, their causes and development.

Wearables and metabolic diseases

Wearable devices provide unprecedented opportunities for monitoring and managing metabolic diseases such as diabetes and obesity. These conditions are usually chronic and necessitate ongoing management, which can be difficult for both patients and healthcare providers. Wearable devices can help to improve metabolic disease management by continuously monitoring a patient's health and providing useful insights and feedback. A wearable device, for example, could be used to track a patient's blood glucose levels or physical activity and provide real-time feedback to both the patient and their healthcare provider. This can aid in the early detection of potential problems or complications, allowing for more effective disease treatment and management. Furthermore, wearable devices can give patients a sense of empowerment and control over their health, which is especially important for people who have chronic metabolic conditions. Overall, wearable devices provide new and exciting opportunities for monitoring and managing metabolic diseases and can help patients with these conditions improve their health and well-being.

Sample temporality: comparing single and continuous measures of wearable devices

Measurements from single time points are informative but are limited in their ability to describe complex dynamics or infer direction of effects. Since they describe a single point in time, they are more likely to suffer from measurement bias that could affect clinical decisions and diagnoses. A recent study showed that resting heart rate from wearables was more consistent than that measured in the clinic [19]. Another work showed that diabetes diagnosis may have substantial differences when made using a single glucose measure as opposed to taking two glucose measures separated in time [20]. The advantage of continuous measures over single time points has already been demonstrated in different fields.

Glycemic control, and diabetes diagnoses traditionally rely on the measurement of glycated hemoglobin (HbA1c), which provides an index of average blood glucose measurement over a period of three months [21]. This measure is relatively easy and inexpensive to obtain, and has been shown to be associated with all-cause and cardiovascular mortality, as well as with diabetic complications [22]. However, HbA1c only provides an approximate measure for glucose control, and lacks information on glycemic response variability and hypoglycemic events, which have been linked to both microvascular and macrovascular complications [21,23]. Moreover, HbA1c may not be accurate in certain circumstances such as hemoglobinopathies [24]. CGM provides continuous measures of the glucose levels in the interstitial fluid, through a tiny electrochemical sensor electrode inserted under the skin. The continuous measures obtained with CGM present a tool to overcome the limitations of HbA1c by providing real time information of glucose levels, rate of change, variability and impending hypo- and hyper- glycemia events [25]. Nowadays, the beneficial impact brought by the integration of a CGM system in diabetes management has been proven. Use of CGM has been shown to improve HbA1c and reduce hypoglycemia events and glycemic variability [26].

The electrocardiogram (ECG), is one of the most useful diagnostics tools in emergency medicine, and specifically in the diagnosis of cardiovascular diseases. ECG is a composite signal, recording the heart's electrical activity. ECG measures performed at the clinic are very short in duration. The transient nature of some cardiovascular events, such as cardiac arrhythmias, requires longer monitoring periods for diagnosis. For example, current guidelines for diagnosis of atrial fibrillation (AF) require an ECG recording in the clinic, followed by a 24-hour Holter or even longer (up to 2 weeks) ECG recording [27]. However, this might not be enough, as a recent study suggested that at least 4 days of Holter ECG recordings are required to identify more than 90% of AF recurrences [28]. This stresses the importance of longer, continuous measures for correct diagnosis and precise clinical care.

The collection of ECG recordings will increase as biosensor technology advances with the introduction of wearable ECG devices, which in comparison to ECG patches are much smaller and can be worn as a watch for a longer period of time. The clinical utility of wearable ECG devices will probably be determined by the capability to modify, analyze, and introduce these data in a meaningful way to patients and healthcare providers.

Modes of continuous data measured by wearable and digital devices

Wearable and digital devices allow the collection of information on diverse aspects of health, lifestyle and body systems. Different modalities collected by wearable and digital devices may differ in their mode of collection, sampling frequency, accuracy, availability and measure duration (Table 1).

Table 1: Data modalities collected by wearable and digital devices reviewed in this perspective

Data source	Measured objective	Mode of collection	Sample frequency/resolution	Typical duration	Typical cohort size
CGM	Interstitial glucose levels	Electrochemical sensor under the skin	4-10 times per hour	Days to years	Hundreds
Physical activity trackers	Step counts/Calories burnt	Smartphones and smartwatches	several times a day-week	Days to years	Millions [29]
Lifestyle logging	Consumed foods/calories	Smartphone apps	several times a hour-day	Days to years	Millions [30]
Sleep monitoring	Saturation, snoring, movement, saturation	Accelerometers, sound level meter, and peripheral arterial tonometry, photoplethysmogram	Multiple times a second	Several nights	Hundreds
Cardiovascular measures	Heart rate, blood pressure, electrocardiogram (ECG), saturation	Smartwatches, portable ECGs, Portable blood pressure monitor, photoplethysmogram	Multiple times a second	Hours to days	Millions [31]

Glucose monitoring

Insulin resistance is a key aspect in several metabolic disorders. It is the main cause of type-2 diabetes, and is further associated with dyslipidemia, hypertension, hypercoagulability and an increased risk of cardiovascular disease [32,33]. Additionally, it is considered by some as the main contributor to the initiation of MetS manifestation [16,17]. In healthy individuals, insulin secretion from the pancreas is responsible for maintaining normal blood glucose levels. Insulin resistance occurs when the sensitivity to insulin mediated glucose disposal is impaired [34]. The progression from a healthy state to insulin-resistance, and diabetes as a result, is a continuous process [33], which could be managed if treated in early stages. Measuring insulin levels is complex and requires special laboratory tests, whereas glucose levels are measured by simple blood tests. It is thus clear that blood glucose levels are a crucial aspect to follow and investigate in metabolic behavior - both in healthy and diseased individuals. Currently approved continuous glucose monitors (CGM) use an enzymatic technology which reacts with glucose molecules in the interstitial fluid generating an electric current, which does not directly measure blood glucose concentration, but is proportional to it. CGM was first available commercially in the year 2000, and since then its accuracy has improved immensely while device size, weight and complexity has decreased [25].

Several studies have utilized CGM data to further stratify or categorize disease states. A recent study devised a new representation of glucose profiles from CGM, exposing three different profiles which they termed “glucotypes”, varying in clinical classification and response to standardized meals [9]. Such discoveries imply that existing clinical definitions of disease may conceal within them a number of sub-conditions which differ in pathophysiology - and their uncovering might contribute to better diagnosis and care.

CGM measures could also be used to investigate and better understand the dynamics of glycemic response in healthy individuals, and not just in disease states. Other works which employed CGM measured on healthy individuals to explore the diversity in glycemic responses found high variability in glycemic response to identical meals [35], and that self-reported hunger could be predicted from postprandial glucose dips 2–3 h after a meal [36].

While CGM is widely used in patients with type 1 diabetes, it is rarely used in people with type 2 diabetes who are not receiving intensive insulin therapy. It is an option for people with type 2 diabetes who are on multiple daily insulin injections (basal/bolus insulin therapy) and need to adjust their insulin dose based on glucose levels, especially those who have frequent hypoglycemia unawareness.

The monitoring of glucose in diabetic patients has been completely altered by the development of CGM sensors. Globally, there are more people using CGM, and it's expected that trend will continue as less invasive and more inexpensive sensors become available.

Significant developments are also anticipated in terms of CGM integration with other systems, including medical devices for diabetes therapy, activity trackers, and other physiological wearable sensors. Better glucose prediction and automatic insulin modulation algorithms, as well as a better understanding of the factors that contribute to abnormal glucose events, will be made possible by the integration of CGM data with data from insulin pumps and other wearable sensors. Finally, this will enable better customization of diabetes therapy to the patient's lifestyle and habits.

While CGMs measure glucose quantitatively and can be used to detect hypoglycemia, the accuracy of most such devices currently on the market or soon to be released is lowest in the hypoglycemic range. There are currently no widely used products for this purpose on the market.

Long-term implanted sensors that measure glucose using enzymatic, optical, or osmotic technologies are also being developed. Noninvasive sensors are optical methods in development that do not involve inserting a needle into the skin or implanting a sensor.

Physical activity trackers

It has long been known that physical activity is a major contributor to health, and that regular physical activity reduces the risk of cardiovascular and all-cause mortality [37,38]. Several trials have shown that regular physical activity is effective in preventing type-2 diabetes, and decreasing the likelihood of developing MetS, especially in high-risk groups [39]. Many devices and mobile applications, available in the market today, provide consumers real-time tracking of their daily activities. Their accuracy in recording physical activity has been shown in several trials [40,41], confirming their reliability and use for research.

Their importance to health status and outcomes has also been shown. For example, a prospective cohort study examining more than 2,000 individuals who were followed up for a mean of 10 years found that participants who walked at least 7000 steps per day experienced lower mortality rates compared with participants who walked less than 7000 steps per day [42].

Almost every smartphone and smartwatch are equipped with varying tracking apps, which automatically monitor steps, physical activity by GPS and pulse rates - which could be translated to metabolic rates. All these present researchers with the opportunity to investigate physical behavior and habits in larger, more diverse cohorts than ever before. A recent study examined data activity across more than 100 countries, and revealed varying levels of activity in different countries [43] with great inequality. This revelation, which can stir medical recommendations for physical activity based on the population characteristics, as well as affect other aspects such as urban planning to promote physical activity, was made possible thanks to the growing use of wearable devices to track physical activity. As the user population of wearable devices expands, we will be able to uncover more aspects affecting daily physical activity - geographic location, cultural differences, weather conditions, occupation and other lifestyle habits, enabling more personalized physical activity recommendations.

Lifestyle logging

Diet and lifestyle habits are crucial factors which directly affect health status and especially metabolic health. In recent years, various apps have been developed which allow logging of diet, lifestyle habits, physical activity and sleep duration. Data collected through these apps present a unique opportunity to investigate the direct effect of diet and lifestyle habits on health, metabolic dynamics, and the environmental factors which influence these habits, in large cohorts. For example, a recent study used self-reported diet tracking information of more than a million participants to show that environmental factors such as income, education and grocery store access are independently associated with higher consumption of fruit and vegetables and lower likelihood of obesity [30]. Additionally, individuals who used smartphones to self-log diet habits were found more likely to lose weight [44,45].

Previous studies have shown that diet habits are directly related to the risk of cardiovascular disease and Mets, and that adaptations to dietary habits could reduce inflammation associated with MetS, lower the risk of cardiovascular mortality and chronic non-communicable degenerative diseases (among them MetS) [46–48].

Diet habits could also serve as a possible intervention target to improve individuals' metabolic state and overall health. Previous studies have shown that response to meals is highly variable among individuals [35,49], emphasizing the need for personal dietary interventions. A study comparing personalized postprandial-targeting (PPT) diet to a general Mediterranean (MED) showed a significantly greater improvement in clinical targets such as time-in-range (TIR) and HbA1C levels in the PPT group [50]. Diet logging apps could serve as a valuable tool in designing, monitoring and promoting dietary interventions. They provide a simple means of communication between health providers or experts to the user, enable continuous monitoring of progress throughout the intervention and allow the users to stay engaged and aware of their progress. Several trials have shown the usefulness of diet logging apps in devising dietary interventions: to promote diet changes in healthy individuals [51], to improve heart disease risk factors through quality-focused diet logging [52] and to allow the monitoring of dietary advice, such as intermittent energy intake, in clinical trials among individuals willing to self-monitor their diet habits [53].

A potential limitation when analyzing self-logging data, and specifically diet logging, is reporting errors and biases [54]. It was previously shown that errors in dietary information, specifically underreport of energy intake and fat intake, can mask the association between nutrition and disease [55]. To address this limitation, methods of validation and calibration need to be developed and employed when working with self-reported diet information [54,56]. New technological advances could also serve as tools for improving and facilitating lifestyle logging.

Incorporation of image recognition in smartphones could present an easier approach to log meals - by simply taking a picture of your meal and uploading it to your automatic-food-recognition diet logging app. Although such technology will improve our ability to track our lifestyle habits, it will still require active manual recording and may be inaccurately interpreted. This will require development efforts to realize, but with the understanding of the crucial role that lifestyle habits, and specifically diet habits, have on our health - this is an effort worth investing.

Sleep monitoring

The gold standard of sleep monitoring is the laboratory polysomnogram - recording brain waves by electroencephalography (EEG), eye movement by electrooculography (EOG) and muscle tension by electromyography (EMG). Combining these records together, the polysomnogram is able to determine how long an individual had slept, durations of different sleep stages, wake time and more [57]. Yet the polysomnogram can only be used in lab settings, which limits the collection of sleep data on large populations and in real-world settings. In recent years, with progress in technology and sensors, many more options are available to monitor sleep outside the lab, using varying methods from movement based monitors, mobile and wearable devices to environmental devices which don't require any direct attachment to the body [58]. These will allow researchers to expand current knowledge of how sleep affects and is affected by health status.

Sleep quality and sleep disturbances such as obstructive sleep apnea, sleep deprivation and shift work have already been shown to be associated with MetS [59,60]. The direction of effect is still debatable - does MetS exacerbate sleep disorders, or might sleep disorders lead to the development of insulin resistance and MetS [59]. Poor sleep quality and short sleep duration, assessed by self-administered questionnaires were associated with increased risk of cardiovascular disease and coronary heart disease events [61]. Individuals with sleep-disordered breathing were also shown to have a higher cardiovascular risk factor [62]. As many of these works were conducted on small cohorts, several of them using polysomnography measured in lab settings, more work is needed to elucidate the relationship between sleep and metabolic disorders. This will require the collection of sleep data on large, longitudinal cohorts, preferably in real-life settings, which might be possible with the advances in technologies allowing the measure of sleep at-home, and in relatively low costs.

The increased consumer focus on sleep awareness, as well as an increased understanding of the importance of sleep, will result in the development of many more wearable devices to quantify the various sleep stages and to assess sleep quality. Based on current trends, these future systems are likely to be smaller and easier to use for patients.

It is important to note that sleep staging is only a subset of full polysomnography, regardless of the sensing modality used, and thus any wearable being developed for sleep staging cannot replace PSG. However, it can be used to triage patients and optimize access to PSG for those who require it the most. It can also be used for long-term sleep monitoring of patients and other research subjects.

Cardiovascular related wearables

In cardiology, wearable heart rate monitors have new potential. Patients have had the option to take their own pulse for a long time, but wearables provide ongoing, passive monitoring, even

while the user is sleeping. These devices may offer an important chance for better management for patients with suspected arrhythmias or for heart rate optimization with medications.
AF, a common cardiac arrhythmia, is becoming a considerable health concern, with rising prevalence estimated to reach 12.1 million diagnosed cases in the U.S. alone in 2030. This rise is not only affected by the aging population, but could be affected by the rising prevalence of AF risk factors such as obesity and diabetes [63]. Diagnosis of AF requires the visual inspection of the ECG. Its intermittent nature and the fact that more than one-third of AF episodes are asymptomatic makes it difficult to diagnose in a single ECG. Studies have shown that longer periods of monitoring allow for higher detection rates of AF [1]. Wearable and digital devices specifically designed to measure heart rate (HR) and ECG signals could constitute important tools in detecting arrhythmias, and specifically AF. A recent study demonstrated the ability of smartwatch measured pulse to detect AF, recruiting more than 400,000 participants, measured over a median of more than 100 days [64]. Though the probability for notification of irregular rhythm was low, a third of the participants who did receive a notification were confirmed to have AF in a subsequent ECG.

Photoplethysmography (PPG) is a medical imaging technique that uses light to measure changes in blood volume in the body. It is commonly used as a non-invasive method for monitoring heart rate and oxygen levels in the blood [65]. PPG is often implemented as a wearable device, such as a smartwatch or fitness tracker, which can continuously monitor an individual's vital signs. The device uses a light-sensitive sensor to detect the changes in blood volume, which are then translated into heart rate and oxygen level readings. PPG is a safe and effective method for monitoring a person's health and well-being and is increasingly being used in a variety of medical and fitness applications.

In addition to monitoring heart rate and oxygen levels in the blood, PPG can be used for a variety of other medical and health-related applications. Some examples of these uses include monitoring the blood pressure of a patient. PPG can be used to measure changes in blood volume, which can provide an indication of a person's blood pressure. In addition, PPG can be used to monitor a person's breathing patterns, which can help identify cases of sleep apnea, a condition in which a person's breathing is interrupted during sleep. Overall, PPG is a versatile and useful medical imaging technique that has many applications in the field of healthcare and medicine [65].

Novel technologies

Standard methods of monitoring body chemistry necessitate invasive blood-based analysis with large laboratory equipment. Alternative biofluid targets to blood, such as saliva, tears, and sweat, represent appealing noninvasive biomarker media with the potential for remote health monitoring outside of controlled laboratory settings. Sweat has a high concentration of electrolytes, metabolites, hormones, proteins, nucleic acids, micronutrients, and exogenous agents. Wearable biosensors are garnering substantial interest due to their potential to provide continuous, real-time physiological information in an array of healthcare-related applications via dynamic non-invasive measurements of chemical markers in biofluids.
Over the past few decades, the developments have been focused on electrochemical and optical biosensors, along with advances with the non-invasive monitoring of biomarkers, bacteria and

hormones, etc. For example, Sweat lactate is of great interest because of its relationship to blood glucose levels. Wearable devices are evolving to incorporate multiplexed biosensing, microfluidic sampling and transport systems, and flexible materials and body attachments for enhanced wearability and simplicity. This combination of features has made these devices more practical and user-friendly, although the fragile nature of these biological recognition elements causes performance decline over time and under different environmental conditions. Biochemical sensors for detecting metabolites in sweat and other bodily fluids appear to be a promising avenue, but they are not yet widely used.

Integration of multimodal temporal data - opportunities and challenges

Integration of the different continuous measures described above would serve as a major benefit in describing complex dynamics of different body systems. Moreover, incorporating continuous measures along with multi-omics data sets could provide a unique opportunity to identify disease markers and pathways. This will allow for a broader understanding of the gradual changes on a phenotypic and genetic level, leading to the development of metabolic diseases. Using the inherited temporal structure of the data, we might be able to disentangle the cause and effect relationship between different measures. The ~~voluntary nature~~ convenient way of use of wearable devices could serve as a benefit in eliminating probable selection bias in research cohorts, and potentially deploying diagnosis tools in wide populations - for actual clinical use or research purposes [64]. Yet, there are still many challenges to face, the first being the effort and funds required to collect diverse measures on large, longitudinal cohorts. Furthermore, to fully investigate the relation between various body systems involved in metabolic health, and their effect on each other - these diverse measures need to be obtained simultaneously, which poses an additional challenge. Several efforts have already started gathering diverse types of information on large, longitudinal cohorts [66–69]. These include some of the continuous measures described above, along with multi-omics data, and with repeated measures over years of follow-up - allowing for the investigation of directions of effects.

There is a need for infrastructure to collect and manage wearable device data. This infrastructure can take many different forms, depending on the specific needs and goals of the data collection process. The infrastructure required for collecting and managing wearable device data is a critical component of any wearable device data collection effort, and must be carefully planned and implemented in order to ensure that the data is collected and managed effectively.

Once data has been collected, we still face technological challenges when approaching the integration of different data types and sources. To exploit all data sources in hand, researchers are required to design analyses and construct models that combine data from different sources, and often with different temporalities (Figure 1). Some previous studies integrated information from several wearable devices [70] or various measures from a single device [19], yet these were performed on small sample size cohorts, and did not contain any single point measures such as multi-omics data. Scaling such analyses to larger cohorts might require the development of more complex, and maybe less interpretable models.

Reliability of the data collected using wearable devices might present another challenge. Despite technological advances and improvements, wearable data might still present inaccuracies and false information [71], leading to incorrect clinical decisions or research conclusions. This needs to be considered when analyzing data originating from wearable devices, possibly by screening potential errors in reading based on prior knowledge. Moreover, validation is an important step in the process of collecting and managing wearable device data and is essential for ensuring that the data is accurate, consistent, and of high quality. There are many ways to validate wearable device data, and the appropriate method will depend on the specific needs and goals of the validation process. It is important to carefully plan and implement the validation process to ensure that the data is accurate and reliable.

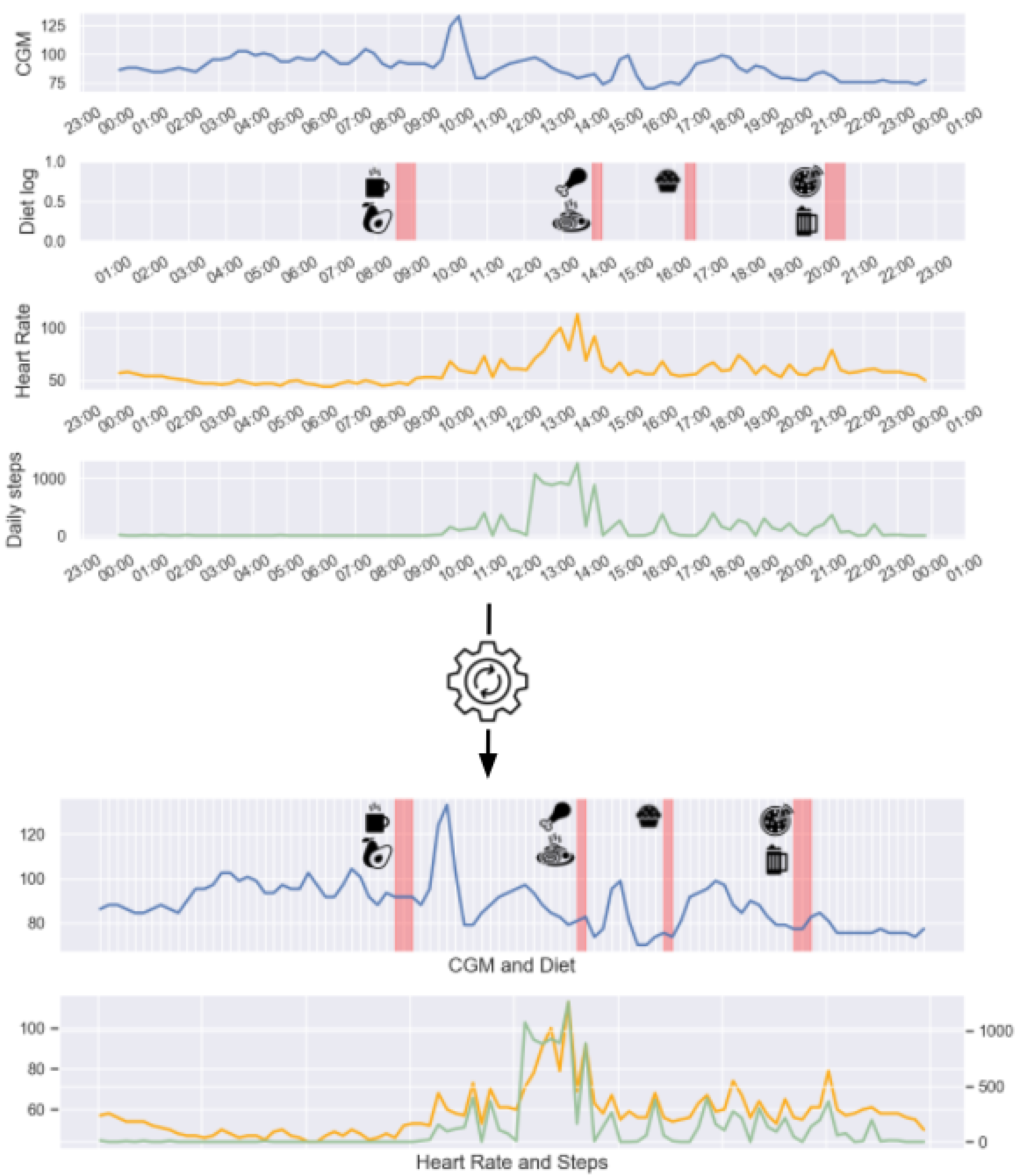

Figure 1: Illustration of the integration and analysis of data from multiple sources of wearable and digital devices, with varying temporalities

Wearable and digital devices, owing to their growing availability and improving capabilities, present an opportunity to characterize larger populations than ever before, in real life settings.
Until now, most data collected for research purposes originated specifically and carefully from designed trials mainly focused on diseased individuals believing that the answers to disease-related questions lies with individuals already displaying the disease. Most diseases, and especially metabolic disorder ones, develop continuously and slowly, sometimes over decades, allowing the placement of individuals on a continuous spectrum - from health to disease. Due to their broad user audience, data collected from wearables does not focus on any specific disease, and is also collected from large populations of healthy customers, from diverse populations. This information can provide new insights on the early stages of disease manifestation, the processes and body systems involved in them and maybe even potential early interventions to prevent further deterioration. ~~In some modes of wearable data, types of data and collection methods are not designed to study specific diseases. This holds the potential to uncover new relationships between these data and various health aspects - leading to new research hypotheses and directions.~~ As a significant portion of the consumer population are typically healthy individuals, wearables present a unique opportunity to deeply characterize different body systems, diverse lifestyle habits, and their interactions, prior to the onset of diseases. ~~The continuous measurements produced by some wearables creates short term longitudinal data that could provide information on the early stages of health deterioration.~~ Such data may also contribute to the development of early interventions that are personally tailored to different individuals.

Nevertheless, their extended use also presents some obstacles. As opposed to carefully designed cohorts, data might be less reliable, and without any gold-standard of data collection and organization to compare to - which is crucial for both clinical decision making and research observations. Designing proper tools to filter, analyze and integrate data from wearable and digital devices is key, and requires further advances. Moreover, to gain broader insights from wearables collected data, initiatives to share data sources and make them accessible to more clinicians and researchers are required. This will not only create larger, more diverse cohorts, but will also allow multidisciplinary researchers worldwide to work with these data sources, promoting new directions of research and our understanding of the progression from health to disease. Initiatives such as the UK biobank [67], the 10K in Israel [66] and All of Us in the US [68] have already begun such efforts - and more need to follow their footsteps. Furthermore, despite the vast and diverse information obtained from wearables - unraveling disease mechanisms, potential biomarkers and potential treatments might require additional information such as multi-omics data, posing a challenge to collect diverse cohorts on large populations.

Clinicians are already using wearable and digital devices to manage diseases such as Diabetes. Their mobility allows for continuous patient management, without the need to see the patient in-clinic, allowing patients to live a less disrupted life. More diseases and conditions, such as cardiovascular disease or events and sleep disorders, could be better managed and monitored using wearables. They could further be used by healthy individuals to improve their health status and lifestyle habits - from logging diet to help in weight loss, to following physical activity and sleep duration, to help individuals understand how to live their best lives.

With the ever improving technology, wearable and digital devices show continuous progress - and in the future might become even more accessible and simple to use. With the growing availability of smartphones and smart-watches, a day where every individual on earth will have wearable data collected for them is in sight. Current wearable devices mostly focus on measuring or characterizing one health aspect or body system, for example, smart-watches mostly track physical activity and HR and CGMs are used to quantify blood glucose levels. One might imagine that wearable devices of tomorrow will be able to produce more extensive information on the measured individual [72]: smart-watches could provide a full set of vital signs at all time, identifying subtle changes in health state, and provide alerts as to the possibility of viral infections [73], heart attacks and atrial fibrillation [64] or glycemic events; neurological sensors might be developed, for example by monitoring eye movements (by wearing glasses) [74], which could inform the user on awakeness levels, or even further - alert on events of stroke, or early development of neurological conditions such as Parkinson's disease [75]; smart sensors will allow for automatic detection of nutritional intake [76], perhaps by taking pictures of meals by smartphones, enabling accurate and unbiased diet logging. Going even further - all this might be available in one simple, non-invasive, mobile device, utilized to promote individual’s health and our understanding of the development of diseases.

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