FACULTY OF MEDICINE
AND HEALTH SCIENCES

Sensors to manage Immune Mediated Inflammatory Diseases

Current Applications and Future Prospects

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Abstract

Background and purpose:

Immune mediated inflammatory diseases (IMIDs) are a group of high prevalent chronic diseases with high comorbidity rate and important secondary effect on patients' mental and cardiovascular health. Sensors, measuring physiological and emotional signs show potential to become a game-changer in IMID care. By enhancing participation of patients, they could lead to better disease control. Moreover, they could lead to new, data-driven, insights in IMID. This master's dissertation examines the current role of sensors in IMID care and provides a selection of relevant and promising sensors that are validated and readily available on the market.

Methods:

A database containing an overview of the most innovative and revolutionary medical sensors measuring vital and emotional parameters was constructed. It is one of the first extensive efforts to create a database of this type. One of the sensors was chosen and tested so that we could empathize with IMID patients and evaluate patient experience. A second database was constructed providing an overview of current scientific insights about sensors in IMID care. By combining clinical evidence, trustworthy sensors and a hands-on experience, this research aims to describe the role of sensors in IMID monitoring and to point out the latest trends and opportunities in sensor development for IMID care.

Results:

43 out of 234 identified sensors were retained and included in the database. Most of these sensors measured at least four different parameters and have FDA and/or CE approval. After three months of use, the Fitbit Inspire 2 and Mindstretch app were rated as easy to use and helpful in providing relevant information which could be useful for an IMID patient to track health and mental wellbeing. After searching relevant publications, 84 out of 320 papers were retained. Of these 84 papers, 70 focused on Multiple Sclerosis (MS) or Type 1 Diabetes (DM1). 79% of the retained papers mainly targeted the role of motor activity.

Discussion and Conclusions:

There are many advanced and validated health sensors available on the market. However, their current use in IMID is limited, and their full potential has yet to be realized. By constructing one of the first comprehensive databases containing sensors measuring vital and emotional signs, <u>we created a powerful reference tool for health care workers and patients to select a sensor that satisfies their treatment goals</u>.

Current scientific literature indicates that sensors could lead to better patient outcomes by strengthening patient participation in disease management and by bringing new, data-driven, insights in IMID. So far, this is mainly in DM1 and MS.

Most of the sensors in our database can measure at least four different parameters such as Heart Rate, Activity, Sleep and Heart Rate Variability (HRV). Given the important mental and cardiovascular comorbidity in IMID, we strongly recommend investigating the role of some parameters such as HRV as a proxy for stress, and thus as a putative predictor for IMID flares.

In conclusion, there is a gap between sensor development and clinical application in IMID. Nevertheless, sensors do have potential to enhance IMID care and lead to better patient outcomes.

Samenvatting

Achtergrond en doelstelling:

Immuun gemedieerde ontstekingsziekten (IMIDs) zijn een groep van veel voorkomende chronische ziekten met hoge comorbiditeit en belangrijke effecten op de mentale en cardiovasculaire gezondheid van patiënten. Sensoren, die fysiologische en emotionele parameters meten, tonen potentieel om een game-changer te worden in IMID-zorg. Door de participatie van patiënten te vergroten, zouden zij kunnen leiden tot betere ziektecontrole. Bovendien zouden ze nieuwe, op data gefundeerde inzichten in IMID kunnen creëren. Deze masterthesis onderzoekt de huidige rol van sensoren in de IMID zorg en geeft een selectie van relevante en veelbelovende sensoren die gevalideerd en direct beschikbaar zijn op de markt.

Methode:

Er werd een databank opgesteld met een overzicht van de meest innovatieve en revolutionaire medische sensoren die vitale en emotionele parameters meten. Het is één van de eerste pogingen om dergelijke databank samen te stellen. Eén van de sensoren werd getest om beter inzicht te krijgen in de beleving voor de patiënt van het gebruik van deze sensor. Een tweede databank werd samengesteld met een overzicht van de huidige wetenschappelijke inzichten over sensoren in de IMID-zorg. Door klinisch onderzoek, betrouwbare sensoren en praktische ervaring te combineren, wil dit onderzoek de rol van sensoren in IMID-monitoring beschrijven en wijzen op de nieuwste trends en mogelijkheden in sensorontwikkeling voor IMID-zorg.

Resultaten:

43 van de 234 geïdentificeerde sensoren werden behouden en opgenomen in de databank. De meeste van deze sensoren meten vier of meer parameters en hebben FDA en/of CE goedkeuring. Na drie maanden gebruik werden de Fitbit Inspire 2 en Mindstretch app als gebruiksvriendelijk beoordeeld en nuttig in het verstrekken van relevante informatie die nuttig kan zijn voor een IMID patiënt om gezondheid en mentaal welzijn te volgen. Na het doorzoeken van relevante publicaties werden 84 van de 320 papers geselecteerd. Hiervan behandelden 70 Multiple Sclerose (MS) of Type 1 Diabetes (DM1). 79% van de geselecteerde papers richtten zich voornamelijk op monitoring van motorische activiteit.

Discussie en conclusie:

Er zijn veel geavanceerde en gevalideerde gezondheidssensoren op de markt. Hun huidig gebruik in IMID is echter beperkt en hun volledig potentieel is nog niet bereikt. Door een van de eerste uitgebreide databanken te construeren met sensoren die vitale en emotionele

signalen meten, creëerden we een krachtig referentie-instrument voor zorgverleners en patiënten om een sensor te selecteren die voldoet aan hun behandeldoelen.
Huidig wetenschappelijke literatuur geeft aan dat sensoren zouden kunnen leiden tot betere resultaten voor de patiënt door versterking van betrokkenheid van patiënten in hun ziektemanagement en het brengen van nieuwe, op data gefundeerde inzichten in IMID. Tot nu toe is dit vooral het geval bij DM1 en MS.
De meeste sensoren in de database meten ten minste vier verschillende parameters, zoals hartslag, activiteit, slaap en hartslagvariabiliteit. Gezien de belangrijke mentale en cardiovasculaire comorbiditeit bij IMID, wordt onderzoek naar de rol van sommige parameters zoals HRV als indicator voor stress, en dus als mogelijke voorspeller voor IMID opflakkeringen, sterk aanbevolen.
Er is een discrepantie tussen de ontwikkeling van sensoren en hun klinische toepassing ervan bij IMID. Desondanks hebben sensoren potentieel om de IMID zorg te verbeteren en te leiden tot betere resultaten voor de patiënt.

List of abbreviations

AS	Ankylosing Spondylitis
BG	Blood Glucose
BMD	Bone Mineral Density
BP	Blood Pressure
CD	Crohn’s Disease
CGM	Continuous Glucose Monitoring
CVD	Cardiovascular Disease
DFU	Diabetic Foot Ulceration
DM1	Diabetes Mellitus type 1
EEG	Electroencephalogram
eHealth	Electronic-Health
HRV	Heart Rate Variability
HR-QoL	Health Related Quality of Life
HS	Hidradenitis Suppurativa
IBD	Inflammatory Bowel Disease
IMID	Immune Mediated Inflammatory Disease
mHealth	Mobile Health
ML	Machine Learning
MS	Multiple Sclerosis
PA	Physical Activity
PREMs	Patient Reported Experience Measures
PROMs	Patient Reported Outcome Measures
Ps	Psoriasis
PsA	Psoriatic Arthritis
PwMS	People With MS
RA	Rheumatoid Arthritis
RPM	Remote Patient Monitoring
SDB	Sleep-Disordered Breathing
SLE	Systemic Lupus Erythematosus
SWS	Slow Wave Sleep

1 Introduction

1.1 General topic & background

1.1.1 Immune-mediated inflammatory disease

Immune-mediated inflammatory diseases (IMID) represent a group of prevalent chronic diseases, that share common inflammatory pathways (1). This group contains more than 80 different disorders including psoriasis (Ps), psoriatic arthritis (PsA), type-1 diabetes (DM1), rheumatoid arthritis (RA), ankylosing spondylitis (AS), hidradenitis suppurativa (HS) and inflammatory bowel disease (IBD). These diseases have similar genetic factors, environmental triggers and pathophysiological mechanisms in common (1).

Epidemiology

Studies show a significant variation in prevalence of IMID in different ethnic populations (2). However, depending on the included diseases, the shared prevalence in western society varies between 4.4 and 9.4% (1–3). Some IMID, such as psoriasis, have similar prevalence among men and women. Others, including RA, are much more prevalent among women (2,3).

Due to rising globalization, IMID are becoming increasingly common in developing countries (4). Consequently, the prevalence of IMID in immigrants increases too. The risk of IMID in immigrants depends on their country of origin, the host country, the immigrant generation, and the time period. This suggests an interplay of genetic factors, non-genetic determinants and gene-environment interactions (4).

Pathophysiology

IMID pathogenesis can be provoked by chronic and acute stress or by sterile inflammation caused by damage associated molecular pattern (DAMPs) or pathogen associated molecular pattern (PAMPs). These factors chronically trigger sympathetic nervous system (SNS) which can induce local or systemic inflammation. On the other hand, local or systemic inflammation can also trigger the SNS. Hyper-SNS activity influences the immune system towards a functional phenotype that can trigger immune-mediated inflammatory disease which results in tissue damage. Draining lymph nodes (DLN) drain the local tissue damage and provoke activation of immune cells in the spleen. As mentioned **(figure 1)**, dysregulation of the autonomic nervous system is a hallmark and causal feature of all IMID. This dysregulation also provokes a disturbance of the hypothalamic pituitary adrenal axis (5).

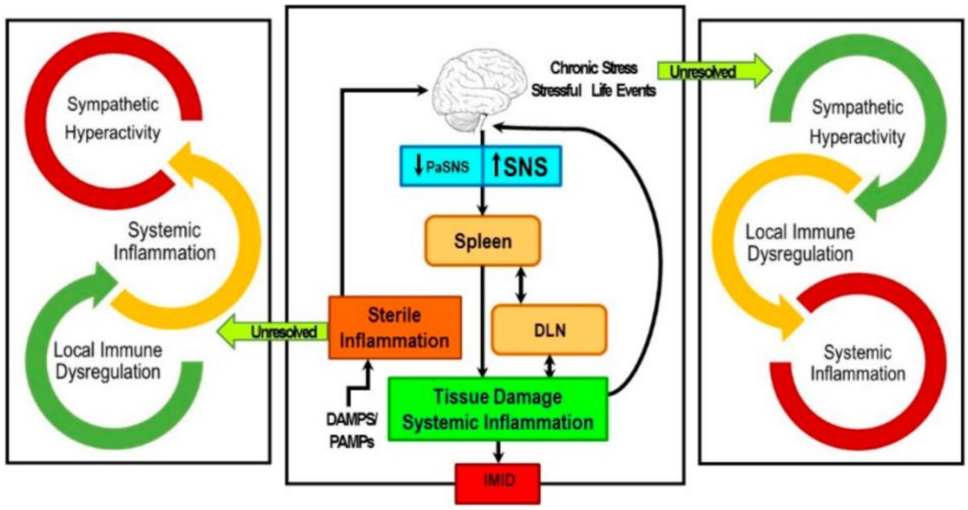

Figure 1. Schematic overview of IMID pathophysiology.

Comorbidity

Up to 9 to 10% of patients with IMID present another IMID (3). The association varies between different IMID, which results in a hazard ratio ranging from 5,4 (Hidradenitis suppurativa, HS) to 62,2 (PsA) when compared to a control population (1). For patients with IBD for example, the number of patients diagnosed with another IMID is up to 22,5% (6). The co-occurrence of IMID results in higher risk of surgery as well as an elevated chance of needing biologicals in IBD (6). Next to other IMID, relevant comorbidities are infectious or cardiovascular disease (CVD), renal disease and malignancies (2,3). These comorbidities can result directly from the IMID or as a side effect of immunosuppressive agents. The most elevated cancer risk among IMID is the risk for lymphoma (3).

Remarkably these diseases all share a substantially increased prevalence of psychiatric comorbidity as well. This includes depression, anxiety disorders, and bipolar disorder (7–9). A study focusing on IBD, Multiple Sclerosis (MS) and RA found that the risk of psychiatric comorbidity increases with an increasing number of physical comorbidities (7). Striking, when keeping in mind that these psychiatric disorders are associated with a reduced quality of life, increased mortality, and that depression and anxiety are leading causes of disability worldwide (8).

Comorbidities make patient care, diagnosis, and treatment much more complex and challenging for the clinician and have important consequences for the patients' health related quality of life (HR-QoL). Therefore, they should be taken into account when taking care of IMID patients.

Mortality

Current evidence supports the observation that patients with IMID have shorter lives than the general population (2,10). The expected survival rates differ within the group of IMID. In RA patients, there is a decrease of expected survival rate of 3-10 years (2). In psoriasis, a decrease of 3.5-4.4 years in life expectancy was established (2). Although IBD is an uncommon cause of death, there still is a shorter life-span expectancy in certain subgroups (2). The strongest predictors of survival are related to comorbidities, disease complications and manifestation of disease apart from the affected organ (2). This explains the four leading causes of death in PsA being diseases of the circulatory (36.2%) or respiratory (21.3%) system, malignant neoplasms (17.0%) and injuries/poisoning (14.9%) (2).

Mortality in IMID is established to be higher for patients with depression, anxiety disorder, and bipolar disorder (10). Moreover, the risk of suicide is increased by 72.5% amongst IMID patients (10). The increase in mortality may reflect different pathways. First there is an association between on the one hand depression, anxiety disorders and bipolar disorders and on the other hand inflammation and immune dysregulation (10). Depression is also associated with dysregulation of the hypothalamic-pituitary axis (10). Furthermore, the management of cardiovascular risk factors, may be worse in patients with psychiatric disorders.

1.1.2 **Digital health**

Digital health embodies the suitable use of digital technology for improving the health and wellbeing of people at individual and population levels, as well as improving patient care through intelligent processing of clinical and genetic data (11–13). It includes concepts such as mobile health (mHealth), telehealth, smart devices, wearables, sensors, health information technology (13,14) and facilitates personalised, predictive and preventive healthcare. Electronic-health technologies (eHealth) is an umbrella term for the use of concepts such as telehealth and mobile health (mHealth) (15).

Telehealth, or tele-medicine, is described as the use of medical information that is exchanged from one site to another through telecommunication tools in order to remotely provide health information and to ultimately improve a patient’s health (16,17). This can be enabled by facilitating communication between clinicians themselves, clinicians and patients, or patients and Mobile Health Technology (16). They embody potential for improving the management of chronic diseases and have the ability to reduce cost for the healthcare system (18)

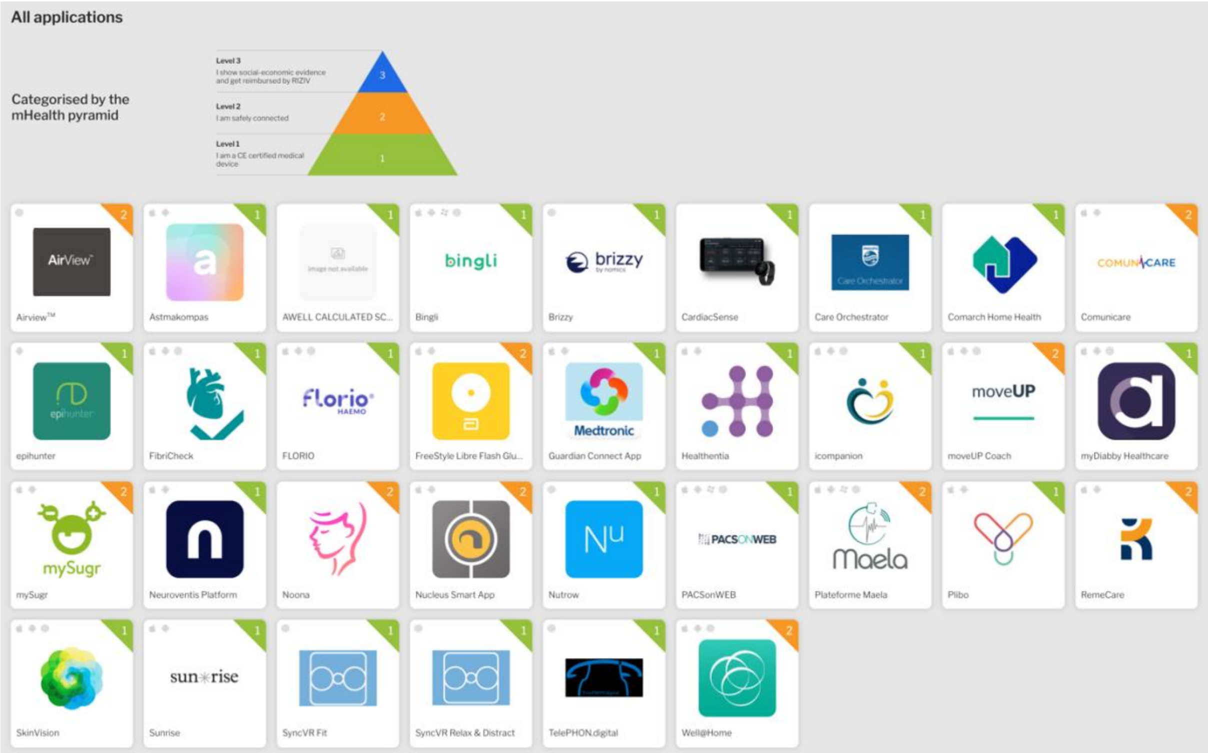

Figure 2. Overview of applications in the Belgian validation pyramid, constructed by mHealthBELGIUM. mHealthBELGIUM is an initiative of the Belgian Federal Government to centralize all relevant information on mobile apps for patients, healthcare professionals and healthcare institutions. CE marking, data protection, communication security, interoperability with other IT systems and how the app is funded are addressed (19). *At the time of submitting this paper (18/11/2021), 33 applications are listed.*

Digital therapeutics

Digital therapeutics are an emerging healthcare phenomenon within the digital health sphere which is proposed to change patient behaviour and treat medical conditions using a variety of digital technologies (13,20). It consists of innovative and evidence-based therapeutic interventions driven by software programs in order to maximize the potential of traditional healthcare (13,21). Healthcare providers often know very little about the time patients spent outside of clinics. By contrast, digital therapeutic technology allows clinicians to better monitor as well as rapidly iterate and improve treatment options. As such, precision medicine at the patient-level can be accomplished (20).

Remote Patient Monitoring

Remote patient monitoring (RPM) is part of digital health and is described as the use of digital tools capable of monitoring relevant data on patients health outside the conventional healthcare setting, in the convenience of a home setting (11). The global reach of modern technology, along with major advancements in computer capacity, has ushered in a new era of digital health system development (11). Patients are expressing a growing need for greater involvement in their healthcare decisions, particularly when it comes to long-term management, as the landscape of western healthcare grows more interconnected (11,22,23).

Remote health monitoring offers an efficient and cost-effective solution that allows the patient to continue to live in the comfort of their home environment. These technologies enable healthcare workers to remotely monitor important physiological signals of their patients in real time, analyse health problems, and provide feedback (24).

Wearable devices (wearables) and other applications such as embeddables, insideables, and ingestibles, provide opportunities to improve healthcare in a variety of settings such as in-clinic care, ambulatory care at home or in remote geographical settings (25). The use of wearables and digital therapeutics enables better clinical observation and insight in populational health status so that more targeted interventions are facilitated (20). In this thesis we discuss the monitoring of vital signs such as body temperature, blood pressure, heart rate, and respiratory rate, as well as monitoring parameters for mental health such as heart rate variability, sleep quality, activity, and stress. Increasing evidence shows that both vital signs and mental health have a notable influence in the presentation and evolution of IMID (8,9,11,26–28).

1.1.3 Sensor application in the current healthcare landscape

Hospital environment

Vital signs are the simplest, cheapest, and arguably the most important information gathered on patients in hospitals. Three classic vital signs; heart rate, body temperature and respiratory rate were introduced into clinical practice between 1860 and 1900. More recently and added to this was blood pressure which is considered a fourth classic vital sign (29). Other medical signs that are routinely captured are oxygen saturation and level of consciousness (30).

In intensive care, medium care, operating rooms, and recovery wards, continuous monitoring of inpatient vital is standard practice. This continuous monitoring is set to be able to detect clinical deterioration in an early stage, allowing prompt intervention (31). However, once patients are discharged to the general ward, vital signs are only monitored intermittently (31).

Consumer environment

Wearables integrated into a wider concept of Internet of Things (IoT) are being considered as one of the technologies which will most likely transform future healthcare and lifestyles (32). Commercially available wearable activity trackers have grown rapidly in popularity since their introduction just over a decade ago. With more than 63 million units sold worldwide in the previous ten years, Fitbit (Fitbit Inc), as of January 2021 acquired by Google, is one of the most popular commercial wearable activity trackers, accounting for roughly 20% of the market for wearable monitoring devices (33). These devices were developed to motivate and assist individuals in self-monitoring and increasing their daily physical activity. They were and still are largely marketed at health- and fitness-conscious customers. They've recently grown in popularity as assessment instruments in physical activity and health promotion studies, as well as a tool to help inform health-care decisions (33).

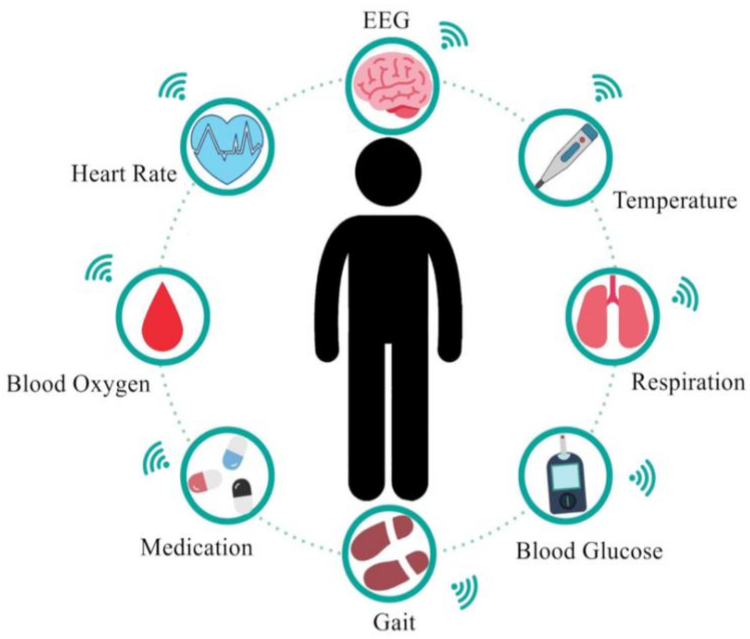

Figure 3. A medical IoT network consists of devices that can collect and analyze data such as brain activity, temperature, respiratory rate, blood glucose, gait, medication intake, blood oxygen, heart rate, etc. (115)

In addition to the success of smart wearables and activity trackers, a growing market of smartwatches also introduced people to wearable tech and health monitoring (32). Recent advances in smartwatches have led to several applications in remote health monitoring and mobile health (mHealth). Smartwatches are a relatively new technology that combines features of smartphones with continuous data monitoring that promote health, such as heart rate, activity, and energy monitoring. Since its introduction in 2014, the Apple Watch has dominated the market of smartwatches with a market share of almost 50% in 2020, followed by Garmin, Samsung, and Huawei (34).

Interest in evaluating consumer wearables for healthcare and longitudinal monitoring has grown in recent years. Several research groups have proven that accurate data can be extracted from wearables in both a clinical and 'real-world' setting (35). These devices, when properly integrated, can record vital indicators constantly and longitudinally throughout the day

(35). Moreover, it can provide feedback to users that allow them to monitor their health, establish direct communication with caregivers and physicians, and perform just-in-time interventions such as medication use based on symptoms (36). Recent research conducted by Dunn et. al even found that vital signs measured continuously and remotely by wearables were successfully associated with several clinical labs such as hematologic clinical laboratory tests (35).

Continuous monitoring

In the current healthcare setting, clinical examinations are often based on infrequent sampling (35). For outpatients this can happen once every few weeks, months or even years. Consequently, the healthcare provider only gets a brief insight in the health status of the patient. However, continuous monitoring of patient parameters could contribute to multiple benefits. In the hospital environment, continuously monitoring vital signs is found to improve outcomes of patients with complications and decrease their length of hospital stay (37). Rising evidence also shows that continuously measuring vital signs results in earlier identification of patient deterioration (38,39).

Probably the most famous application of continuous monitoring is the development of continuous monitoring blood glucose (BG) sensors. These provide insights in the BG dynamics and can alert the patient in case of imminent hypo- or hyperglycemia. Continuous glucose monitoring devices have been proven to improve the safety and effectiveness of diabetes management by reducing hypoglycemia incidence and glycemic variability (40). Moreover, the availability of real-time BG values has led to the development of patient support systems helping the patient to improve insulin dosage tuning and infusion (40).

Besides glucose monitoring, another well-established kind of continuous monitoring is blood pressure. Current guidelines of blood pressure management from the American Heart Association and the American College of Cardiology recommend confirming a hypertension diagnosis with ambulatory blood pressure monitoring. This has the advantage of differentiating hypertension from white coat hypertension or masked hypertension (41,42). The ambulatory monitoring of blood pressure can be done using various small and user-friendly devices (41). Recently Biobeat even developed FDA- and CE-certified wrist and chest monitors which can cufflessly monitor blood pressure.

1.2 Application of sensors to address IMID challenges.

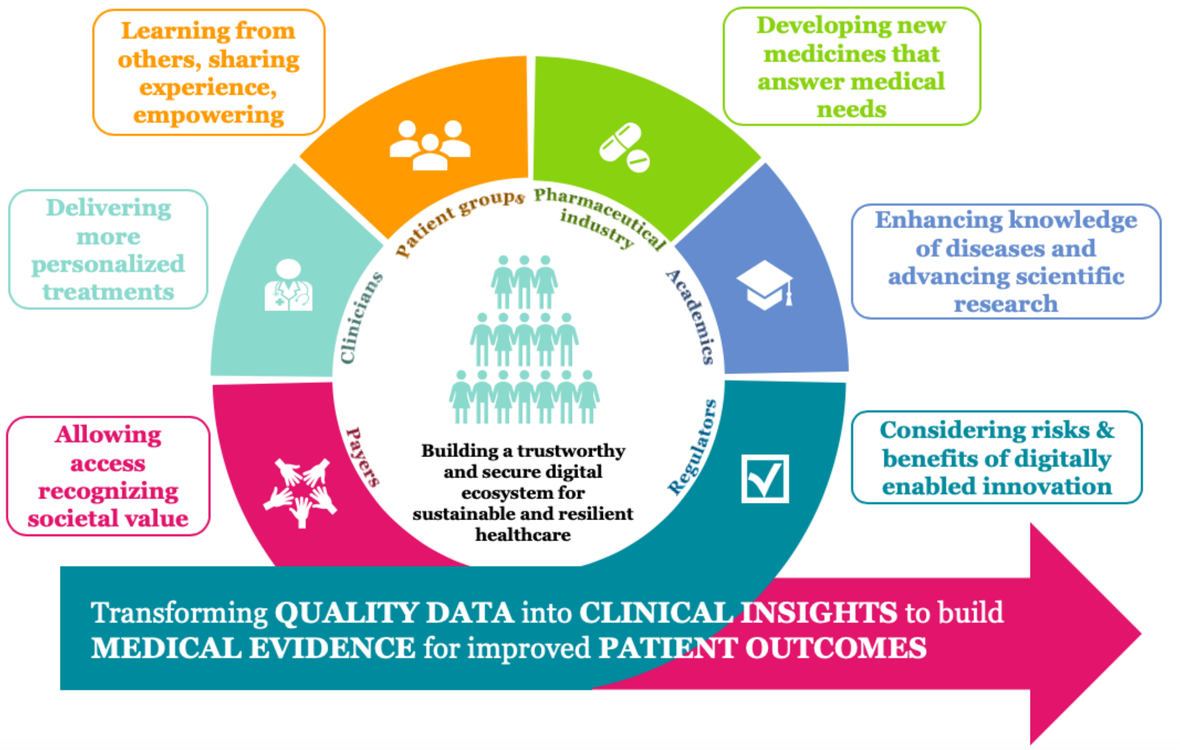

Figure 4. The digital revolution in healthcare visualised. (43)

1.2.1 Gaining new insights

The genetic network in IMID is extremely complex. That is why it is currently very difficult to predict and measure the risk of certain disease manifestation in IMID patients. Therefore, a different approach is needed to be able to predict and counteract such manifestations.

Several environmental risk factors are determined in IMID disease. However, the interplay between genetic and environmental triggers needs to be further defined. Upcoming technologies in the digital health landscape have potential to enhance the understanding of IMID and even predict flare-up of diseases. Comprehensive data sets are obtained by combining historical and real-time unstructured patient data collections. Patterns and correlations that were previously missing can be discovered using the newest advances in big data analysis, statistical modelling, and machine learning (ML) on these datasets. (44).

Furthermore, changes in activities of daily living such as eating, walking, sleeping or toileting patterns appear long before patients consult the health facilities or even before the start of disease manifestation (44). This argues for the development and implementation of a personalized early warning system.

1.2.2 **Personalization of therapy**

Despite all efforts, patients with IMID still have an impaired HR-QoL utility score (0.75) compared to the general population (0.89). Factors correlated with low utility score are smoking, current use of biologicals and female sex (45). This impairment in QoL is partially caused by the impact of comorbidities and adverse drug reactions. According to patient-reported outcomes, patients prefer to receive specific information on this adverse drug reactions tailored to their own situation (46). This situation-dependent approach is also important because although successful treatment of IMID is important, immunosuppressive agents may contribute to an increased risk for infection and cancer (2).

Considering personalized models outperform population-level models by a wide margin (35), the deployment of a tool, evaluating disease activity, therapy response, and comorbidity development could bring substantial improvements in a patients' disease experience. This tool can be developed by applying advanced analytics on data points such as vital and emotional signs provided by continuously monitoring sensors, advanced blood tests measuring a variety of markers or patient symptoms reported by mobile applications. Additionally, this tool could be the basis for the development of patient-oriented applications showing disease activity or even prediction of flare-up. This kind of applications can have positive effects on patient involvement and adherence.

According to current insights, the anti-inflammatory effect of exercise and lifestyle modification, is extremely important in IMID (44). However, a majority of patients are living sedentary lives, completely depending on their medication. Aforementioned application, in the form of a virtual health coach assisting the patient at each step of lifestyle modification, could mean a significant improvement in patient involvement and activation (44).

1.2.3 **Patient monitoring**

As mentioned earlier, IMID embodies a vast array of diseases. Diseases which may present themselves in a multitude of symptoms. Different ways of monitoring can thus be used depending on how these diseases present itself.

When considering IBD as an example, IBD has a persistent and reappearing nature which can be both physically and functionally disabling. It can cause significant disruption to patients' daily routines and put them at risk for negative and perhaps life-threatening health effects. IBD patients report feeling under-informed about their illness, as well as socially isolated and unable to adequately articulate their experiences. (11). By using real-time self-monitoring data to integrate patients' everyday disease experiences with professional provider expertise, RPM tools have the potential to greatly improve modern methods of treating IBD. Additionally habitual physical activity can be assessed as a modulator of patients' quality of life (47). Recent research shows that IBD patients who take on a more active role in the decision-making process in their own care obtain better health outcomes, higher functional capacity, and improved quality of life compared to IBD patients who did not (11).

Another example of IMID monitoring is for example activity tracking in rheumatic diseases. Research has shown that physical activity is strongly linked to disease flares and that activity monitoring could be used for early detection of these flares (48). Alternatively or additionally sensors could be used to remotely monitor morning stiffness and joint function (49).

Cardiovascular parameters

As the terminology indicates, Immune-mediated inflammatory diseases are characterized by an imbalance between pro-inflammatory and anti-inflammatory cytokines. The consequence of this inflammatory state is an accelerated vascular aging, marked by arteriosclerosis and vascular remodelling, which results in an increase of the morbidity and eventually mortality from cardiovascular events (50).

These complications indicate that there is a need for a broad approach towards IMID. This can be achieved by the transition of IMID care to a more multidisciplinary approach and the development of personalized risk stratifications. Today, this personalized risk stratification could be based upon routine function tests measuring cardiovascular and IMID parameters (50). Nevertheless, the implementation of continuously measuring sensors, could pave the way to personalized precision medicine, resulting in optimal care for each IMID patient. Furthermore, the availability of this data provided by consumer devices, creates the possibility for early diagnosis and prevention of CVD (50).

Mental health parameters

Although the interactions between psychological stress and IMID needs further definition, psychological stress carries numerous health-related adverse effects and does appear to play a role in the natural history of some, if not all, IMID (9). Evidence that psychological stress can increase inflammation and worsen the course of immune-mediated inflammatory disease (IMID) is steadily accumulating. Research has for example shown that depression, anxiety disorders and bipolar disorder are associated with inflammation and immune dysregulation (9,10). Although the inflammatory processes of different IMID affect different organ systems, all are associated with a higher prevalence of anxiety disorders compared to the general population (51). Other potential contributing factors are the association of depression with a dysregulation of the hypothalamic-pituitary axis, or the poor health behaviours that are associated with depression and bipolar disorder (10).

A Canadian study conducted by Bernstein (26) found that persons with active IBD were more likely to report distress, avoidant coping and lower well-being compared to healthy controls. Whereas persons with inactive IBD were no different than controls on those parameters. Hence, it is the disease activity that plays a crucial factor in the negative psychological attributes, and not IBD per se. This emphasises the importance of closely monitored patient-centred care.

These anxiety disorders, as well as depression and bipolar disorder are associated with an increased mortality risk among persons with IMID. Although psychiatric disorders account for much of the elevated risk, risk of suicide and suicide attempts are nonetheless elevated in IMID (10).

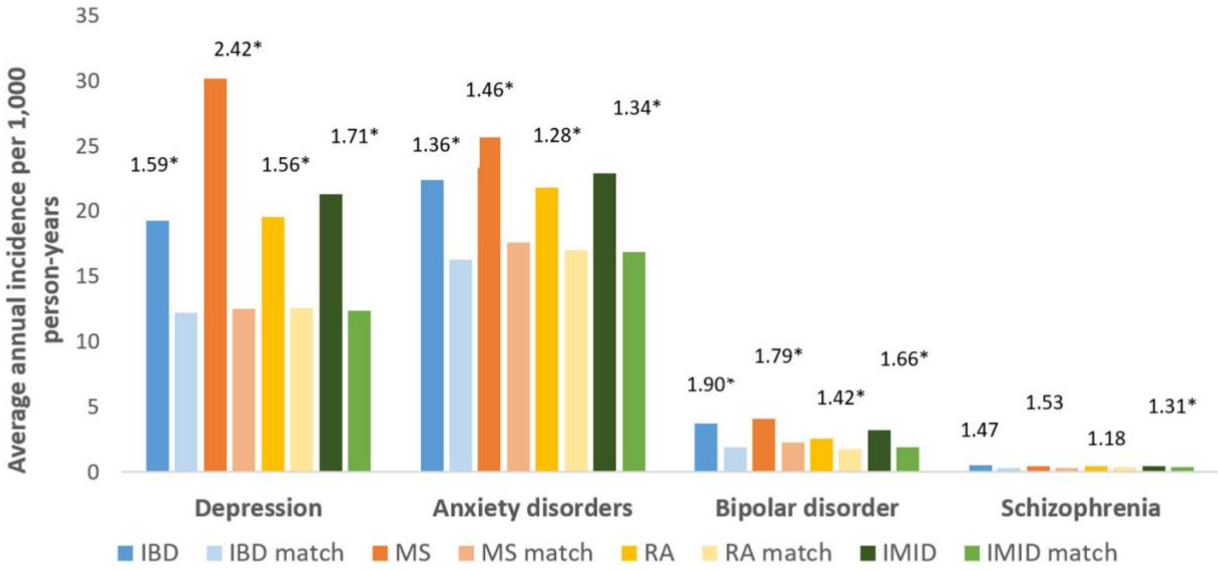

Figure 5. Average annual incidence per 1000 person-years of psychiatric disorders in immune-mediated inflammatory disease (IMID) and matched cohorts (IMID match) (8)

1.3 Research question

'What is the role of sensors in remote IMID patient monitoring, and can they lead to better patient outcomes?'

The research question is formulated using the PICOT guidelines as described by W. Fandino (52).

PICOT	**P**opulation	Patients with IMID
	Intervention	The use of sensors in remote patient monitoring
	Comparison	Current standard medical care
	Outcome	Hard and soft clinical endpoints, list of validated sensors
	Timeframe	Continuous monitoring

A scientifically and structured assessment of this research project by using the FINER criteria (52).

FINER	**F**easible	Enough technical expertise can be acquired to conduct this project.
	Interesting	This project could fill a gap between development and clinical use of medical sensor devices.
	Novel	This project has not been performed yet.
	Ethical	This project will bring no physical nor psychological harm.
	Relevant	This research aims to impact the approach of clinicians, patients, and authorities towards IMID management.

Key points

- Sensors give valuable insight in the health status of patients.
- Comorbidities highly affect the health status of IMID patients.
- Impaired mental health negatively affects disease manifestation of IMID.
- Cardiovascular disease and impaired mental health are both major consequences of IMID.
- This research aims to evaluate the role of sensors measuring mental and vital signs in IMID.

2 Hypotheses

Sensors, measuring physiological and emotional signs all over the body show potential to become a game-changer in IMID care. These technologies can be implemented in the management of IMID care enhancing patient outcomes and leading towards a data-driven understanding of IMID.

There is a wide range of certified and valuable sensors available waiting to be used in everyday practice. However, there is still a long way to go until their full potential will be reached. We suspect that this lack of clinical implementation is caused by a lack of clinical research and validation.

3 Methods

To answer the research question and assess the hypothesis, two databases were constructed. The first database contains an overview of the most innovative and revolutionary state of the art medical sensors, whilst the second provides clinical evidence about sensors in IMID monitoring.

Comparing these two databases creates a unique combination of two perspectives. The sensor database contains state-of-the-art medical sensors and their validation, and thus intends to represent latest technological innovations which could be used for IMID patients. This database consists of a selection of sensors with enormous potential for the management of IMID, but for which there isn't necessarily clinical evidence in IMID care yet. The second database contains an overview of current evidence about sensors in IMID and is thus intended to represent relevant data from a clinical point of view. This way, it becomes possible to evaluate the current value of sensors in IMID.

By combining clinical evidence and trustworthy sensors, this research aims to describe the role of sensors in IMID monitoring and to point out the latest trends and opportunities in sensor development for IMID care. Finally, we intend to make recommendations, based on the clinical evidence, so that state-of-the-art sensors can be implemented in clinical practice leading to better patient outcomes.

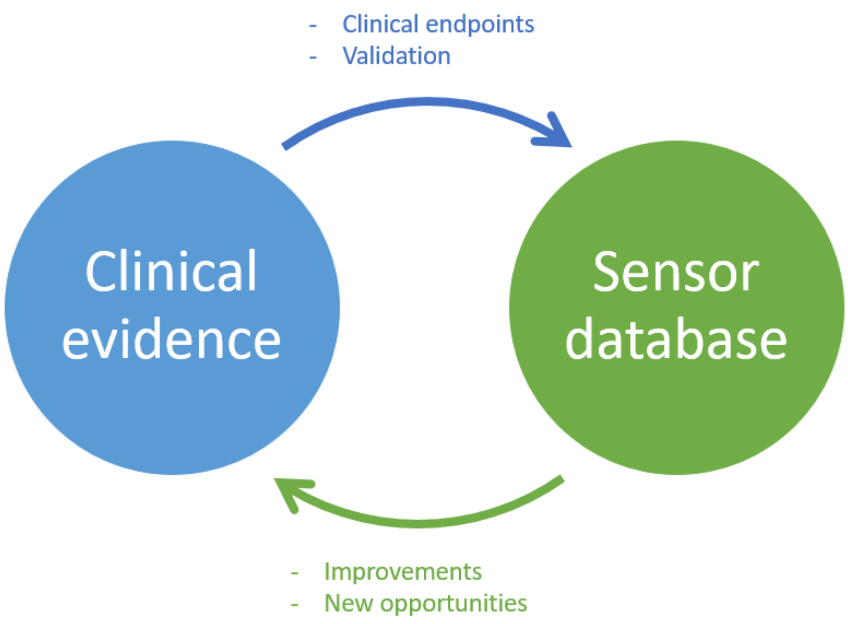

Figure 6. Two databases to investigate both clinical evidence and latest product development in remote patient monitoring sensors.

After selecting latest innovative sensors and defining their clinical value, the next step is to try them out ourselves. One of the sensors was chosen and tested during a time period of three month so that hand-on experience as well as insights in everyday use could be obtained. This way we could empathize with patients and evaluate patient experience.

3.1 Database construction – Sensors

3.1.1 Selection

To construct a database that contains a selection of state of the art medical sensors, a pragmatic search strategy was performed. Due to lack of one central database, the sensors are brought together from a variety of sources including medical technology platforms, market reports, google alerts and many others.

The bulk of the sensors was found by screening Medical technology journals, platforms and news sites such as ‘BioSpace’, ‘PharmiWeb’, ‘MobiHealthNews’, ‘Outsourcing-Pharma’, ‘Health Europa’, ‘Med-TechNews’. These platforms are specialized in monitoring and reporting new innovations in the healthcare sector.

Next to consulting specialized news platforms, an important part of the search was performed via Google. To withhold the latest developments of sensors, the biggest players on the market were defined and their products were consulted via their websites. Terms such as ‘vital signs’, ‘sensor’, ‘emotional signs’, ‘wearable’, ‘smartwatch’, ‘monitoring’, ‘stress’ … were used.

To define the key players in the sensor market, an analysis of relevant market reports was performed. Afterwards, the sensors of these market players were evaluated and eventually included in the list. Market reports of different subjects were analysed among which ‘ingestible sensor market’, ‘optical pulse sensor market’, 'sensor-patch-market', ‘medical sensor market’.

Additionally, two lists of remote patient monitoring techniques, published in response to SARS-CoV-2 pandemic, were analysed. It concerns the ‘Emergency used authorisation of patient monitoring devices (FDA) and a list published by the ‘Taiwan Research-based Biopharmaceutical Manufacturers Association’ of digital health technologies they consider useful in Covid-19 pandemic. From the first list, six sensors were retained, from the latter, four.

Seen that many sensors are linked to a mobile application as an interface for the patient, a database with certified apps was consulted. More specific www.digitalhealth.be, a directory with FDA/CE certified apps curated by *Healthskouts* containing 217 apps was searched.

To evaluate sensors recognized by Belgian authorities, www.mhealthbelgium.be is consulted. This website contains 33 mHealth applications at the time of submitting this thesis (18/11/2021), of which 23 currently have level one status, 10 have level two status and 0 have level three status. To achieve level one status, an app must have CE mark and meet regulation for medical instruments. Level two status is based on interoperability and connectivity to the eHealth platform. Finally, level three status is reserved for apps for which the socioeconomic added value has been demonstrated and which are financed, after approval by the National Institute for Health and Disability Insurance of their funding request.

During the construction of this database, the Google Alerts function was used to receive weekly updates on news regarding new sensors. Used search terms were ‘digital health’, ‘sensor’, ‘monitoring’, ‘mental health’ and ‘emotion’.

3.1.2 **Database design - Sensors**

Following fields were used.

ID: Each product was assigned an individual identifier.

Brand: The manufacturer of the product.

Model: Model name or model number of products.

Measurement: All different parameters which the product can measure. Measurements were categorized (Table 1). When products are able to monitor multiple parameters, multiple measurement fields are allocated.

Measurement category: Measurements were assigned to one of the measurement categories; ‘vital signs’, ‘activity’, ‘mental signs’ and ‘circulatory’ (Table 1). Each measurement was allocated with the proper measurement category.

FDA: 0: no FDA-approval; 1-value: FDA approved or 510k clearance.

CE: 0: no CE-certification; 1-value: CE certification.

Evidence (DOI): The digital object identifier (DOI) of available evidence.

URL: URL to website of product.

Special remarks: Remarks, if any

Table 1. Measurements and their respective measurement category.

Measurement	Measurement category
Temperature	‘vital signs’
Heart rate	‘vital signs’
Blood pressure	‘vital signs’
Respiratory rate	‘vital signs’
Oxygen saturation	‘vital signs’
Pulse capnography	‘vital signs’
ECG	‘circulatory’
Hearth rate variability	‘circulatory
Cardiac output	‘circulatory
INR	‘circulatory’
Motor activity	‘activity’
Level of consciousness	‘mental signs’
Stress	‘mental signs’
Sleep	‘mental signs’
Emotions, anxiety	‘mental signs’
Eye tracking	‘mental signs’
EEG	‘mental signs’

3.1.3 Sensor assessment

Products were assessed and selected based on the number of measurements, FDA and/or CE approval, available research using and validating the product, and the innovation and novelty of the product. Products which measure multiple measurements are considered added value. Certainly, when multiple measurement categories are included. To be included in the database, sensors had to measure at least one vital or emotional sign **(table 1)**.

A quality assessment of technologies can be made based on presence of FDA and CE certification. FDA certification can be provided by the manufacturer but can also be checked using the Global Unique Device Identification Database (GUDID). No such publicly accessible platform is currently available for CE approval, and therefore this was checked with the manufacturer.

3.2 Database construction – Clinical evidence

3.2.1 Selection

To be able to answer the research question, medical research databases were explored to establish the current role of sensors in IMID care. To find all relevant papers, we started with a wide scope and methodically narrowed it down until the most relevant papers regarding the research question were found.

Research question:

> "What is the role of sensors in remote patient monitoring in IMID and can they lead to better patient outcomes?"

Within the scope of IMID care we searched for the role of RPM, and more specifically, for sensors as a tool for RPM. Of these sensors, those of interest are those who monitor vital or emotional signs, circulatory parameters, or activity.

A query was constructed for all terms of interest. Both PubMed and Embase were searched for applicable indexed terms. I.e., Medical Subject Headings (MeSH) for PubMed and Embase Subject Headings (Emtree) for Embase. In absence of satisfactory indexed terms, keywords were selected. These search terms were attributed to different levels in this layered structure and were iteratively combined using 'AND'-functions to construct the final query.

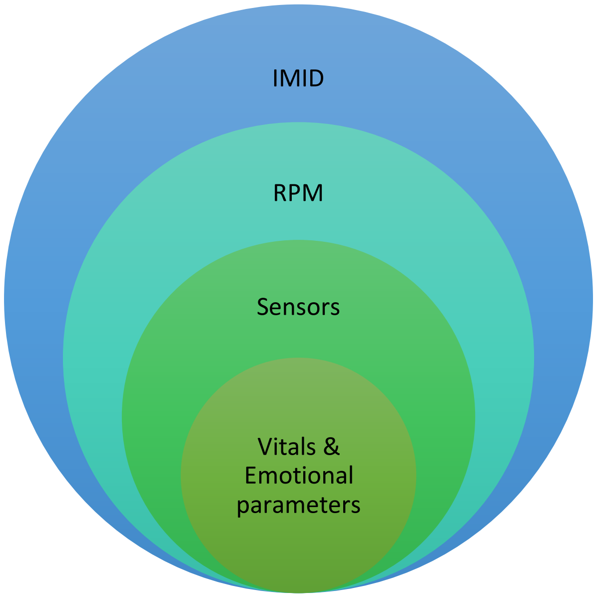

Figure 7. Four layers to obtain relevant evidence to address the research question.

For all searches, a time period of 10 years was chosen in order to select recent publications. Older papers were not considered relevant seen the rapid technological progress in the field of study. Publications had to be written in English.

Evidence search on IMID

Because IMID is a non-strictly defined group of diseases, the search on remote patient monitoring in IMID was restricted to seven diseases in this group representing a general prevalence of 5-7% (4). The selected IMID are inflammatory bowel disease (IBD), psoriasis (Ps), rheumatoid arthritis (RA), ankylosing spondylitis (AS), diabetes mellitus type 1 (DM1), systemic lupus erythematosus (SLE) and multiple sclerosis (MS).

One of these seven diseases must be mentioned to mark a paper as relevant.

Evidence search on RPM in IMID

RPM is the monitoring of patients using sensors, apps, data-structures and so on. One of these technologies (table 2) should be mentioned to include the paper.

Evidence search on sensors used in RPM in IMID

In order to select the papers using non-invasive sensors for RPM, papers had to include at least one type of sensor (table 3).

Evidence search vital, mental, circulatory or activity parameters measured by sensors in RPM in IMID

Finally, the paper had to contain at least one vital, mental, circulatory or activity parameter (table 4).

3.2.2 Database design – Clinical evidence

DOI: Digital object identifier of publication

Title: The title of the publication.

Disease: One or more of following diseases will be assigned: inflammatory bowel disease (IBD), psoriasis (Ps), rheumatoid arthritis (RA), ankylosing spondylitis (AS), diabetes mellitus type 1 (DM1), systemic lupus erythematosus (SLE), multiple sclerosis (MS).

Measurement: All different parameters which the paper discusses. Measurements were categorized (Table 1). When papers discuss multiple parameters, multiple measurement fields are allocated.

Measurement category: Each measurement is assigned to one of these categories: ‘vital signs’, ‘activity’, ‘mental signs’, ‘circulatory’. (Table 1) This will facilitate the comparison between the state-of-the-art sensors, and the sensors used in research papers.

Outcome: Conclusion or outcome of each paper which satisfies the inclusion criteria.

Availability: Full text available. 0: Not available; 1: Available

Relevance: Paper relevancy for research, paper must include IMID and use of sensor. 0: Not relevant; 1: Relevant

3.3 Hands-on experience with sensor

To assess different features, patient-experience, and ease of use for both patient and healthcare provider, one sensor was tested during a time-period of three months. Several sensors were selected based on their estimated potential to create value in IMID care. Therefore, sensors were selected from the sensor database (supra) based on following criteria:

Assessed qualities were the ability to both monitor mental health and vital signs, presence of available clinical evidence for at least one of these measurements and FDA-certification and/or CE-certification. Sensors which provide a high number of qualitative measurements and provide interfaces for patients and healthcare professionals are given priority seen that we consider this as facilitators for the implementation in IMID care. This resulted in the selection of 43 potential sensors.

The Fitbit Inspire 2 was selected based on the high presence of Fitbit-products in scientific literature, their high market share, and the ability of the sensor to monitor both vital and mental signs. The Fitbit Inspire 2 was bought with own funding. To illustrate the usability of this sensor in clinical practice, an additional service was selected. During an online symposium organized by Healthskouts we were introduced to Mindstretch, a product developed by BioRICS. Mindstretch measures energy expenditure using the Fitbit Inspire 2. The selection of this product was further substantiated by a substantial number of validating studies of the BioRICS algorithms.

To evaluate the patient experience, three factors were assessed. Firstly, we aimed to evaluate the ease of use and overall feasibility. Secondly, we aimed to assess the effects on health promotion of patients, such as effects on the activity level and therapy motivation of the patient. As such we aimed to get insights on the possible effects the sensor could have on the Patient Reported Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs).

Thirdly, we assessed the price of the product, taking the cost of current standard equipment into consideration. When considering the view of the healthcare professional, we evaluated the ease of use as a healthcare provider and the feasibility of implementation in IMID-care.

4 Results

4.1 Sensors

234 products were identified through the search process, of which 43 sensors were selected based on previously established criteria. Figure 8 shows an example of a possible database search. The full database can be accessed online: [Sensor Database].

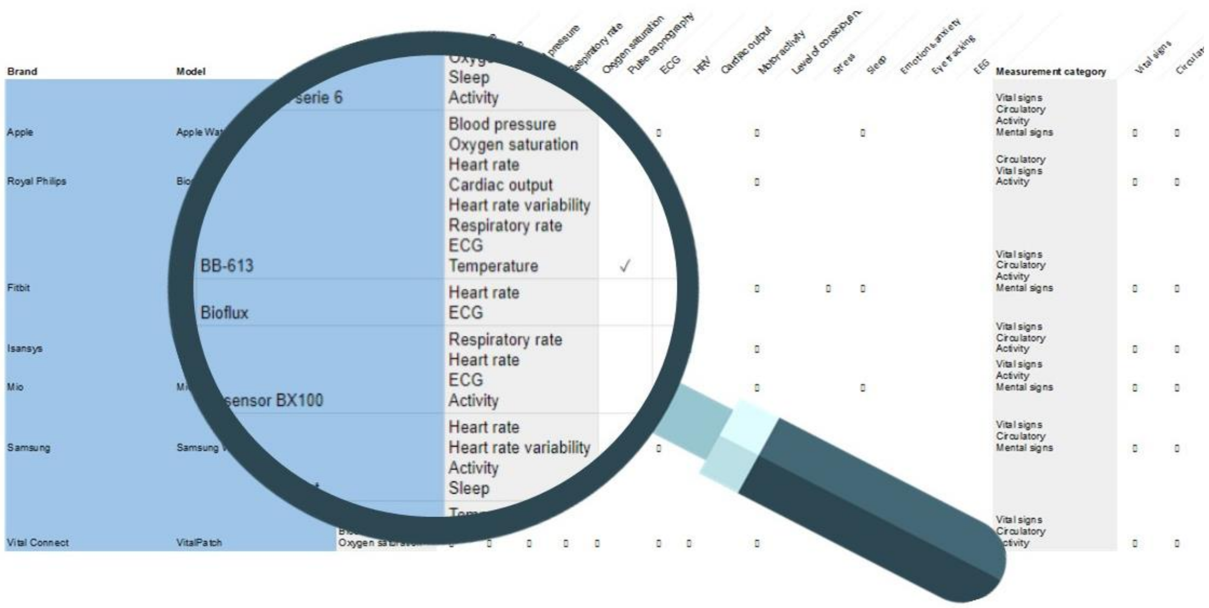

Figure 8: Screenshot taken from the constructed database. In this example FDA and CE approved sensors are selected which can measure Heart Rate, ECG, and Activity.

4.1.1 Measurements

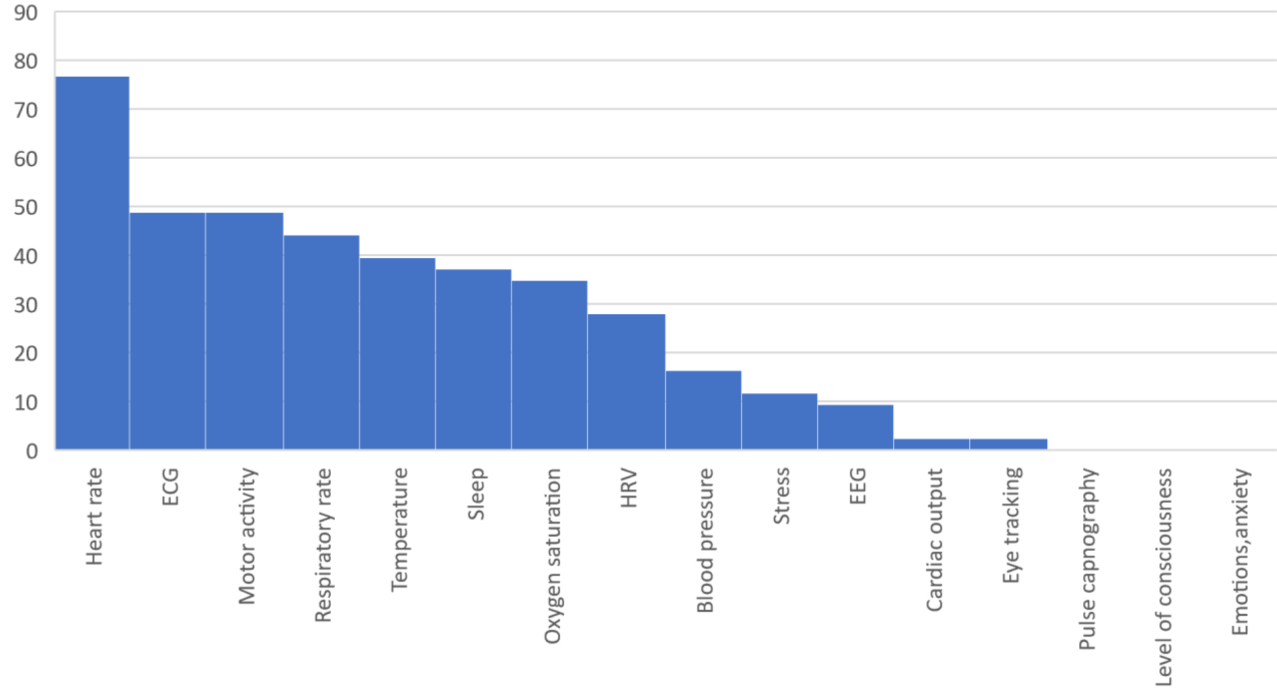

Figure 9. Graph showing which measurements are monitored most within the list of selected sensors (n=43).

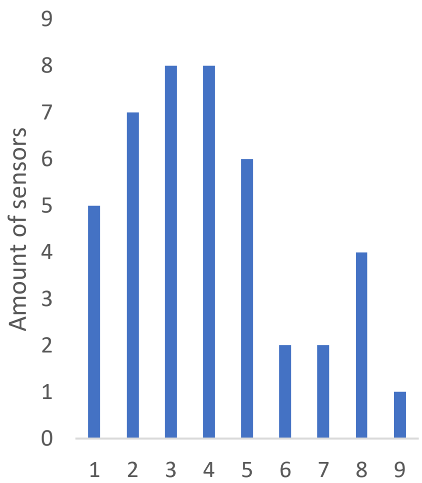

Figure 10 Number of measurements included sensors monitor (n=43).

Heart rate is the most measured parameter (74%), followed by ECG (49%) and motor activity (47%). Sleep is the most measured parameter concerning mental health, 37% of sensors measure sleep activity. No sensors were retained measuring pulse capnography, level of anxiousness, and anxiety.

A majority of sensors measure 4 or more parameters, 21% of sensors measure 6 or more parameters.

36 sensors measure vital signs, 24 circulatory parameters, 22 mental signs and 21 activity.

A majority of sensors (74,42%) measure parameters from more than 1 measurement category.

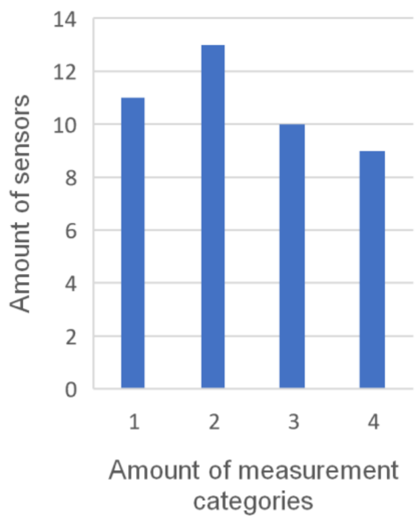

Figure 12. Amount of measurement categories sensors are able to monitor (n=43).

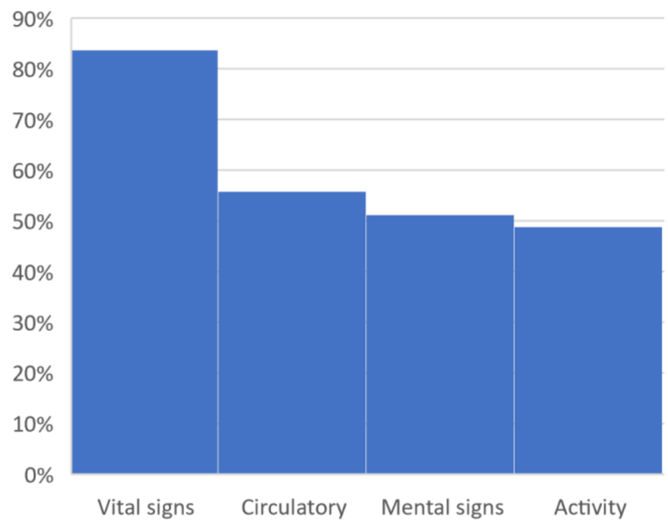

Figure 11. Measurement categories monitored by selected sensors.

4.1.2 **Approval**

28 sensors have FDA certification, 24 CE certification. 15 sensors have both FDA and CE clearance.

4.2 Clinical evidence

The search for papers about sensors used in IMID care on Pubmed and Embase resulted in respectively 76 and 244 research papers. After eliminating common results, a total of 320 papers were retained.

These 320 papers were screened by reading the full text to assure the needed conditions were fulfilled. After screening, 84 papers were retained and included in this research paper. Full database can be accessed online: [Evidence database].

4.2.1 Diseases

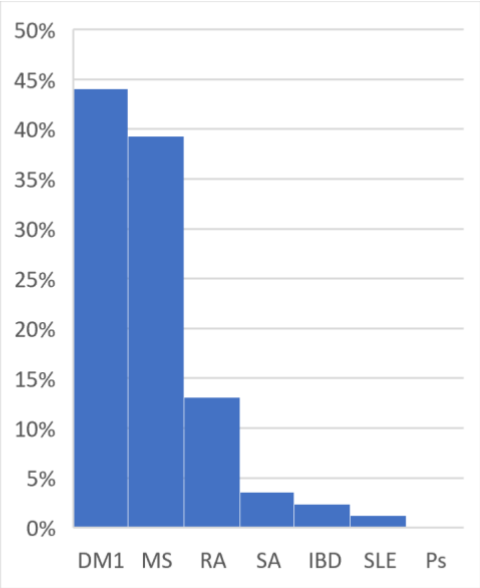

Figure 13: The relative distribution of research papers in IMID. (n=84)

Of a total of 84 research papers, 37 mentioned the use of sensors in DM1, 33 in MS, 11 in RA, 3 in S, 2 in IBD, 1 in SLE and 0 in Ps. Noteworthy is the uneven spread of the amount of research between different diseases. Furthermore, almost all papers investigate the use of sensors for one single disease. Only three papers mention more than one IMID. This is remarkable seen the high prevalence of IMID comorbidity.

4.2.2 Measurements

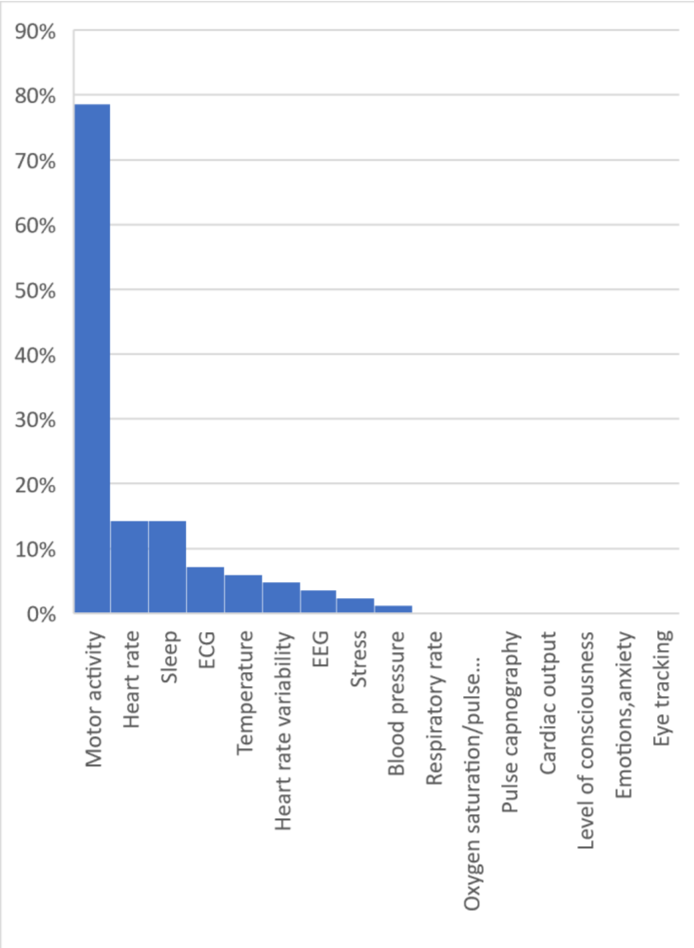

Figure 14: Percentage of papers discussing relevant measurements.

When comparing all relevant measurements, motor activity is by far most examined in research. No less than 66 out of 84 papers discussed the effect and measurement of motor activity. heart rate and sleep were measured by 12 papers, ECG by 6, temperature by 5, HRV by 4, EEG by 3, stress by 2 and blood pressure by 1. Regarding respiratory rate, oxygen saturation, pulse capnography, cardiac output, level of consciousness, anxiety and eye tracking, no papers were retained.

4.2.3 Measurement categories

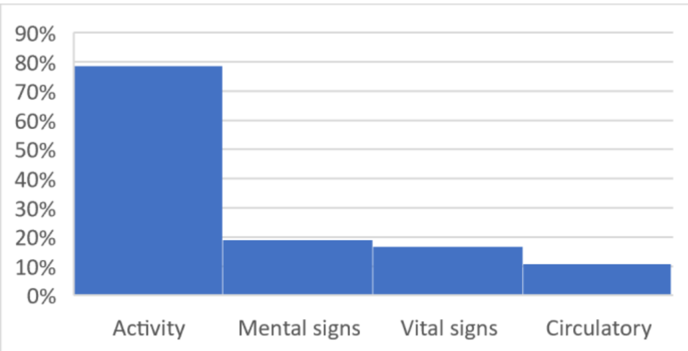

Figure 15. Percentage of measurement categories discussed in selected literature (n=84).

Out of 84 papers, 66 mentioned activity tracking, 16 mentioned mental parameters, 14 mentioned vital signs and 9 papers took circulatory parameters into account.

4.3 Hands-on Experience

Fitbit and Mindstretch were used for 3 months. This resulted in 62 days of recorded data. The Fitbit Inspire 2 is easy to use. Data such as real-time heart rate, steps taken, activity parameters, resting heart rate, burnt calories, sleep score, weight, and water intake can be easily accessed through the device. The device has extra functionalities such as alarms, timers, a relaxing function, and the possibility to monitor sport activities. The long battery life and small form factor of the device renders it low maintenance and unobtrusive to wear. The price of the Fitbit with one year of Fitbit Premium included was 79 euro. Mindstretch charges a monthly fee of 6.99 euro.

The Fitbit app connects via Bluetooth with the Fitbit device and presents the user with previously recorded data. The Fitbit app provides insights in data from heart rate, activity, and sleep (figure 21). Fitbit also provides users with a web-based dashboard where all the recorded data can be viewed (figure 22). The Mindstretch-app is linked to the Fitbit-app and automatically interprets recorded data. Mindstretch provides users with an overview of their daily mental energy expenditure. If the users use more mental energy than it can regain, users receive a daily balance score of less than 50%. This way, users get a monthly overview of which days are mentally exhausting and which are not (figure 23). When selecting a specific day, the users can get a more in-depth analysis of how much energy was spent throughout the day (figure 24).

The user can view a monthly overview of their energy expenditure or get a more detailed insight when selecting specific days. Mindstretch gives the user the ability to label activities, this way, the user can get more insights in which activities give or consume energy.

Examples shown in figures 24 and 25 show a particularly active day, as measured by Fitbit. Figures 26 and 27 show the same day, as monitored by Mindstretch. Example shown in figure 28 shows a more mentally challenging period as they were recorded during an exam period.

4.4 Interpretation of results

Multiple Sclerosis

Besides clinically evident symptoms, such as gait difficulty, upper-limb weakness, visual symptoms, spasticity, ataxia, falls, brainstem and cerebellar dysfunctions, symptoms like fatigue, cognitive, psychiatric, and autonomic disorders or pain, are frequently reported in people with MS (PwMS) (63–65).

Sleep

PwMS experience abnormal sleep cycles and various sleep disorders (63,65). This can in itself impact the daily function of MS patients, as well as lead to symptoms of fatigue (63,65,66). Fatigue being the most common symptom in MS with a prevalence of 80%, which PwMS describe as one of the most disabling symptoms (64), as it impacts both daily living, personal and work life, and overall reduces quality of life (64,66). Currently, two types of measurements can be distinguished for measuring fatigue: Patient reported outcome measures and measures of changes in motor or cognitive functions (66). The latter being more objectively and based on f.e. the decline of cognitive processing speed (66). Alternatively sleep analysis can be used to investigate the potential link between sleep quality and neurological dysfunction. A study conducted by Chinnadurai SA et al. found polysomnographic abnormalities to be frequently detected in patients with MS (67). Additionally, a study by Chitnis T et al. found REM percentage and leg movement during sleep to be correlated with disability scores, indicating potential links between sleep quality and neurological dysfunction (65). It should however be noted that further study is required to investigate cause versus effect relationships (65). Moreover, gait analysis could be used as an indicator for fatigue (64). However, prior research examining various gait analysis systems revealed varying or even contradictory associations between fatigue and gait characteristics in MS patients and should therefore be further examined (64).

Fall risk

PwMS tend to fall more often than the general public, this presents a significant problem considering the high probability of injury these falls can inflict (68,69). Nearly 50% of people with MS fall in a six-month period and around 30 to 50% fall multiple times (69,70). Smartphone sensors or wearable sensors such as tri-axial accelerometers or pressure sensors have been and can be used for assessing physical function and more specifically monitor biomechanical measures associated with fall risk or detecting falls (68–71). Lower accelerometer-based step counts were linked to slower gait speed and a higher risk of falling (71). Moreover, fatigue was found to have a significant influence on fall risk, balance performance, and fear of falling (64). As a result, measures to alleviate fatigue can help minimize fall risk and injuries while also increasing overall quality of life (64).

Besides fall detection, accelerometers and digital technologies such as smartphones can also be used to detect changes during ambulation or for monitoring ataxic gait (64,72,73). Multiple sclerosis frequently causes ambulatory disability, causing patients with MS to be more sedentary than the general population (74). Such mobility restriction have been linked to annual productivity loss, increased caregiver time and decreased patients quality of life (75). Physical inactivity can also exacerbate already disabling symptoms and increase the risk of sedentarism-related morbidity (74,75). Considering gait impairment being a hallmark of MS, objective gait evaluation in both routine clinical care and clinical research trials is needed to improve gait and balance follow up in PwMS (76).

Mobility

Due to the progressive nature of the disease, mobility impairments can gradually contribute to decreased activity and quality of life (77). Therefore, as an indication of advancing neurological problems, it is important to monitor these patients' mobility (77). During various stages of illness progression, PwMS might exhibit postural instability, gait unpredictability, and fatigue (72). It has already been established that cadence-based measurements, gait speed, and ambulation-related signal perturbations were distinguishable features that separated MS patients from healthy people (71,72). Similarly, pressure sensors implanted or integrated into shoes to record changes in foot-ground pressure, have also been found to be sensitive in detecting gait impairment in PwMS (71). In MS, the average daily step count can be used as a clinically relevant metric for targeted intervention and as a sensitive longitudinal outcome measure (78). Complementary, accelerometric data processing can be used to adequately differentiate ataxic patients from healthy controls (73). Continuous remote activity monitoring of MS patients with a wrist-worn accelerometer is feasible and reveals clinically relevant ambulatory disability not captured by standard measurements (78). However, a key topic that requires clarification concerns the body location where the sensors should be worn. Some authors suggest a waist-worn accelerometers are a more accurate technique to monitor movement than wrist worn devices (54,71).

Rheumatoid Arthritis

In patients with chronic inflammatory rheumatic diseases, a relation has been established between physical activity (PA) and a reduction in pain, depression, and disease activity. More PA leads to an improvement in joint mobility, physical function and cardiovascular disorders (48). Yet, there is a big difference in the amount of PA between people in good health and people with rheumatoid arthritis. The latter have approximately 200 less minutes of PA per week (48). In the general population, it has already been established that activity trackers can positively impact PA (48). It is however not yet conclusively proven that similar effect can be found with the use of activity trackers in patients with RA (48,60,79). A pilot study by D. Heale et al. showed no significant effect in adolescents with juvenile idiopathic arthritis, while Davergne et al. found a positive effect for the duration of the study but not in prolonged follow-up (48,60,79). C. Li et al. demonstrated a positive effect of wearable activity trackers on AP when combined with physical therapist counselling (61). None of these studies reported on long term results.

Plausible reasons for this difference are the pain and fatigue often experienced by patients with arthritis. Their disease could be the reason for their difficulties with physical activity. Given the important effects of PA in these patients, improving PA might be more efficient with RA specific guidance.

Sleep

Research using sleep and activity trackers showed that patients with RA significantly sleep less than the healthy population. Remarkable is that more PA was positively related with total sleeping time while sedentary behavior was negatively related with total sleeping time (80). This is an important finding seen the high rate of sedentary behavior among RA patients and the impact of impaired sleep on the HR-QoL (80).

Despite challenges related to data quality and validation of applications, our findings suggest that data collected by sensors can become meaningful in clinical practice. One major reason is that there is an important link between patient reported information and objective measurements (81). Moreover, some current evaluated RA-specific sensors show that accurate and usable measurements are possible and can lead to more insight in RA and its impact on patients' lives (81–83).

Only few studies have been conducted on the potential of PA data to predict flare up of RA. Yet, pilot studies indicate that the application of ML on this data can be used to detect patient reported flares with great accuracy (48,84). This way, activity trackers could lead to improved disease control by early identification of flare-up. All this with minimal impact on a patient's life because all data collection is passive. Although current studies are a proof of concept, there still is a long way to go until development and validation of such an early warning system will result in a ready to use application in clinical practice.

Axial Spondyloarthritis

Flares in Rheumatoid Arthritis (RA) and Axial Spondyloarthritis (SpA) appear to have objective consequences on daily life, particularly in terms of physical activity (60,84). They are important given the contribution to the disease's unpredictability, as well as the link between inflammation and structural degradation (84). Physical activity, such as daily walking and aerobic exercise, can be measured accurately and over time utilizing connected activity trackers. These monitors provide feedback on physical activity as well as visualization of activity patterns based on duration, intensity, and frequency. Objectively measuring physical activity over time can give the physician valuable insights of the treatment efficacy.

Self-monitoring of physical activity, such as with wearable activity trackers can increase physical activity of people with disabilities. By measuring daily movement and providing feedback, this technology aims to educate and motivate consumers to engage in more physical exercise and improve overall health (60). Research conducted by Davergne et al. found daily steps of people using wearable activity trackers to be significantly higher than those who did not (60).

High quality mobility trackers are already available, such as sensors from Dorsavi, Hinge Health and Sword Health (85–87). These sensors are however not included in our sensor database seen their focus on measuring motor activity only. Whereas our database focus on sensors capable of measuring multiple parameters such as vital and emotional signs, often in combination with activity.

Systemic Lupus Erythematosus

Maintaining an active lifestyle can help people with inflammatory arthritis minimize their risk of cardiovascular disease and metabolic syndrome. Pain, sleep quality, and weariness are all improved by physical activity (88). Which research shows consumer-grade accelerometers can encourage by utilizing behavior modification approaches such as goal setting, self-monitoring, feedback, and rewards. Although the results of the study were not statistically significant, it showed that an 8-week multimodal counseling program could boost physical activity in participants with inflammatory arthritis, but not those with SLE (88).

Inflammatory Bowel Disease

Despite a paucity of evidence, PA seems to have a positive effect on bone mineral density (BMD) in children with IBD (89). This is important since reduced BMD is a risk factor for fractures in children with IBD. Further research into the relationship between PA and HR-QoL in children with IBD is needed.

Diabetes Mellitus 1

Diabetes mellitus is a chronic and complex metabolic disorder that can lead to chronic complications (90,91). It necessitates the use of self-management measures to minimize acute and long-term consequences (91). Sufficient diabetic management, i.e. keeping blood glucose levels within recommended ranges, is linked to slowing down or preventing the progression of these complications (90). However, it is apparent that there is no one-size-fits-all diabetes self-management tool which would fully satisfy the needs of each individual patient (90).

Glycemia is the most important parameter in the monitoring of DM1. Continues glucose monitoring (CGM) provides insight in blood glucose concentration over time, enabling insulin dosing in patients with DM1. To estimate glycemia accurately, sensors measuring sleep, activity, HRV, infection parameters, and emotional factors can be used (92,93). Algorithms integrating this data are already being used and aim to detect situations influencing glycemia such as meal intake, exercise, infection, and emotional status (92).

Sleep

Different studies indicate interacting mechanisms between diabetes, obesity, sleep architecture and cardio-metabolic outcomes (94–96). Perfect et al. states that adolescents with DM1 suffer from impaired slow wave sleep (SWS) which leads to higher glucose levels, behavioral difficulties, lower grades and reduced HR-QoL (95). A paper by Elrokshi et al. adds on these findings that this impairment in SWS is not explained by their BMI (96). Also, it found that adolescents with DM1 have a high rate (44.8%) of Sleep-disordered Breathing (SDB), which can lead to cardiovascular consequences (96). Both studies conclude that sleep assessment and intervention should be included in standards of care in patients with DM1.

Next to impaired sleep quality and SDB, DM can also influence the sleep of physically active individuals by a nocturnal hypoglycemia. Aerobic exercise can cause an average reduction in Total Sleep Time of about 70 minutes (94). This finding is important given the role of PA in prevention of long-term complications in patients with DM1.

Exercise

As mentioned above, exercise impacts insulin sensitivity and can thus lead to hypoglycemic events. To remove barriers for patients with DM1 to be physically active, hypoglycemia should be addressed. The implementation of heart rate signal to inform insulin dosing can reduce the risk for hypoglycemia during and after exercise in patients with DM1 (97–101). Similarly, step count data can also be used to inform insulin dosing, but this may come at a cost of increased time in hyperglycemia (98). Also, the combination of Metabolic Equivalent of Tasks and skin temperature reading has been described as the optimal input to inform insulin dosing (102).

Bertachi et al. proposed a ML technique to integrate and manage data from both CGM and an activity tracker. By using a support vector machine, they reported a decrease in nocturnal hypoglycemia events of 70% (103). Therefore, they conclude that ML may be a feasible and effective tool to tackle this problem.

Automated meal detection

Patients using an insulin pump for automated insulin dosing still have to report their meals. This is important seen that forgotten or non-reported meals can lead to hypoglycemia. An automated meal detection system has been introduced combining CGM and activity monitoring (104). This could be used to inform patients in case of a forgotten meal. Also, it could be integrated in of the artificial pancreas to enhance automated insulin dosing.

Hypoglycemic events

Severe hypoglycemic events are the most severe acute complication of DM1. Yet, about 25% of the patients can not recognize impending hypoglycemia properly and nocturnal events are feared (53,105,106). Because hypoglycemia unawareness is associated with glucose dysregulation and impaired HR-QoL (107), the search for new approaches remains important. Next to non-invasive sensor monitoring, also real-time data processing of electroencephalogram (EEG) signals is described as a solution to improve hypoglycemia awareness (107–109). These EEG First exploring studies indicate that this technique is able to detect hypoglycemia before there is severe hypoglycemia with cognitive effects (107,108). These EEG changes may be superior to ECG when it comes to sensitivity and specificity, yet it is clear that a multiparameter system, including EEG, should be considered (109). Also, the use of non-invasive EEG in hypoglycemia detection should be further investigated.

Prevention of foot ulceration

Diabetic foot ulceration (DFU) is a severe complication of long-term glucose dysregulation. They often evolve into chronical ulcerations which can lead to limb amputation. A study by Ming et al. investigated the application of an insole equipped with a temperature sensor combined with telemedical guidance (110).

Research about blood pressure in DM1

High blood pressure is a known risk factor in DM1 for the development of micro- and macrovascular complications. Yet, the 24h blood pressure, measured by wrist-watch device, turns out to be higher in diabetic patients compared to healthy controls. In fact, blood pressure is highest in patients with diabetic complications (111). This is striking given the importance of adequate blood pressure control in the prevention of further complications. Validated continuous blood pressure monitors such as Biobeat monitors are readily available on the market and could be used in DM1 patients.

Integration of measurements into insulin dosage information

Physical activity has proven to be difficult to incorporate in the everyday life of people with DM1 (91). Due to the multiple factors such as duration and intensity of exercise, the timing and quantity of administered insulin and the carbohydrates consumed that influence glucose levels (91). This introduces the potential importance of using activity trackers in diabetes management. Wearable activity trackers have been proven to offer good levels of accuracy for step counts and distance, but lower validity for other variables such as energy expenditure and sleep quality (91,112).

In conclusion, DM1 is a difficult disease to manage properly because of the variety of factors influencing glycemia. Yet, the implementation of body sensors measuring a variety of parameters and algorithms make it possible to control these factors.

5 Discussion

We constructed a database of state of the art certified and high-quality sensors. It is one of the first databases worldwide to provide an overview of sensors measuring a combination of vital, circulatory, and emotional signs. Moreover, a database containing all relevant literature about the current use of sensors in IMID was build. These databases constitute an accessible directory for clinicians who are looking to implement sensors into clinical practice. By combining clinical evidence and trustworthy sensors, this research aims to describe the role of sensors in IMID monitoring and to point out the latest trends and opportunities in sensor development. Ultimately, we intend to make recommendations to facilitate the implementation of sensors in IMID care so that their potential can be fulfilled, and they can lead to better patient outcomes.

First of all, the implications of this research and what impact the implementation of sensors could have on patients, healthcare professionals, governments and manufacturers is explained. Then, one example of a sensor and application that has been tested by the authors of this thesis is discussed. Also, advice is given towards the direction of further research and the limitations of this research are discussed.

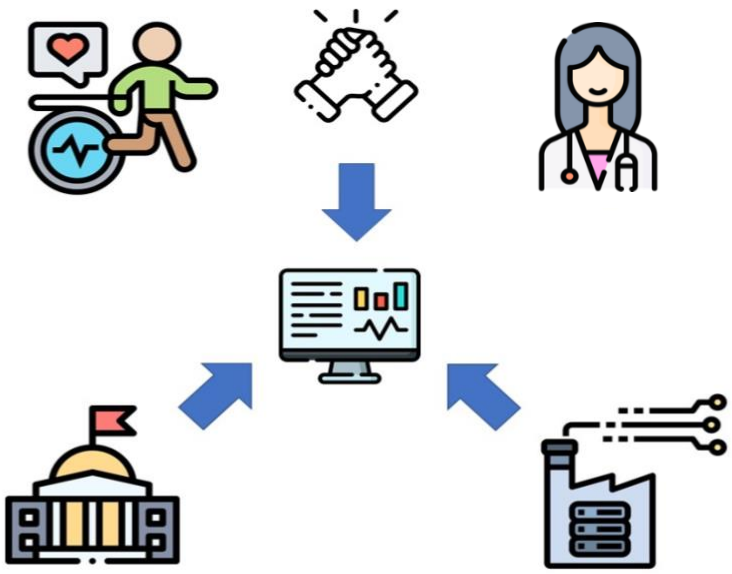

Figure 16: The constructed database can be consulted during consultation. Then, the sensor that satisfies both the patients and the doctors treatment goals can be selected. Moreover, authorities involved with validation can consult this database to find high quality sensors that should be validated and reimbursed. Furthermore, manufacturers can use the database to see which sensors already exist, which sensors are still lacking and find partners to deliver solutions to patients. Icons: Flaticon.com

5.1 Implications for clinical practice and consequences

When properly integrated, the data collected by wearables such as a Fitbit device can help both the healthcare provider and patient. Research shows that such data can be successfully analyzed and interpreted using algorithms (21,53–55). Moreover, incorporation of sensors into IMID care could make a substantial difference for patients. They might feel more empowered to live with their disease in the best way possible. Also, there could be a significant impact on motivation to make behavioral changes in one's lifestyle. This could facilitate the work and effectivity of physiotherapists, clinicians, and dieticians. Furthermore, insight in their own parameters will allow patients to understand their disease better. Providing patients with their personal data would allow them to objectify their complaints and communicate them to healthcare workers. This will ensure they feel better understood and will enable clinicians to understand their patients' goals and expectations. The possibility to take patient reported outcomes into account is an important aspect of value-based healthcare after all.

For healthcare workers, sensors may not only provide relevant measurements, but may also facilitate collaboration. Clinicians will be able to better decide which care is required at what moment by visualizing a patient's status. Furthermore, they will be enabled to offer continuous care and to take into account objective patient reported outcomes. However, there are currently some thresholds for clinicians to employ sensors. While researching sensors, we found that there is a lot of evidence about sensor technical efficacy, but less about long-term clinical application. As a result, sensors are hardly included in guidelines so far.

We would advise manufacturers to focus on collaboration with hospitals or industry partners to be able to deliver complete solutions rather than single products. Current Health is one example of a platform making use of sensors to tailor clinical monitoring and patient engagement to the individual patient so they can support care across clinical conditions (56). Also, the package tested in this thesis, a Fitbit sensor and the Mindstretch app, is an example of a specific solution to support patients with tracking stress.

Given the high prevalence and costs of IMID, as well as the potential for sensors to improve disease control and prevent complications, authorities should make efforts to integrate digital health solutions into clinical practice. They should provide a platform for industry and academia to collaborate on validation research. Also, reimbursement is required for the implementation of sensors and digital health solutions. Belgium has already made progress in this area. MoveUP for example, an App to gain insight into the rehabilitation of patients at home, is likely to be the first app to be reimbursed in the near future. Finally, a health economic evaluation of the entire service, from the product to the patient, should be performed. To fully realize the potential of sensors, changes in healthcare financing would be required. One solution is to switch from payment by performance, in which a clinician receives no compensation other than real-life consultations, to a different payment model, such as the Cappuccino model. In this model, created by Guus Schrijvers, and further researched by prof. Annemans, healthcare professionals are compensated for preventive and coordinating activities. Another approach to support holistic care in IMID is to implement a specific program, such as the Multidisciplinary Oncological Consult for specific cancers (57) or the care pathway for patients with chronic kidney disease or Diabetes Mellitus type 2 (58).

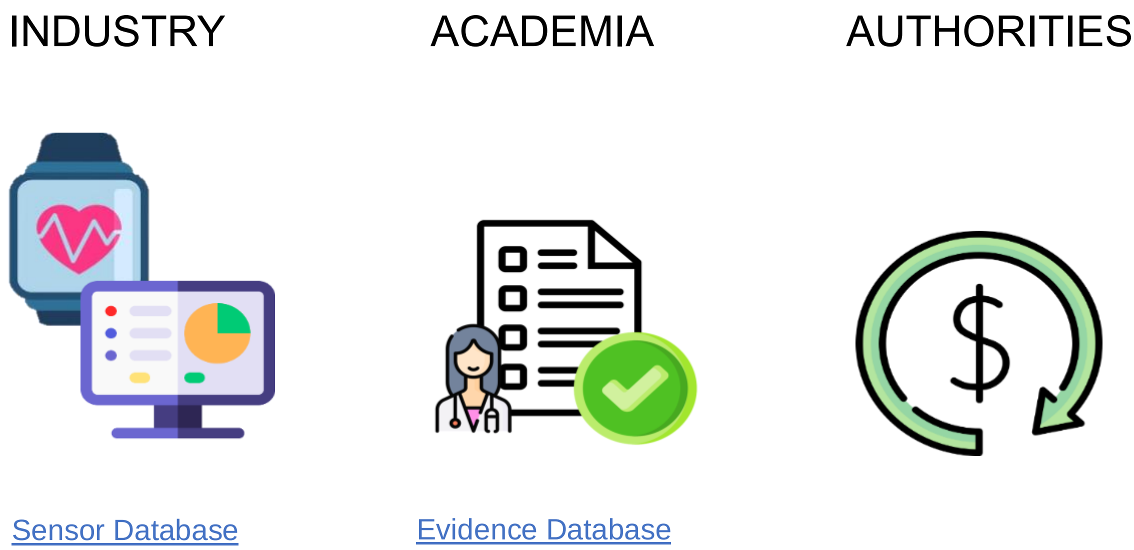

Figure 17. Necessary conditions for sensors to be used in clinical practice. Industry, academia, and authorities are all involved. Our sensor database gives insight in sensor development while the evidence database gives insight in clinical evidence. Icons: flaticon.com

As a first condition for sensors to be implemented in clinical practice, manufacturers should provide certified sensors of high quality with an interface usable for both patients and healthcare workers. Our sensor database (Figure 17) shows that there are a lot of high-quality certified sensors available, such as Fitbits, Apple watch and many others. To objectify their clinical value, clinical studies should be conducted in University Hospitals to know if the implementation of these sensors would result in better patient outcomes. Fibricheck for example, measures atrial fibrillation is validated and considered useful in clinical practice (59). In this case, the measurement of vital and emotional signs in IMID, clinical research is limited as it is mainly focused on DM1, MS and activity. This is shown in our evidence database (Figure 17). Finally, reimbursement of these technologies is necessary for implementation of these technologies in clinical practice. At the time of submitting this thesis (November 18, 2021) no health apps are reimbursed in Belgium. Yet, the first reimbursement of a health app is expected soon.

Sensor implementation could benefit patients, clinicians, manufacturers, and governments if the necessary adjustments are made. Therefore, making the necessary efforts to achieve this is worthwhile.

5.2 Hands on experience

Psychiatric comorbidity is important in IMID but is currently hard to monitor. However, almost no research has been done examining the use of sensors measuring mental sings in IMID. Yet, there are sensors available on the market who aim to monitor mental health. Therefore, we tested one of these sensors (Fitbit), combined with an app (Mindstretch), to gain insight in its applicability in clinical use.

In our opinion both Fitbit and Mindstretch are affordable, user friendly and contributed to a more health-conscious mindset. We adhered to a more attentive attitude towards sleep quality and felt encouraged to reach daily step counts. Scientific literature supports these findings and shows evidence for the motivational effect these products can provide (60,61). It should however be noted that we, the authors, do not have chronic illnesses and that our experience only consisted of a use period of several months. Long term adherence, which may be necessary for patients with chronic illnesses, such as IMID diseases, could well decline without interim evaluation or motivation. Fitbit provided the user with highly insightful and in-depth information about data and overall trends. The app also provides users with the ability to set goals and work towards them. Moreover, Fitbit provides the option to easily export data, as well as to be linked to other applications, such as Mindstretch.

Using Mindstretch, it was easy to track mental energy expenditure on hourly, daily, weekly, and monthly basis. However, we found that we were less motivated to use certain additional functionalities, such as manually labelling activities. Instead, we tended to retro-actively look at certain days and interpret the expenditure-graph with the course of activities throughout the day in mind. Mindstretch has an established presence in scientific literature for sleep and drowsiness detection (62). We see potential for its use in clinical practice as a tool for lifestyle behavior change in IMID patients who are vulnerable for mental health issues. However, right now it is marketed primarily as a tool for personal use or use within a company or sports setting. For implementation in a medical context, additional features such as easy data export and the development of a web-based interface for both the patient and the healthcare provider are crucial.

Both consumer-oriented products are easy to use and, in our opinion, show potential to be implemented in a healthcare setting. A Fitbit device combined with the Mindstretch app measures heart rate, activity, sleep, and energy expenditure. As a result, this combination makes it useful for patients with IMID. Particularly patients suffering from mental health issues, which are common in IMID, may benefit from the addition of the Mindstretch app. It could provide them with insight in their mental health and might ultimately even be used for the prediction of flare up.

5.3 Advice for further research

The continuation of research on this topic is critical for implementation of sensors in IMID care. One of the primary goals of this thesis is to provide insight into the current situation so that future research can be directed to the areas where it is most needed.

As reported in the results, 70 out of 84 papers about sensor use in IMID are about DM1 and MS, and mostly measure activity. The fact that there is much less research about other IMID or other parameters, may indicate that sensor use in these diseases or parameters is less useful. However, it appears likely that some parameters such as blood pressure, ECG, HRV and temperature do have potential considering their ability to monitor stress and cardiovascular health, which are both very important in IMID.

Particularly, research about HRV as a proxy for measuring stress should be conducted in IMID patients. Firstly, because stress and mental illnesses are strongly connected with IMID. Secondly, because HRV is measured by almost one third of the sensors in our database. Thirdly, because HRV is correlated with both stress and immune function (113). And especially, because there is a lack of research about remote monitoring of mental parameters in IMID patients. Therefore, we recommend further research to investigate the application of sensors measuring HRV and emotional parameters in patients with IMID.

Another remarkable finding was that 79 percent of all relevant papers focused on activity level, followed by only 14 percent on heart rate and sleep. This is a significant finding considering that the majority of sensors in our database are capable of measuring at least four different parameters. This emphasizes the importance of physical activity across illnesses, but also suggests that other measurements have yet to be researched. Therefore, we suggest investigating the value of combining multiple measurements in IMID patients with comorbidities. In patients with cardiovascular comorbidity for example, the combination of activity, blood pressure and sleep could be measured. These are all factors that could have impact on the IMID and on the cardiovascular health.

In summary we recommend further research to examine the role of sensors in IMID broader than MS or DM1. We also suggest focusing on more measurements than just physical activity so that comorbidities as well can be monitored. Given the importance of mental diseases in IMID, the application of stress monitoring via HRV should be investigated. Finally, we recommend conducting clinical research that is not limited to a single measurement. We believe this will result in more realistic and usable conclusions.

5.4 Validity and Limitations

This research has focused on the application of non-invasive sensors measuring vital, circulatory, or emotional signs and activity. Other types of sensors could possibly play a role in IMID care as well but were not included in this research.

The database constructed in this thesis is the result of a pragmatic online search for existing sensors measuring vital or emotional signs. Because no conclusive protocol has been used, some relevant sensors may be missing. However, the goal of this database is to give insight in the range and diversity of existing sensors rather than giving a complete overview of all sensors measuring health data. Similar databases such as the ones created by Vandrico of HumanFirst already exist but are less specifically focused on vital and mental signs.

To be included in the database, sensors had to measure at least one vital or emotional sign. Therefore, some excellent sensors measuring motor activity such as the ones made by Dorsavi, Hinge Health or Sword Health are not included in the database.

FDA or CE certification of the included sensors have been researched as good as possible. CE certification was assumed only if the manufacturer claims to have a CE mark and FDA approval was acquired from the GUDED database containing FDA cleared medical devices. Furthermore, FDA approval may apply for a product, but also just for a certain feature, the Apple Watch for example has FDA approval for its ECG feature. Nevertheless, for practical reasons, this was assumed as equal in our sensor database.

An important sidenote to make when discussing digital solutions in healthcare, is the amount of people who are not digitally literate. The US Department of Education published that worldwide, 23% of adults aged 16 to 65 are not digitally literate (114). When looking at Flanders or the US, this number comes down to 16% (114). When addressing the entire population, this figure is likely to be much higher. Given that people over the age of 65 or from lower socioeconomic backgrounds are already more vulnerable to comorbidities or poor disease control, it is important to consider that a digital solution may not benefit them. As a result, it is critical to continue thinking of different ways to tackle problems in IMID care.

6 Conclusion

There are many advanced and validated health sensors available on the market. However, their current use in IMID is limited, and their full potential has yet to be realized.

We constructed a database containing 43 state of the art sensors measuring a combination of vital, circulatory, and emotional parameters. It is one of the first databases of this type that has been constructed. This database is an accessible directory for clinicians who are looking to implement sensors into clinical practice. It can be used by healthcare workers and patients to select a sensor that satisfies both the patients and the doctors treatment goals. Moreover, authorities and manufacturers could consult this database to facilitate sensor validation and development.

While most of the sensors in our database measure activity and multiple vital and emotional signs, clinical research about their use in IMID is still limited. Activity monitoring is often evaluated but research about vital or emotional signs often lacks. This is remarkable given the high comorbidity rate of psychiatric and cardiovascular disease in patients with IMID. The potential of sensors across different parameters or diseases should be examined. More specifically, remote monitoring of mental health, which is currently rarely measured, could be investigated by measuring parameters such as Heart Rate Variability.

In this master's thesis an overview of state-of-the-art sensors was combined with clinical evidence and hands on experience to gain insight in the entire process, from sensor development to clinical usage. We believe that given the necessary adjustments patients, clinicians, manufacturers, and authorities could all benefit from the implementation of sensors in IMID care. We hope that our recommendations and insights can help in the evolution towards continuous and patient centered care.

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8 Appendix

8.1 Evidence search on IMID

Topic	Pubmed		Embase	
	Mesh	Keywords	Emtree	Keywords
Immune mediated inflammatory disease		'Immune mediated inflammatory disease', 'IMID'		'Immune mediated inflammatory disease', 'IMID'
Psoriasis	'Psoriasis'[mh]	'Psoriasis'	'Psoriasis'/exp	'Psoriasis'
Rheumatoid arthritis (RA)	'Arthritis, rheumatoid'[mh]	'Arthritis, rheumatoid'	'Rheumatoid arthritis'/exp	'Arthritis, rheumatoid'
Systemic lupus erythematosus (SLE)	'Lupus Erythematosus, Systemic'[mh]	'Systemic lupus erythematosus'	'Systemic lupus erythematosus'/exp	'Systemic lupus erythematosus'
Multiple sclerosis (MS)	'Multiple sclerosis'[mh]	'Multiple sclerosis'	'Multiple sclerosis'/exp	'Multiple sclerosis'
Inflammatory Bowel disease (IBD)	'Inflammatory bowel diseases'[mh]	'Inflammatory Bowel disease'	'Inflammatory Bowel disease'/exp	'Inflammatory Bowel disease'
Spondylitis ankylosing (SA)	'Spondylitis Ankylosing'[mh]	'Spondylitis Ankylosing'	'Ankylosing Spondylitis'/exp	'Spondylitis Ankylosing'
Diabetes Mellitus type 1 (DM1)	'Diabetes mellitus, type 1'[mh]	'Diabetes Mellitus type 1'	'insulin dependent diabetes mellitus'/exp	'Diabetes Mellitus type 1'

Table 2. Used indexed terms and keywords for the evidence search on IMID.

PubMed

‘Immune mediated inflammatory disease’ OR ‘IMID’ OR ‘Psoriasis’[mh] OR ‘Psoriasis’ OR ‘Arthritis, rheumatoid’[mh] OR ‘Arthritis, rheumatoid’ OR ‘Lupus Erythematosus, Systemic’[mh] OR ‘Systemic lupus erythematosus’ OR ‘Multiple sclerosis’[mh] OR ‘Multiple sclerosis’ OR ‘Inflammatory bowel diseases’[mh] OR ‘Inflammatory Bowel disease’ OR ‘Spondylitis Ankylosing’[mh] OR ‘Spondylitis Ankylosing’ OR ‘Diabetes mellitus, type 1’[mh] OR ‘Diabetes Mellitus type 1’

Embase

'immune mediated inflammatory disease' OR 'imid' OR 'psoriasis'/exp OR 'psoriasis' OR 'rheumatoid arthritis'/exp OR 'arthritis, rheumatoid' OR 'systemic lupus erythematosus'/exp OR 'systemic lupus erythematosus' OR 'multiple sclerosis'/exp OR 'multiple sclerosis' OR 'inflammatory bowel disease'/exp OR 'inflammatory bowel disease' OR 'ankylosing spondylitis'/exp OR 'ankylosing spondylitis' OR 'insulin dependent diabetes mellitus'/exp OR 'diabetes mellitus type’

8.2 Evidence search on RPM in IMID

Topic	**Pubmed**		**Embase**	
	Mesh	Keywords	Emtree	Keywords
Ambulant monitoring	‘Monitoring, Physiologic’[mh]	‘remote monitoring’, ‘remote patient monitoring’	‘Ambulatory Monitoring’/exp	‘remote monitoring’, ‘remote patient monitoring’
wearables	‘Wearable Electronic Devices’[mh]		‘wearable computer’/exp	
sensor	‘Biosensing Techniques’[mh]		‘sensor’/exp	
smartwatch		‘smartwatch’		‘smartwatch’

Telemedicine	'Telemedicine'[mh]	'Mobile Health', 'Health, Mobile', 'mHealth', 'Telehealth', 'eHealth'	/	'Mobile Health', 'Health, Mobile', 'mHealth', 'Telehealth', 'eHealth'
Wrist device		'wrist device'		'wrist device'
Fitbit		'fitbit'		'fitbit'
Telecare		'telecare'		'telecare'
Telemetry	'Telemetry'[mh]		'Telemetry'/exp	
Telehealth	/	/	'telehealth'/exp	/
Remote sensing technology	/	/	/	/
Machine learning	/	/	'Machine learning'/exp	
Biofeedback	'Biofeedback, Psychology'[mh]		'Biofeedback'/exp	
medical informatics	'Medical Informatics'[mh]		'Medical Informatics'/exp	
Fitness trackers	/	'Fitness tracker'		'Fitness tracker', 'activity tracker'
Integrated care	'Delivery of Health Care, Integrated'[mh]			
Digital biomarkers		'Digital biomarker'		'Digital biomarker'
Digital medicine		'Digital Medicine'		'Digital Medicine'
Digital therapeutics		'Digital thrapeutics'		'Digital therapeutics'
Remote Patient Monitoring	/	'telemonitoring'	'Telemonitoring'/exp	
eHealth	/	/	/	/
Digital health		'Digital health', 'digital'		'Digital health'
Decision making	/		'decision support system'/exp	
mHealth	'Mobile application'[mh]		'Mobile application'/exp	

Artificial intelligence;	'Artificial Intelligence'[mh]	'algorithm'	'Artificial Intelligence'/exp	'algorithm'
Digital technologies	'Digital technology'[mh]		'Digital technology/exp	
Smartphone	'smartphone'[mh]		'smartphone'/exp	
Digital pill		'digital pill'		'digital pill'

Table 3. Used indexed terms and keywords for the evidence search on RPM in IMID.

PubMed

'Monitoring, Physiologic'[mh] OR 'remote monitoring' OR 'remote patient monitoring' OR 'Wearable Electronic Devices'[mh] OR 'Biosensing Techniques'[mh] OR 'smartwatch' OR 'Telemedicine'[mh] OR 'Mobile Health' OR 'Health, Mobile' OR 'mHealth' OR 'Telehealth' OR 'eHealth' OR 'wrist device' OR 'fitbit' OR 'telecare' OR 'Telemetry'[mh] OR 'Biofeedback, Psychology'[mh] OR 'Medical Informatics'[mh] OR 'Fitness tracker' OR 'Delivery of Health Care, Integrated'[mh] OR 'Digital biomarker' OR 'Digital Medicine' OR 'Digital therapeutics' OR 'telemonitoring' OR 'Digital health' OR 'digital' OR 'Mobile application'[mh] OR 'Artificial Intelligence'[mh] OR 'algorithm' OR 'Digital technology'[mh] OR 'smartphone'[mh] OR 'digital pill'

Embase

'ambulatory monitoring'/exp OR 'remote monitoring' OR 'remote patient monitoring' OR 'wearable computer'/exp OR 'sensor'/exp OR smartwatch OR 'mobile health' OR 'health, mobile' OR 'mhealth' OR 'telehealth' OR 'ehealth' OR 'wrist device' OR 'fitbit' OR 'telecare' OR 'telemetry'/exp OR 'telehealth'/exp OR 'machine learning'/exp OR 'biofeedback'/exp OR 'medical informatics'/exp OR 'fitness tracker' OR 'activity tracker' OR 'digital biomarker' OR 'digital medicine' OR 'digital therapeutics' OR 'telemonitoring'/exp OR 'digital health' OR 'decision support system'/exp OR 'mobile application'/exp OR 'artificial intelligence'/exp OR algorithm OR (digital AND 'technology'/exp) OR 'smartphone'/exp OR 'digital pill'

8.3 Evidence search on sensors used in RPM in IMID

Topic	Pubmed		Embase	
	Mesh	Keywords	Emtree	Keywords
Wearables	'Wearable Electronic Devices'[mh]		'wearable computer'/exp	
Sensor	'Biosensing Techniques'[mh]		'sensor'/exp	
Smartwatch		'smartwatch'		'smartwatch'
Wrist device		'wrist device'		'wrist device'
Fitbit		'fitbit'		'fitbit'
Biofeedback	'Biofeedback, Psychology'[mh]		'Biofeedback'/exp	
Fitness trackers	/	'Fitness tracker'		'Fitness tracker', 'activity tracker', 'health tracker'
Digital pill		'digital pill'		'digital pill'
Patch		'patch		'patch
Tracker		'tracker'		'tracker'
Thermometer	'thermometers'[mh]		'medical thermometer'/exp	
EEG	'Electroencephalography'[mh]		'Electroencephalogram'/exp	
Sleep monitor	'Polysomnography'[mh]		'Polysomnograph'/exp	
ECG	'Electrocardiography'[mh]		'electrocardiogram'/exp	
Consciousness monitor	'Consciousness monitor'[mh]		'Consciousness monitor'/exp	
Eye tracking	'eye-tracking technology'[mh]		'eye tracking'/exp	

Table 4. Used indexed terms and keywords for the evidence search on sensors used in RPM in IMID.

PubMed

‘Wearable Electronic Devices’[mh] OR ‘Biosensing Techniques’[mh] OR 'smartwatch’ OR 'wrist device’ OR 'fitbit’ OR ‘Biofeedback, Psychology’[mh] OR 'Fitness tracker’ OR 'digital pill' OR 'patch' OR 'tracker' OR ‘thermometers’[mh] OR ‘Electroencephalography’[mh] OR ‘Polysomnography’[mh] OR ‘Electrocardiography’[mh] OR ‘Consciousness monitor’[mh] OR ‘eye-tracking technology’[mh]

Embase

'wearable computer'/exp OR 'sensor'/exp OR 'smartwatch' OR 'wrist device' OR 'fitbit' OR 'biofeedback'/exp OR 'fitness tracker' OR 'activity tracker' OR 'health tracker' OR 'digital pill' OR 'patch' OR 'tracker' OR 'medical thermometer'/exp OR 'electroencephalogram'/exp OR 'polysomnograph'/exp OR 'electrocardiogram'/exp OR 'consciousness monitor'/exp OR 'eye tracking'/exp

8.4 Evidence search vital, mental, circulatory or activity parameters measured by sensors in RPM in IMID

Topic	**Pubmed**		**Embase**	
	Mesh	Keywords	Emtree	Keywords
Temperature	‘body temperature’[mh]		‘body temperature’/exp, ‘skin temperature’/exp	
Vital signs	‘vital signs’[mh]		‘Vital sign’/exp	
ECG	‘Electrocardiography’[mh]		‘electrocardiogram’/exp	
Heart rate	‘heart rate determination’[mh]		‘heart rate and rhythm’/exp	
Blood pressure	‘blood pressure determination’[mh]		‘blood pressure monitoring’/exp	

Respiratory rate	/		'breathing rate'/exp	
Oxygen saturation/ pulse oximetry	'oximetry'[mh]		'oximetry'/exp	
Pulse capnography	'capnography'[mh]		'capnometry'/exp	
Cardiac output	'cardiac output'[mh]		'hearth output'/exp, 'hearth output measurement'/exp, 'cardiac output monitor'/exp	
Activity	'motor activity'[mh], 'exercise'[mh]		'physical activity'/exp, 'daily life activity'/exp	
INR	'international normalized ratio'[mh]		'international normalized ratio'/exp	
Hearth rate variability		'hearth rate variability'	/	
Level of consciousness	'consciousness'[mh]		'attention'/exp	
Stress	'stress, psychological'[mh]		'physiological stress'/exp	
Sleep	'sleep'[mh]		'sleep'/exp	
Cognitive health		'cognitive health'		'cognitive health'
Mental health	'mental health'[mh]		'mental health'/exp	
Emotions, anxiety	'emotions'[mh]		'emotion'/exp	
Eye tracking	'eye movement measurements'[mh]		'eye movement'/exp	
EEG	'Electroencephalography'[mh]		'Electroencephalogram'/exp	

Table 5. Used indexed terms and keywords for the evidence search on physical and emotional parameters measured by sensors in RPM in IMID.

PubMed

'body temperature'[mh] OR 'vital signs'[mh] OR 'Electrocardiography'[mh] OR 'heart rate determination'[mh] OR 'blood pressure determination'[mh] OR 'oximetry'[mh] OR 'capnography'[mh] OR 'cardiac output'[mh] OR 'motor activity'[mh] OR 'exercise'[mh] OR

‘international normalized ratio’[mh] OR ‘hearth rate variability’ OR ‘consciousness’[mh] OR ‘stress, psychological’[mh] OR ‘sleep’[mh] OR ‘cognitive health’ OR ‘mental health’[mh] OR ‘emotions’[mh] OR ‘eye movement measurements’[mh] OR ‘Electroencephalography’[mh]

Embase

'body temperature'/exp OR 'skin temperature'/exp OR 'vital sign'/exp OR 'electrocardiogram'/exp OR 'heart rate and rhythm'/exp OR 'blood pressure monitoring'/exp OR 'breathing rate'/exp OR 'oximetry'/exp OR 'capnometry'/exp OR 'heart output'/exp OR 'heart output measurement'/exp OR 'cardiac output monitor'/exp OR 'physical activity'/exp OR 'daily life activity'/exp OR 'international normalized ratio'/exp OR 'attention'/exp OR 'physiological stress'/exp OR 'sleep'/exp OR 'cognitive health' OR 'mental health'/exp OR 'emotion'/exp OR 'eye movement'/exp OR 'electroencephalogram'/exp

8.5 Figures

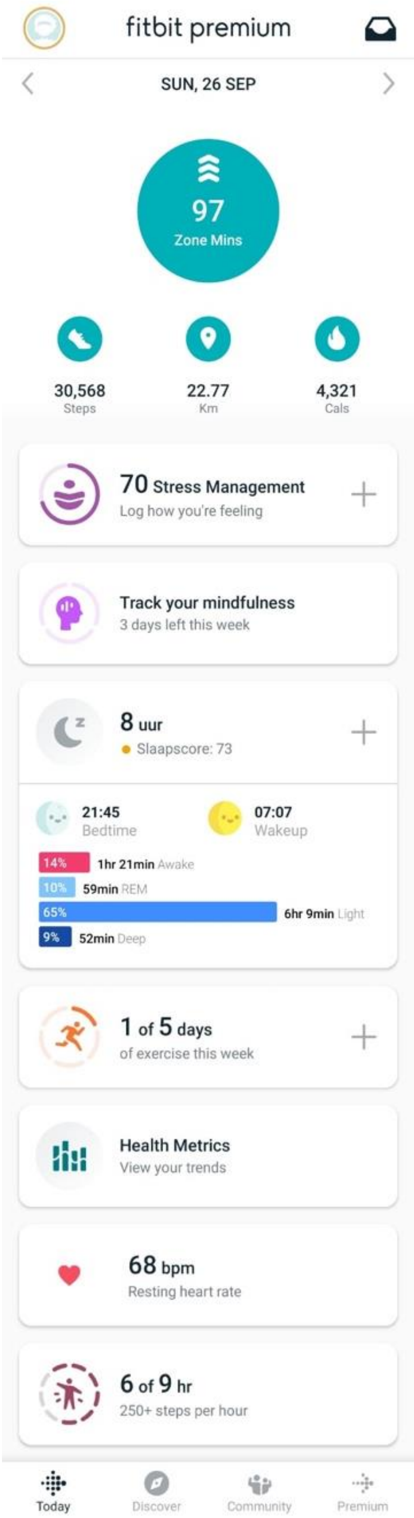

Figure 18. Screenshot taken from the mobile Fitbit app on a particularly active day. Selected day shows information on activity, stress management, heart rate, sleep score, and resting heart rate.

Figure 19. Screenshot taken from Fitbit website; selected day shows the same day as shown in figure 24. Users get a different and more in-depth overview of recorded data.

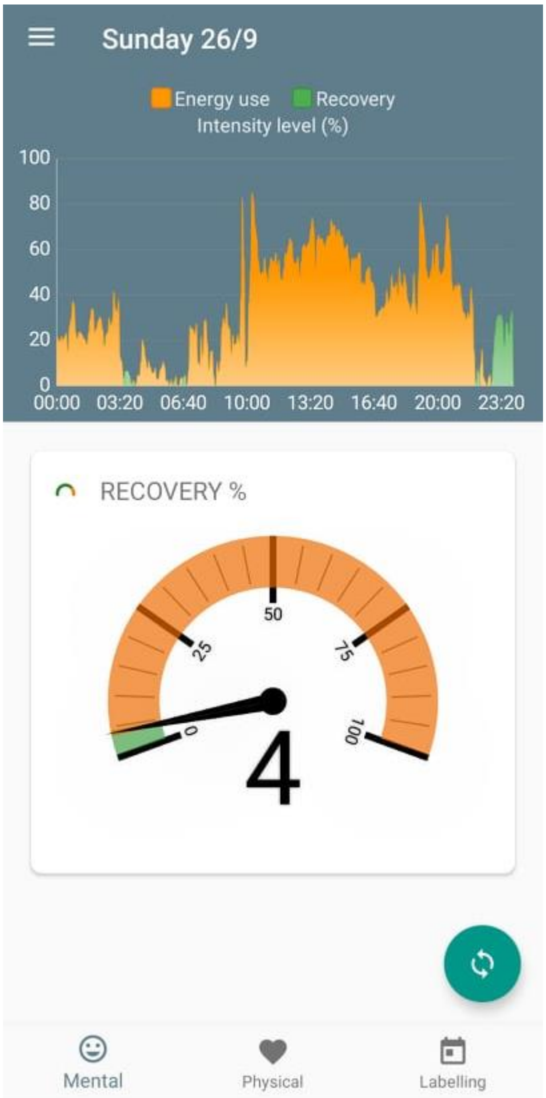

Figure 21. Screenshot taken from Mindstretch on a physically demanding day. Wake up time 7:07h, hike starts at 9:15h.

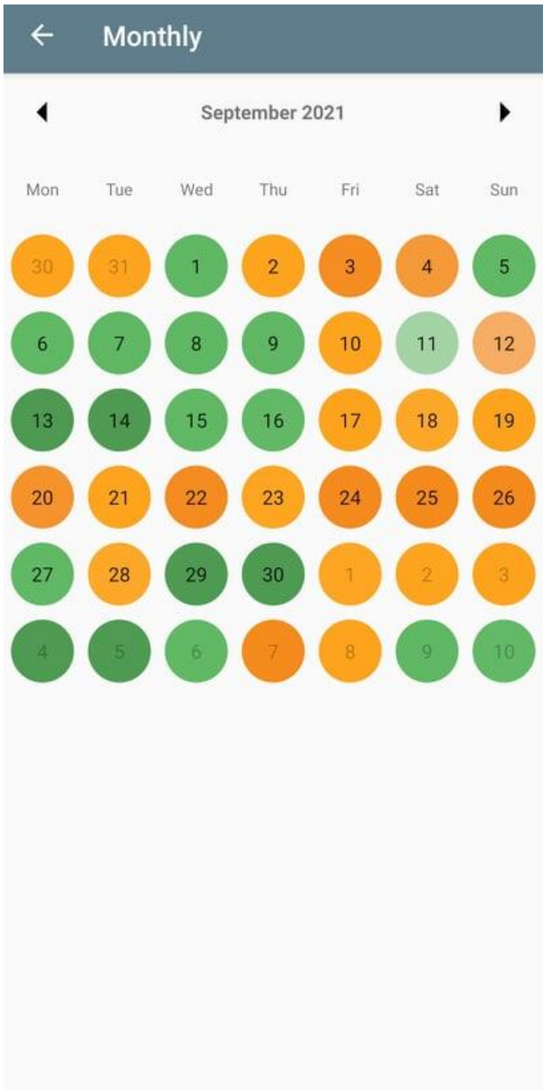

Figure 20. Energy expenditure viewed in the monthly overview. Higher levels of energy expenditure can be detected throughout a trip (18/09-28/09). 22/09 until 26/09 consisted of hiking in a mountainous nature park and show elevated energy expenditure.

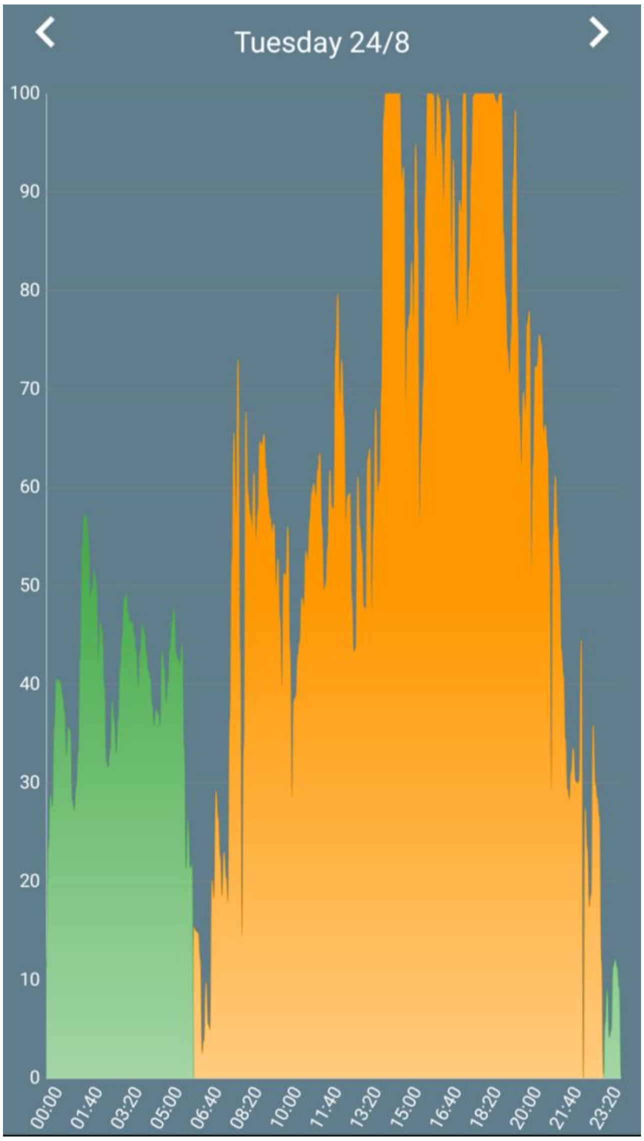

Figure 22. Screenshot taken from Mindstretch app on a particularly mentally and physically demanding day. Figure shows energy expenditure throughout a day with an exam in the morning and physically demanding work in the afternoon. Wake up time was 6:06h. Exam started at 8:30h and lasted till 11:30h. High levels of energy expenditure in afternoon show high intensity physically demanding work.