Digital Biomarkers in Living Labs for Vulnerable and Susceptible Individuals: An Integrative Literature Review

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Purpose: The study aimed to identify which digital biomarkers are collected and which specific devices are used according to vulnerable and susceptible individual characteristics in a living-lab setting.

Materials and Methods: A literature search, screening, and appraisal process was implemented using the Web of Science, Pubmed, and Embase databases. The search query included a combination of terms related to "digital biomarkers," "devices that collect digital biomarkers," and "vulnerable and susceptible groups." After the screening and appraisal process, a total of 37 relevant articles were obtained.

Results: In elderly people, the main digital biomarkers measured were values related to physical activity. Most of the studies used sensors. The articles targeting children aimed to predict diseases, and most of them used devices that are simple and can induce some interest, such as wearable device-based smart toys. In those who were disabled, digital biomarkers that measured location-based movement for the purpose of diagnosing disabilities were widely used, and most were measured by easy-to-use devices that did not require detailed explanations. In the disadvantaged, digital biomarkers related to health promotion were measured, and various wearable devices, such as smart bands and headbands were used depending on the purpose and target.

Conclusion: As the digital biomarkers and devices that collect them vary depending on the characteristics of study subjects, researchers should pay attention not only to the purpose of the study but also the characteristics of study subjects when collecting and analyzing digital biomarkers from living labs.

Key Words: Digital biomarkers, living lab, vulnerable individual, susceptible individual

INTRODUCTION

Living labs are experimental platforms in which users are studied in their everyday habitats.[1] They are the extensions of laboratory experiments that aim to obtain more accurate and natu-

ralistic user information by gathering more long-term data and allowing for the observation of everyday activities.[2] In recent years, the development of health devices, such as wearable devices and smart home assistants, has enabled the living-lab approach to be applied more frequently in health-related studies, such as research on personal hygiene and health.[3]

Although biomarkers have been widely promoted as an advance to current diagnostic schemas, these now conventional biomarkers face several limitations: they are expensive, difficult to access, invasive or inconvenient, and do not accommodate a high-frequency measurement strategy.[4] To improve this current clinical paradigm, digital biomarkers can now provide an alternative, rapidly developing approach. Digital biomarkers here refer to objective, quantifiable, physiological, and behavioral data, which are collected and measured via digital devices, such as embedded environmental sensors, portables, or wear-

ables. Digital biomarkers allow for objective, ecologically valid, and long-term follow-up with frequent or continuous assessment that can be minimally obtrusive or function in the background of everyday activities. Moreover, these frequent measures can capture individual variability in performance that may be the earliest indicator of change; and thus, they can detect incidences of exacerbation of a disease. Even more potentially transformative, this approach may also allow us to discover novel and innovative digital indicators, such as gait-speed variability over time.[5]

In particular, with the development of the Internet of Things, there is a growing movement in the field of digital-biomarkers research to bring these technologies out of the laboratory and into the larger community in so-called "living lab" or "life laboratory" settings.[4] This is because the real-life data on physical activity collected in living labs are objectively monitored and measured, and are thus less likely to be subject to investigator or patient-induced bias.[6]

Given the lack of study that has been reviewed focusing on the characteristics of subjects in living lab that collected digital biomarkers, we performed an integrative review. The integrative review method can summarize empirical and theoretical literature on a topic of interest.[7]

Therefore, the current study aimed to perform an integrative review of studies that examine the health of vulnerable and susceptible individuals by collecting and analyzing digital biomarkers in living-lab settings. The specific goals of this study were as follows: 1) to identify which digital biomarkers—specific to vulnerable and susceptible individuals—are being collected in living labs; 2) to identify which specific devices are being used to collect digital biomarkers from vulnerable and susceptible individuals in living labs; and 3) to identify which specific health problems are being addressed in living labs.

MATERIALS AND METHODS

The present study was performed according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[8] Three reviewers separately conducted literature retrieval and data extraction, with controversy and inconsistency resolved through discussion and consensus.

Literature search
A literature search, screening, and appraisal process was implemented by first searching the Web of Science, Pubmed, and Embase databases using Medical Subject Headings (MeSH) terms. We conducted a search for studies published from January 1, 2010 to July 1, 2021. Our search query, targeting title/abstract/topic, was restricted to the English language and included a combination of "digital biomarkers," "devices that collect

digital biomarkers," and "vulnerable and susceptible groups." The MeSH keywords selected for each topic were as follows: digital biomarkers ("biomarkers"), devices that collect digital biomarkers ("Internet of things," "self-monitoring," "wearable electronic devices," "smartphone," "patch test," and "mobile applications"), and vulnerable and susceptible groups ("aging," "aged," "child," "disabled persons," "vulnerable populations," "extreme heat," "extreme cold weather," "developing countries," "transients and migrants," "farmers," "fisheries," "environment pollution," and "disease"). The keywords for living lab were "daily living," "living life," "daily life," "real life," "real time," and "living lab."

The population, intervention, comparison, and outcome framework was used to construct a search strategy with the assistance of a review team. When devising a search strategy, this search tool is used as an organizing framework for listing terms by the main concepts in the search question; it is especially useful when it is not possible to have an experienced information specialist as a member of the review team.[9]

Inclusion and exclusion criteria
This review included studies in which digital biomarkers were collected/used in a living-lab approach to monitor vulnerable and susceptible individuals. Quantitative, qualitative, or mixed-methods studies were considered. Studies were excluded if they were not related to living labs or digital biomarkers, were not focused on vulnerable and susceptible individuals (e.g., studies on children), or were concept papers. Studies that did not meet the inclusion criteria were not selected.

Study selection
The titles and abstracts of the studies identified through the search strategy were screened independently for eligibility by three review authors. Eligibility was based on the aforementioned inclusion and exclusion criteria. Full-text screening was also performed independently. Disagreements were resolved by discussion. If necessary, a fourth review author acted as arbitrator.

Data extraction
The findings of the studies included in this review were synthesized in a narrative format and organized by the different perspectives adopted. Data were extracted using a customized template that included the following items: first author, publication year, country or countries in which the study was performed, study design, participants, purpose, intervention (digital biomarkers and devices that collect digital biomarkers), and outcome (Table 1).

Table 1. Summary of Articles Reviewed

#	First author (year)	Country	Design	Participants (n)	Purpose	Digital biomarkers device	Digital biomarkers	Outcome
1	Ramadhan (2018)[32]	Iraq	Mixed methods study	Visually-impaired person (55)	To provide VIPs with a means for safe and independent mobility and continuous contact with their families and caregivers, who are able to track their location	Wearable device (on the user's wrist)	Acceleration	User stumble
2	Seelye (2017)[12]	USA	Prospective cohort study	The aged with intact cognition (21) or MCI (7)	To effectively discriminate between MCI and cognitively intact groups using continuous driving monitoring	Sensor (routine driving)	PAs (more sensor monitored driving (distance, time, and highway) and variability in daily driving)	Cognitive impairment
3	Elhakeem (2018)[19]	UK	Observational study	Participants aged 60–64 years (1622)	To examine associations of objectively measured PA and sedentary time with cardiovascular disease biomarkers	Sensors (combined heart rate and movement sensors)	PAs	Cardiovascular Disease
4	Amiri (2017)[36]	USA	Case-control study	Patients with autism (2)	To recognize and monitor the autism behavior activity which may be harmful to the person	Wearable watch	Acceleration in stereotypical motor movements: hand flapping and body rocking)	Autism
5	Schultz (2020)[31]	USA	Qualitative study	Aged 3–4 (11)	To bridge the gap between child development and environmental epidemiology research by trialing novel methods of gathering ultrafine particle data with a wearable air sensor, while simultaneously gathering language and noise data with the Language Environment Analysis system	Backpack	PM, carbon monoxide, temperature, humidity, and non-functional noise	Child development
6	Mannini (2017)[28]	Italy	Case-control study	Children with EOA and DCD, and young healthy children (control) (37)	To classify EOA and DCD and evaluate accuracy using inertial sensors and supervised classifiers	Waist band (wearable inertial measurement units)	Gait-related velocity, acceleration	EOA, DCD
7	Bloem (2019)[34]	Netherlands	Prospective cohort study	Patients with Parkinson's disease (650)	To discover of novel biomarkers and new targets for therapeutic interventions in Parkinson's disease	Wearable watch	ECG	Parkinson's disease
8	Eisenhauer (2020)[43]	USA	Qualitative study	Overweight or obese med in the rural (80)	To check the feasibility and time-consuming variability of MI+ for obese men, and supporting weight loss	Smartphone	BMI (weight, height), BP, PR	Weight loss, prevention of cardiovascular disease

Table 1. Summary of Articles Reviewed (Continued)

#	First author (year)	Country	Design	Participants (n)	Purpose	Digital biomarkers device	Digital biomarkers	Outcome
9	Kim (2018)[20]	Korea	Retrospective study	Aged with stroke patients (80) and normal elderly (50)	To detect stroke in advance using big data and bio-signal analysis technology, and contribute to human health promotion	Hyper-connected self-machine learning engine, face tracking and eye tracking camera	Daily life data, motion data, body pressure, EEG, ECG, EMG, galvanic skin reflex, abnormality in appearance due to stroke or other heart diseases	Stroke
10	Derungs (2020)[35]	Switzerland	Mixed methods study	Stroke patients who use wheelchair (5)	To show that wearable sensors and digital biomarkers offer opportunities to investigate changes during the recovery process in patients after stroke	Wearable motion sensors	Acceleration and direction	Stroke
11	Faurholt-Jepsen (2015)[38]	Denmark	Mixed methods study	Patients with diagnosis of bipolar disorder (61)	To test the hypotheses that automatically generated objective data collected using smartphones correlate with clinical ratings of depressive and manic symptoms in patients with bipolar disorder	Smartphone	Number of incoming calls/day, duration of incoming calls/day (sec/day), number of incoming text messages/day, number of outgoing calls/day, duration of outgoing calls/day (sec/day), and number of outgoing text messages/day	Bipolar disorder
12	Dodge (2012)[5]	USA	Prospective cohort study	Aged with intact cognition (58), nonamnestic MCI (31), and amnestic MCI (8)	To explore in-home walking speeds and variability trajectories associated with mild cognitive impairment	Sensor (passive infrared sensors)	PAs (walking speeds)	Cognitive impairment
13	Kim (2021)[25]	Korea	Prospective cohort study	Children with TD or developmental disabilities (370)	To evaluate the possibility of using drag-and-drop data as a digital biomarker and to develop a classification model based on drag-and-drop data with which to classify children with developmental disabilities	Mobile device	Touch coordinates	TD
14	Saner (2021)[17]	Switzerland	Qualitative study	One of 24 old- and oldest-old, community-dwelling adults (1)	To detect early signs of HF decompensation based on prospective data acquisition and retrospective correlation of the data	Sensors (passive infrared motion sensing system, contact-free piezoelectric sensor)	Respiration rate, heart rate, PA (the sum of time spent outside per day, toss-and-turn in bed, sleep onset delay), ECG	HF
15	Leach (2018)[10]	USA	Qualitative study	Aged without dementia (20)	To characterize the day-to-day variability in postural sway in non-demented older adults	Balance board (Nintendo Wii balance board)	Day-to-day variability of postural sway	Cognitive impairment

Table 1. Summary of Articles Reviewed (Continued)

#	First author (year)	Country	Design	Participants (n)	Purpose	Digital biomarkers device	Digital biomarkers	Outcome
16	Kim (2018)[37]	Korea	Mixed methods study	Patients with snoring or cessation of breathing during sleep (120)	To identify acoustic biomarkers indicative of the severity of SDB by analyzing the breathing sounds collected from a large number of subjects during entire overnight sleep	Microphone	Breathing sound, EEG, ECG, EMG	SDB
17	Chu (2020)[23]	Taiwan	Case-control study	Children with ADHD and control (63)	To determine potential indicators extracted from a mobile EEG device and an actigraph and to validate them for diagnosis of ADHD.	Mobile EEG device, motion watch	Attention, meditation, activity	ADHD
18	Lekkas (2021)[40]	USA	Case-control study	Patients with PTSD (150)	To test the efficacy of passively collected, GPS-based location data for the prediction of PTSD diagnostic status in a high-risk cohort with a history of trauma	Smartphone	GPS	PTSD
19	Millar (2019)[26]	UK, Sweden	Prospective cohort study	Children with ASD, another NDD, or neurotypical development (760)	To tests the accuracy of a new computational serious game assessment for the early identification of autism in preschool children	iPad	Gesture-related parameters (duration, maximum velocity, deviation from a straight line, peak acceleration)	Autism
20	Ma (2020)[39]	China	Mixed methods study	Patients with disordered breathing during sleep (25)	To reduce the cost and time required to diagnose OSAS	Portable sensor	SpO2 (percentage of hemoglobin in the blood), breathing rate, and pulse rate	OSAS
21	Bondioli (2021)[21]	Italy	Mixed methods study	Children with ASD or neurotypical development (50)	To present a novel Internet of Things support in the form factory of a smart toy that can be used by specialists to perform indirect and non-invasive observations of the children in naturalistic conditions	Smart toy	Force and the movement direction	ASD
22	Wettstein (2015)[15]	Israel, Germany	Prospective cohort study	Patients with Alzheimer's disease (50), MCI (115), and cognitively healthy people (192)	To explore differences in the out-of-home behavior of community-dwelling older adults with different cognitive impairment	GPS tracking device that is convenient to the participant (belly pouch, shoulder bag, etc.)	PAs (walking distance, walking decision, and walking speed)	Cognitive impairment
23	Mancini (2016)[11]	USA	Prospective cohort study	Non-faller (16), single fallers (12), recurrent fallers (7)	To determine if quality of turning during daily activities is associated with falls and/or cognitive function	Wearable device (three Opal inertial sensors)	PAs (number of turns per hour, turn angle amplitude, turn duration, turn peak velocity, and number of steps to complete a turn)	Falls, cognitive impairment

Table 1. Summary of Articles Reviewed (Continued)

#	First author (year)	Country	Design	Participants (n)	Purpose	Digital biomarkers device	Digital biomarkers	Outcome
24	Takemoto (2015)[14]	USA	Observational study	Older adults (279)	To explore relationships between these transportation variables as well as physical, psychological, and cognitive functioning	Wearable device (GPS and accelerometer)	PAs (average daily number of trips, distance, and minutes traveled for pedestrian and vehicle trips)	Physical, psychological and cognitive functioning
25	Rabinovitch (2016)[30]	USA	Pilot study	Elementary school children with asthma (30)	To identify increases in morning PM exposure occurring within home, transit, and school microenvironments and determine their associations with asthma-related inflammation and rescue medication use	Backpack	PM	Airway inflammation
26	Neto Leal (2021)[44]	Malawi	Mixed methods study	Child (181)	To validate technologies that help with the better understanding of child development in poor countries	Hand pad, head band, proximity sensor	ECG, EEG	Prevention of heart disease
27	Asghari (2021)[18]	Iran	Mixed methods study	Aged people (400)	To predict for colorectal cancer	IoMT devices and sensors (1. Bio-medical Sensors 2. Wearable intelligent devices 3. Personal area network)	Vital signs, blood sample values, and electronic health records	Colorectal cancer
28	Wilbur (2018)[45]	USA	Mixed methods study	Fishermen (10)	To determine the feasibility of using a wearable biometric device in combination with observational data and biomarkers of acute stress to assess the potential short- and long-term negative health impacts associated with Alaska commercial salmon gillnet fishing	Wearable biometric garment	Accelerometry, heart rate variability, respiratory	Risk of cardiovascular disease
29	Ness (2017)[27]	USA	Prospective cohort study	Children with ASD or neurotypical development (35)	To test usability and optimize the system's components, biosensors, and procedures used for objective measurement of core and associated symptoms of ASD in clinical trials	Headgear, eye-tracker, ECG pads, wristband, sleep watch	ECG, EEG, and electrodermal activity	ASD

Table 1. Summary of Articles Reviewed (Continued)

#	First author (year)	Country	Design	Participants (n)	Purpose	Digital biomarkers device	Digital biomarkers	Outcome
30	Caldani (2020)[22]	France	Cross-sectional study	Children with ASD, ADHD, reading impairment, and neurotypical development (80)	To test the functional VOR responses in children with NDDs to measure functional performance of the vestibular system	Head band	VOR	ASD, ADHD, reading impairment
31	Verswijveren (2021)[29]	Australia	Cross-sectional study	Aged 8–9 (351)	To investigate the theoretical impact of reallocating a specific amount of sedentary time with an equal amount of total and ≥1-minute bout-accumulated time spent in different activity intensities, on inflammatory biomarkers	Waist band	Acceleration	Cardio-metabolic health
32	Zygouris (2017)[16]	Greece	Prospective cohort study	Healthy older adults (6) and aged patients with MCI (6)	To provide a preliminary investigation on whether a VR cognitive training application can be used to detect MCI in persons using the application at home without the help of an examiner	VR (virtual reality cognitive training application)	PAs (mean duration time per subject in VR applications)	Cognitive impairment
33	Suzuki (2010)[13]	Japan	Prospective cohort study	Aged with cognitive decline (6) and normal group (44)	To investigate the correlation of daily activity to the decline in cognitive function	Sensor (passive infrared sensors)	PAs (activities of daily life)	Cognitive impairment
34	Khullar (2019)[24]	India	Mixed methods study	Children with ASD or neurotypical development (35)	To propose an assistive intervention for supporting the overloaded sensory responses in hypersensitive individuals with ASD	Electronic toy or bag companion	Air quality, light intensity, tactile movement, sound loudness	Reduction in hyperactive states
35	Wintgens (2016)[33]	Germany	Mixed methods study	Patients with inflammatory bowel disease (157)	To allow patients to regularly monitor their own inflammatory status by testing fcalpro levels in the comfort of their own home	A stool extraction device and camera of iPhone app	Stool samples	Inflammatory bowel disease
36	Kim (2020)[42]	Korea	Mixed methods study	Migrant women workers (16)	To contribute to health promotion activities of middle-aged Korean-Chinese women and establish a culture of health promotion in the community	Mobile application	Walking steps	Improvement of homecare health management for a better end of life

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BMI, body mass index; BP, blood pressure; DCD, developmental coordination disorder; ECG, electrocardiogram; EEG, electroencephalography; EMG, electromyography; EOA, early-onset ataxia; GPS, global positioning system; HF, heart failure; MCI, mild cognitive impairment; NDD, neurodevelopmental disorders; OSAS, obstructive sleep apnea syndrome; PA, physical activity; PM, particulate matter; PR, pulse rate; PTSD, post-traumatic stress disorder; SDB, sleep disordered breathing; TD, typical development; VIP, visually impaired person; VOR, vestibulo-ocular reflex.

RESULTS

Study selection

A total of 2303 articles were retrieved. Of these, 408 were reviewed after removal of duplicates. From the review, it was determined that 223 failed to meet the inclusion criteria (Fig. 1). Full-text articles (n=185) were obtained for studies that met the inclusion criteria, and they were subsequently examined; 149 of these were excluded as they did not focus on living labs. Therefore, the literature search revealed a total of 36 relevant articles.

Study characteristics

The study characteristics are reported in Fig. 2 and Table 1. The studies were published between 2010 and 2021: 6 studies (16.7%) were published between 2010 and 2015 and 30 studies (83.3%) were published after 2016.

Twelve of the 36 studies were from Europe: Germany (n=2), Italy (n=2), Switzerland (n=2), United Kingdom (n=2), France (n=1), Denmark (n=1), Greece (n=1), and Netherlands (n=1). Twenty of the 36 studies were from the United States, and 10 were from Asia; four of these were from Korea.
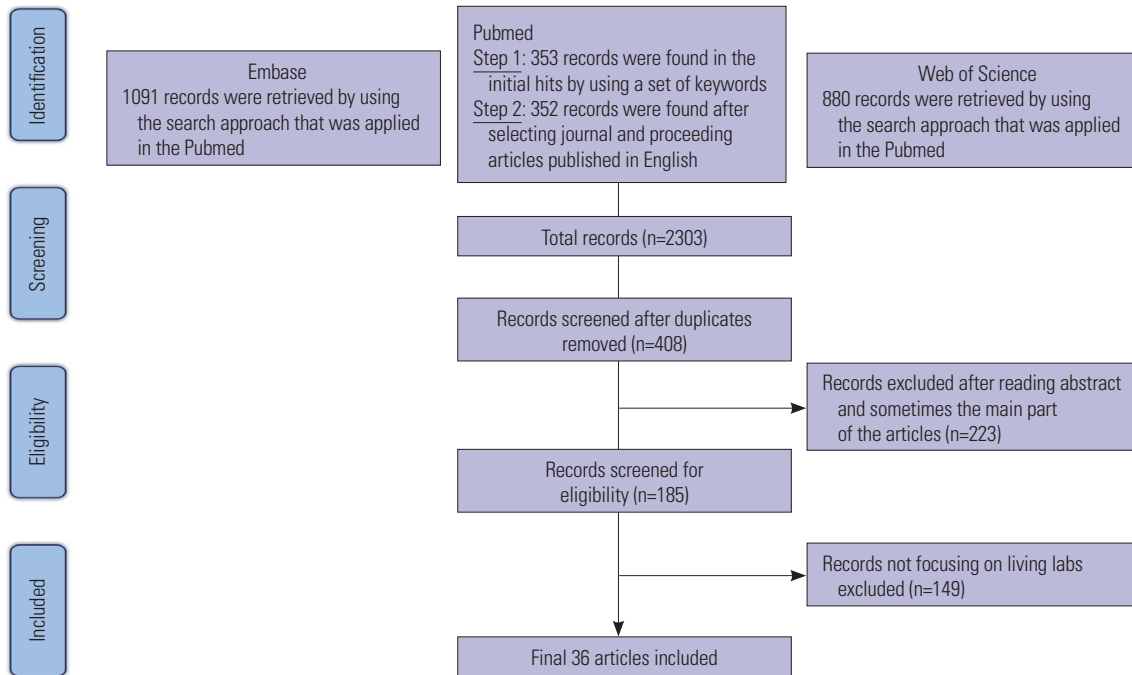

Fig. 1. PRISMA flow diagram of study selection. PRISMA, preferred reporting items for systematic reviews and meta-analyses.
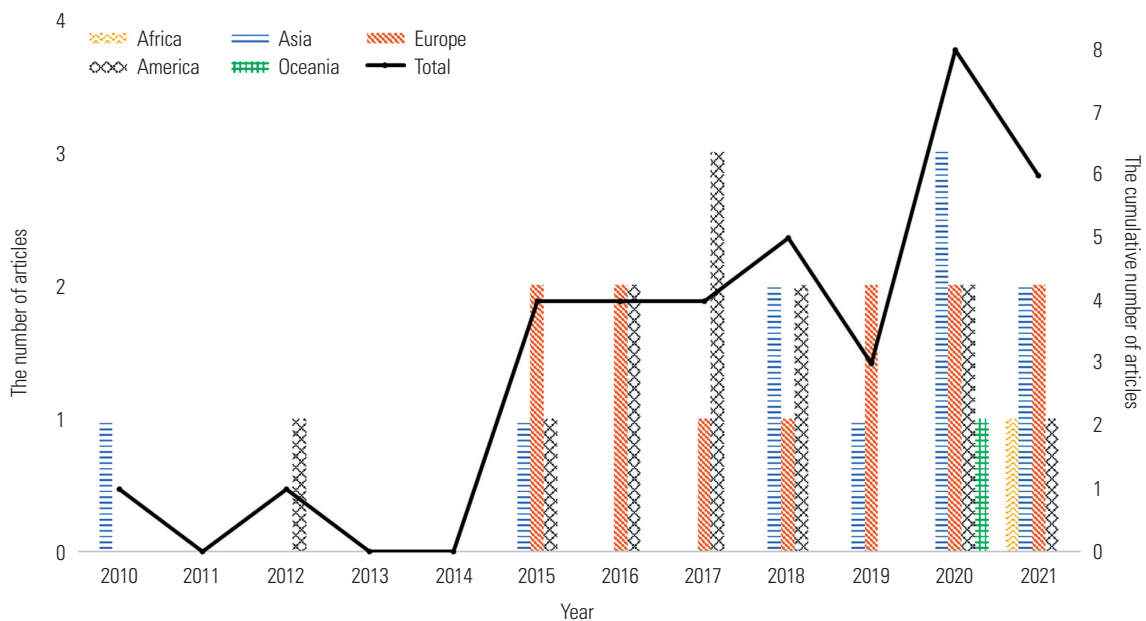

Fig. 2. Number of articles by country and year.

Elderly people were the target population in 20 studies, and children in 11 studies. Disabled people were the target population in nine studies, while other characteristics, such as region (e.g., rural), were the target of the other four studies.

The present study examined living-lab research that collected and analyzed the digital biomarkers of vulnerable and susceptible groups to identify the characteristics of each group (Table 2).

Elderly people

Seven of the 12 studies targeting elderly people were on cognitive impairment, four on severe diseases (heart failure, cardiovascular disease, colorectal cancer, and stroke), and two were observational studies of digital biomarkers.

In the living labs targeting elderly people, the main digital biomarkers measured were values related to physical activity, such as turning, walking speed, stride, number of steps, daily activity radius, sleep time, wake time, number of times tossing and turning, number of bathroom visits, out-of-home activities, and so on. Physical activities have been especially measured as digital biomarkers in all studies of mild cognitive impairment and Alzheimer's disease.[5,10-16] Most digital biomarkers for physical activities in these studies were used to evaluate the activities of daily living (ADL), and the studies suggested that higher scores or values related to assessment of ADL may lower the risk of cognitive impairment. Studies on severe disease include Senar, et al.,[17] Asghari,[18] Elhakeem, et al.,[19] and Kim, et al.[20]

These papers not only measured physical activities but also vital signs (heart rate, respiration rate, body temperature, and blood pressure), as well as values such as electroencephalogram (EEG) and electrocardiogram (ECG).

Most of the 13 studies used sensors for their measurements, including passive infrared motion sensors, driving sensors, contact-free piezoelectric sensors, and patch sensors.[5,12,13,17-20] In the other five studies, wearable devices, virtual reality applications, and balance boards were used.[10,11,14-16] Seelye, et al.[12] and Suzuki, et al.[13] measured the physical activities of older adults using passive infrared sensors.

There are several limitations to studying the elderly using living labs. First, when measuring digital biomarkers, it is critical that the targeted population understand how to use the measurement device.[16] This can be a problem with older populations. Moreover, some have a history of severe disease[5,11,14-16,19] and may have difficulties with mobility.[11,14-16] Additionally, all of these studies mentioned a small sample size as a limitation.

Children

Seven of the 11 studies targeting children were related to neurodevelopmental disorders (NDD),[21-27] two were motor development and ability studies,[28,29] and two were environmental exposure studies.[30,31] Most of the study subjects were patients with the targeted disease. Verswijveren, et al.[29] recruited unspecified children aged 8−9 years using established data. In seven out of 10 cases, biomarkers were measured using wear-

Table 2. Digital Biomarkers and Collection Devices by Characteristics of Target

Target	Elderly people	Child	Disabled people	Disadvantaged people
Type of digital biomarkers	Physical activities (turning, walking speed, stride, number of steps, daily activity radius, sleep time, wake-up time, number of times tossing and turning, number of bathroom visits, time out, etc.), vital signs (body temperature, blood pressure, heart rate, and respiratory rate), ECG, appearance	PM, carbon monoxide, temperature, humidity, non-functional noise vestibulo-ocular reflex, gesture related parameters (duration, maximum velocity, deviation from a straight line, peak acceleration), attention, meditation, activity, EEG, eye-tracking, ECG, electrodermal activity, gait-related velocity, acceleration, air quality, light intensity, tactile movement, sound loudness, force, movement direction, touch coordinates	ECG, EEG, electromyography, acceleration, direction, oxygen saturation, GPS, breathing rate, pulse rate, stool samples, the number of incoming calls and outgoing calls	Walking steps, exercise time, ECG, respiration, EEG, BMI
Method of collecting digital biomarkers	Sensors (infrared sensors, bed sensors, motion sensors, etc.), wearable devices, and other measurement tools, including balance boards and GPS tracking receivers	Wearable device (backpacks, head band, motion watch, headgear, eye-tracker, ECG pads, wristband, sleep watch, waist band), smart toy, mobile device	Smartphone, wearable device (watch, motion sensors, wristband, portable sensor), microphone, a stool extraction device	Smartphone, band, hand pad, head band, proximity sensors, mobile application

BMI, body mass index; ECG, electrocardiogram; EEG, electroencephalography; GPS, global positioning system; PM; particulate matter.

able devices, such as backpacks, head bands, wristbands, waist bands, headgear, watches, eye trackers, pads, and other mobile devices and smart toys.

Rabinovitch, et al.[30] and Schultz, et al.[31] measured location-based particulate matter (PM) exposure in elementary school children with physician-diagnosed asthma and preschool children (aged 3–4 years), respectively. A sensor-based backpack was used for PM measurement; these devices provided a space for children to put their personal belongings, and were designed to be externally friendly and provide comfort. The two studies were similar in that they targeted children, but they differed in their limitations due to the different ages targeted. When preschool children are involved in a study, it becomes necessary to ensure that the participants can use the wearable device, and that it can be worn without discomfort. According to Schultz, et al.,[31] after measuring the biomarkers, the device itself was investigated, and more than 50% of the respondents answered that they were uncomfortable with the PM-measuring backpack.

In one study on NDD, a difference in biomarkers was confirmed by including both children diagnosed with the disease and a control group. This study aimed to detect the disease in children in the early stage. These studies used wearable and other types of devices. Caldani, et al.,[22] Chu, et al.,[23] Ness, et al.,[27] and Khullar, et al.[24] all used wearable devices. In the studies in which the measurement devices were directly attached to the body, vestibulo-ocular reflex, attention, biomarkers such as meditation, activity, eye tracking parameters, EEG activity, and ECG were measured. Finally, a mobile device and smart toy were used to detect the biomarkers indicative of autism spectrum disorder or developmental disabilities after observing the children's behavior and patterning it through machine learning and deep learning.

In the study related to motor development and ability, the velocity and acceleration obtained through movement were measured for digital biomarkers in a living lab. Therefore, the study was conducted with elementary school students and older children who could perform various activities; a wearable device in the form of a waist band was used for measurement. In addition, all of these studies mentioned small sample size as a limitation.

Disabled people

Nine studies on individuals with disabilities were reviewed. All cases in which there were defects in physical or mental abilities were collectively referred to as "disability." Four of the nine studies targeting disabled people were related to physical disorders,[32,33] including Parkinson's disease[34] and stroke.[35] Five studies investigated mental disorders.[36-40]

The types of digital biomarkers used in these studies varied according to the disorder. In most studies, measurements such as ECG,[34,37] pulse rate,[39] and acceleration[32,35,36] were collected as digital biomarkers since the subjects' body data or location data were required in their daily lives. In particular, watches[34,36] and

waist- or writstbands[32] were widely used, as were voice recognition,[37] smartphones,[38,40,41] and portable sensors.[39] The biomarker collection methods varied according to the type of biomarker and type of disability. Derungs, et al.[35] used wearable motion sensors as they could monitor patient movements in daily life without specific tests, which can be burdensome for patients. The sensors allowed for continuous evaluation of their mobility behaviors and activities. Faurholt-Jepsen, et al.[38] used smartphones to collect digital biomarkers as the patients carried smartphones throughout most of their days and data could be collected automatically. Since wearable sensors could cause discomfort to patients during sleep, recording equipment attached to the ceiling was used for patients with sleep disordered breathing.[37] For those with post-traumatic stress disorder,[40] there may be physical "avoidance," especially in patients with highly heterogeneous disorders.

The data collected by digital biomarkers were mainly used to diagnose and predict each subject's disorder or to confirm the degree of disability. Ma, et al.[39] diagnosed obstructive sleep apnea syndrome by examining the occurrence of apnea. Lekkas and Jacobson[40] predicted PTSD diagnostic status using global positioning system-based location data. Wintgens, et al.[33] tested fecal calprotectin level using stool samples. Faurholt-Jepsen, et al.[38] measured the level of clinically rated depressive and manic symptoms in patients with bipolar disorder based on data on the number of incoming and outgoing calls per day. This was the case of representing social activity data as a type of digital biomarker, since patients with more signs of depression have a tendency to decrease the number of outgoing calls they make per day.[41] Ramadhan[32] used an accelerometer to detect when a subject stumbled, and was able to alert subjects and their guardians in real time.

Using living labs to study disabled people comes with several limitations. First, limited data can be automatically transferred to the application after data collection. In this case, subjects often had difficulty in self-monitoring, and needed someone to gather and report the data.[38] Second, some countries lack the required components to implement monitoring systems; or, in countries with tight regulations, the cost of implementing monitoring systems may be substantially increased. As a result, the possibility that these systems could be made available to the public is limited.[32]

Disadvantaged people

Four studies on disadvantaged populations were found. One study[42] was on immigrants, a marginalized class; and three studies[43-45] looked at susceptible and vulnerable regions, targeting fishing villages, rural areas, and developing countries.

Kim, et al.[42] applied a mobile app-based living lab approach to health improvement. The number of walking steps, exercise time, and heart rate of the subjects were measured by linking the mobile app and smart band. Participants were also encouraged to provide their health information (e.g., cardiovascular

disease, musculoskeletal disorders, menopausal symptoms, anti-aging, stress management, weekend pharmacies and hospitals, weight control, healthy eating, stretching, strength training, and cancer screening). Through self-monitoring of the measured values, the participants checked their physical activity and health status, which allowed them to adapt and improve their health and cultural life. However, there was a difficulty in that education on the use of wearables and devices is essential for the underprivileged.

Wilbur, et al.[45] measured the heart rate variability as well as breathing and sleep quality using an automatic measurement method with an attached sensor to study the association of these biomarkers with stress. In the study by Neal Neto, et al.,[44] EEG was measured with a headband to record childhood developmental changes, and ECG was collected using a hand-pad held by the thumb. For younger children who could not hold the hand-pad, the pad was placed in contact with the child's wrist and fixed with a cable. The ECG measurement data helped the authors understand heart disease. In the study by Eisenhauer, et al.,[43] self-monitoring was conducted by measuring physical activity biomarkers. A mobile application and smart scale were linked, and body mass index (height and weight) and physical activity (blood pressure, pulse, and exercise volume) were measured through self-reporting.

In the three studies classified by regional disadvantage, the types of wearable devices differed respectively. Wilbur, et al.[45] obtained biomarkers using the sensors attached to clothing and analyzed by monitors since the characteristics of the subjects' jobs made direct device management and operation difficult. Neal Neto, et al.[44] used wearable devices with parental consent, after confirming that they could be safely worn by children. Since this study targeted an environmentally vulnerable region, the study subjects had to move sufficiently for measurement. Moreover, considering that the measurement target was children, portability and usage method were the most important qualities for wearable devices. However, in the study by Eisenhauer, et al.,[43] continuous monitoring and observation were performed, as the measurement of wearable devices and self-reporting was important. Feedback between the observers and participants was accomplished by sending text messages in real-time. As a result, data loss was reduced.

DISCUSSION

This study reviewed the types of digital biomarkers and the digital biomarker collection devices used in living lab studies on the health of vulnerable populations. It also reviewed the characteristics of the living lab operations themselves according to the individual populations studied.

Vulnerable and susceptible individuals, such as elderly people, children, people with disabilities, and people at risk of social exclusion, might benefit more from living-lab approaches.

Living labs are appropriate for developing healthcare services and investigating health problems for remote, rural areas and vulnerable individuals.[46]

Using digital biomarkers in living labs enables personalized monitoring while saving time and costs. In particular, in the study by Derungs, et al.,[35] a personalized therapy schedule was provided by checking the motion data of each patient. In this way, it is possible to provide customized treatment for each individual's disease,[35] which will soon lead to improvement in their lifestyle. In addition, it enables data collection in real-time, and since data is transmitted as soon as it is collected, it also reduces the risk of missing data.[38]

In the studies reviewed, digital biomarkers were mainly collected using non-invasive devices. The adopted digital biomarker type reflected the purpose rather than the characteristics of the subject. The reviewed articles had various purposes such as health changes after disease, health effects due to environmental exposure, disease/disability/depression diagnosis, and health promotion. ECG was measured for all targets, but it was measured only when the purpose was "diagnosis."[17-20,22-24,27,34,37,43,44]

The method of collecting the digital biomarkers reflected the population characteristics of targeted subject. All subjects covered in this study had difficulty with using the devices. Especially, for the elderly and disabled, sensor-based wearable devices were used to detect movements, which were collected as digital biomarkers. This is because sensor-based devices do not require an explanation on how to use them, and they are less affected by the presence of others. However, Kim, et al.[20] suggested that measurements using sensors may not take into account an older adult's level of device use. In addition, it is not necessary for the elderly to directly wear a device, and it is possible to objectively collect a substantial amount of information on subjects' internal activities over the long term.[20] In contrast, children were able to collect digital biomarkers using various types of wearable devices, but they had to be accompanied by guardians. Therefore, Schultz, et al.[31] stated that establishing a trusting relationship with parents and children is an important component of research participation. Of course, with other target individuals, a high degree of trust is also required between patients and healthcare providers.[38]

There were some negative views on living labs when they caused inconvenience or when there were difficulties in using the wearable devices.[44] Small and simple wearable devices are needed, and training on device use is essential for targets.[42,44] In addition, some studies involving older adults were conducted only with people living alone, as there could be a bias depending on the presence or absence of assistance.[5]

In living-lab research, it can be difficult to attract research subjects. Recruiting participants is difficult since participation places a significant burden on the subject in child observation studies; and therefore, careful attention must be paid to the recruitment method.[31] Some researchers emphasized the impor-

tance of initial participant recruitment and retention methods.[42,43]

Like this, measuring digital biomarkers by operating living lab can be more complicated as the characteristics of each subject must be reflected. Nevertheless, the use of digital biomarkers can lead to better research in accuracy of result. Wu stated that the accuracy increased by 10%–20% when the variables for digital biomarkers were used, compared to the accuracy analyzed with questionnaire data.[47]

As we reviewed, there is a multitude of sensors and devices that can be used. However, there is no agreed-upon standards for these digital biomarkers for now. Most importantly, the current evidence base is not large enough to indicate which standards are most effective.[4] As more studies measure digital biomarkers, these standards will certainly be needed.

While much of the literature focused only on a narrow perspective use of a single device or technology (e.g., a wearable or cognitive testing app), we confirmed the characteristics of digital biomarkers in living lab according to the study subject. Since digital biomarkers and devices that collect them vary depending on the characteristics of the study subjects, researchers are recommended to pay attention not only to the purpose of the research but also the characteristics of the study subjects when collecting and using digital biomarkers from living labs.

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AUTHOR CONTRIBUTIONS

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