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Digital measurement of mobility in pulmonary arterial hypertension: A structured review of an emerging area

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Abstract

This review examined literature that has examined mobility in pulmonary arterial hypertension (PAH) using digital technology. Specifically, the review focussed on: (a) digital mobility measurement in PAH; (b) commonly reported mobility outcomes in PAH; (c) PAH specific impact on mobility outcomes; and (d) recommendations concerning protocols for mobility measurement in PAH. PubMed, Scopus, and Medline databases were searched. Two independent reviewers screened articles that described objective measurement of mobility in PAH using digital technology. Twenty-one articles were screened, and 16 articles met the inclusion/exclusion criteria and were reviewed. Current methodologies for mobility measurement in PAH with digital technologies are discussed. In brief, the reviewed evidence demonstrated that there is a lack of standardisation across studies for instrumentation, outcomes, and interpretation in PAH. The validity and reliability of digital approaches were insufficiently reported in all studies. Future research is required to standardise digital mobility measurement and characterise mobility impairments in PAH across clinical and real-world settings. The reviewed evidence suggests that digital mobility outcomes may be useful clinical measures and may be impaired in PAH, but further research is required to accurately and robustly establish findings. Recommendations are provided for future studies that encompass comprehensive reporting, validation, and measurement.

Keywords

Mobility, digital health technology, wearables, inertial sensors, pulmonary arterial hypertension, gait, physical activity

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Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease that is characterised by increased pulmonary vascular resistance and arterial pressure, with right ventricular dysfunction.[1] Loss or reduction of mobility is one of the earliest manifestations of cardio-pulmonary conditions, such as PAH.[1] Therefore, mobility impairment is useful to measure in PAH, as it is reflective of underlying deficits due to biological and pathogenic processes.[2,3] Mobility capacity (i.e. how much someone can do) is usually measured in PAH through the 6-min walk test (6MWT),[4] which has been associated with adverse outcomes and reduced right ventricular function.[5] Mobility perception (i.e. what a person thinks they can do) is typically measured in PAH using self-reported subjective questionnaires, such as

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World Health Organization Functional Class (WHO FC).[6] Mobility performance (i.e. what a person actually does) involves monitoring the duration, quality, and intensity of actual mobilisation within patient habitual (real-world) environments.[7] Mobility outcome measures may be useful biomarkers for clinical trials; for example, a recent report suggested that daily step count may be a potential prognostic biomarker for hospitalisations in PAH (i.e. those with PAH who had <5000 steps per day over 1 week had increased risk of hospitalisation).[8]

PAH clinical trials have traditionally focussed on mobility capacity (6MWT) or perception (WHO FC) as markers for disease progression and as endpoints in clinical trials.[9,10] This is due to there being no mobility performance outcomes that are currently accepted by regulators for use in clinical trials for PAH. Additionally, mobility capacity and perception assessments do not require specialist knowledge, training, or equipment, so are inexpensive and accessible for use in a variety of clinical settings. However, there are many limitations to traditional mobility capacity and perception tests. For example, capacity and perception tests are intermittently performed at clinic site visits and therefore lack ecological validity (i.e. just because someone can or thinks they can do something does not mean that is what they actually do in their real life).[7] Similarly, global capacity measures do not provide disease-specific impairment (or improvement) in mobility (i.e. specific characteristics/outcomes that map to specific underlying neural, musculoskeletal, or cardio-pulmonary deficits). Mobility capacity tests also have study design issues, such as a lack of standardisation across raters/sites,[11] impact from learning effects,[12] motivation, understanding, and increased measurement error with greater mobility impairment.[13] Wearable sensors offer a solution to these limitations, providing the ability to objectively measure mobility within clinic and remote settings to provide relevant outcomes for use in clinical trials.[14]

Mobility is one of the most advanced concepts being assessed digitally within clinical settings and remotely.[7] Wearable sensors can provide comprehensive mobility performance outcomes across two domains: (a) mobility quality outcomes (e.g. spatial–temporal gait characteristics); and (b) mobility quantity outcomes (e.g. activity measures of bout duration, intensity, count/frequency, expenditure, etc.).[15] These mobility outcomes from wearables have begun to be deployed in PAH studies. Advances in wearable sensor technology have led to relatively small devices that are capable of continuously recording over long periods (hours/days/weeks/months) of time in clinical or remote settings.[14] This opens opportunities to gather specific/discrete mobility performance outcomes that are relevant for specific clinical cohorts and ecologically valid, with outcomes derived from data captured in any place or time. However, there is no "gold-standard" protocol or methodology for mobility measurement with wearable or digital sensors in PAH, which leaves investigators who wish to conduct this research with a choice of numerous protocols (tests, sensor type, location, attachment, etc.) that differ in many respects and may lead to inconsistent results. In the process of developing robust and accurate protocols, it is helpful to have evidence-based recommendations. This review therefore focussed on understanding the previous work that has assessed mobility using digital devices in PAH to provide some guidance regarding methodology selection and implementation within healthcare or clinical trials.

This literature review aimed to specifically examine: (a) digital mobility measurement in PAH; (b) commonly reported mobility quality and quantity outcomes in PAH; (c) PAH specific impact on mobility outcomes; and (d) recommendations concerning protocols for mobility measurement in PAH. Understanding how mobility is currently being measured in PAH with digital technologies and providing evidence-based recommendations for future mobility studies in PAH will lead to a more standardised approach, which will ultimately benefit patients through more effective and accurate data to inform healthcare or clinical trial outcomes.

Methods

Search strategy and information sources

The key terms involved the clinical condition (i.e. "PAH"), mobility (i.e. "gait," "physical activity," etc.), and a digital technology (i.e. "motion capture," wearables, etc.) in the title, abstract, or keywords (Figure 1). Key terms were matched and exploded with medical subject headings (MeSH) in each separate database where appropriate. Databases searched included PubMed (with Medline), Scopus, and IEEE Xplore with no start date imposed on the search to 31 December 2023. As this was a literature review, no patient consent is required.

Selection process

An initial title screen for relevant articles was performed by the reviewer (SS) once the results of the searched databases had been combined. After the initial title screen, both titles and abstracts of the articles were reviewed by two independent reviewers (SS and ER). A review of the full text was required if it was not clear from the title, abstract or keywords whether the study met review criteria.

Eligibility criteria

Articles were included if they reported an objective digital measurement of mobility in PAH. Specifically, studies were only included if they used a digital technology, such as 3D motion capture, walkway mats, inertial measurment units (IMUs), pedometers, etc., to measure mobility, specifically

Search String Key Terms
Pulmonary Arterial Hypertension: "Pulmonary Arterial Hypertension" OR PAH OR "primary pulmonary hypertension" OR "precapillary pulmonary hypertension" OR "primary obliterative pulmonary vascular disease" (TITLE-ABS-KEY)
AND
Mobility: "Mobil*" OR Gait OR "Physical Activity" OR actigraphy OR "Locomot*" OR "Ambulat*" OR "Walk*" OR "Step*" OR "Stride*" OR distance OR Pace OR "Gait Speed" OR "Gait Velocity" OR "step velocity" OR cadence OR Rhythm OR Variability OR "Symmet*" OR "Asymmet*" OR "Swing Time" OR "Stance Time" OR "double limb" OR "Double support" OR "single limb" OR "single support" OR "Stance Time" OR kinematic OR kinetic OR "activity intensity" OR "activity duration" OR "bout duration" OR "energy expenditure" OR MVPA OR intensity OR sedentary OR "low intensity" or "moderate intensity" OR "vigorous intensity" OR "step count" OR "vector magnitude count" OR "vector magnitude unit" OR "activity count" OR MET OR "metabolic*" (TITLE-ABS-KEY)
AND
Digital technology: Wearable OR Sensor OR "motion capture" OR "3D motion" OR 'walkway mat' OR "force plate" OR "video" OR "2D video" OR "pressure sensor" OR "Inertial Sensor" OR pedometer OR accelerometer OR gyroscope OR magnetometer OR barometer OR nearable OR airable OR digital OR "digital technology" OR "digital health technology" (TITLE-ABS-KEY)
(*indicates a wildcard and TITLE-ABS-KEY indicates a title, abstract or keyword search)

Figure 1. Search strategy.

mobility quality (i.e. gait), and/or mobility quantity (i.e. physical activity).

Articles were excluded if they only reported clinician rated mobility assessment, such as 6MWT/distance or similar subjective assessments. Additionally, we did not consider wider literature on patients with pulmonary hypertension or other chronic lung conditions or articles that combined patients with PAH in wider cohorts (i.e. grouped all pulmonary hypertension patients together),[16] as we specifically focussed on PAH. Only full original research journal articles were included, with commentaries, editorials, conference proceedings, and reviews excluded.

Data items and collection process

Data were extracted by the reviewer (SS) and synthesised into tables by two reviewers (SS and ER), with a third reviewer used to confirm data entry (NN). Data included demographics, gait or physical activity tasks/study protocol, measurement instruments, outcome measures, and key findings.

Results

The evidence base

The search strategy yielded 73 articles, excluding duplicates (Figure 2). The initial screening of titles and abstracts resulted in 21 articles of interest, of which 16 were identified for inclusion consistently across reviewers (SS, ER). Reasons for exclusion of articles are noted in Figure 2, including not being a full original article (i.e. a letter to the editor, commentary or conference proceeding),[8,17,18] involving a wider clinical cohort[16] and not being in English.[19]

Study design

The reviewed studies were primarily observational studies, with only four interventional studies (i.e. clinical trials) that included mobility measurement with a wearable device in PAH (Table 1). One of the interventional studies was a Phase 2 clinical drug trial;[20] two others were Phase 4 clinical drug trials;[21,22] and another study was a pilot trial of a technology-based intervention for activity levels.[23] Mobility outcomes on clinical trials were primary[21,23] (although the Phase 4 trial that included mobility quantity outcomes as a primary outcome was an exploratory study to examine mobility endpoints), secondary,[20] or exploratory[22] outcomes. Most reviewed studies took place in free-living settings, with few studies examining clinic-based mobility, and largely involved mobility performance outcomes rather than capacity testing (i.e. 6MWT) (Table 2).

Participants

Reviewed articles ($n = 16$) investigated people with PAH with a mean age of ~42 years old (Table 1). Both male

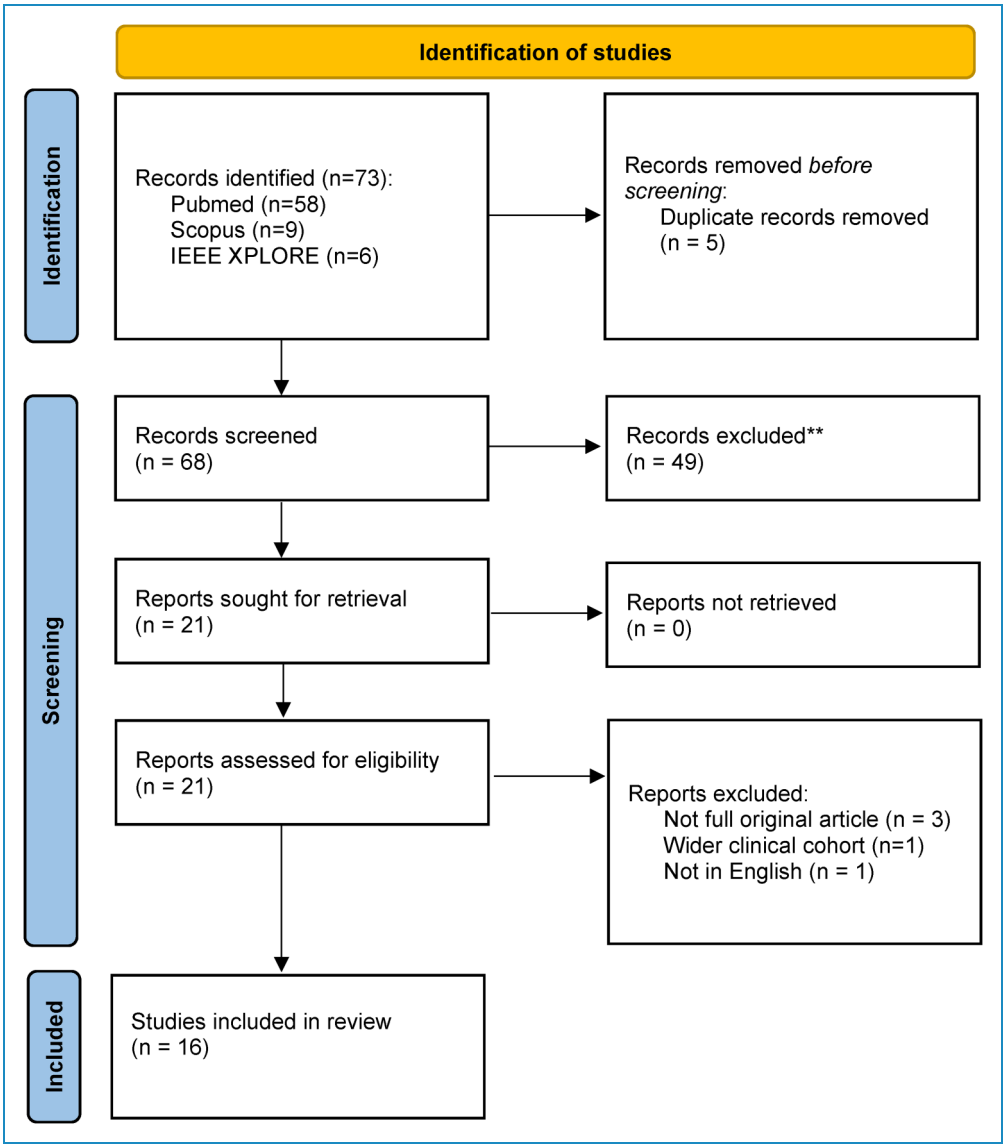

Figure 2. Flow chart of study design. This illustrates the yield of the search strategy at each stage of the study selection process.

and female participants were recruited to most studies; however, female participants were the majority group in all reviewed studies, and one focused entirely on female patients with PAH.[24] One study involved children with PAH[25] (Table 1). Only three reviewed studies included a healthy control cohort for direct comparison of mobility metrics to PAH and three clinical trials included a non-intervention group[23,25–27] (Table 1).

Instruments

Sensor Type. Mobility was measured using unimodal inertial sensors (biaxial or triaxial accelerometer or IMU) or multi-modal devices (combined accelerometer/IMU and photoplethysmography or electrocardiography sensors) that were either research-grade ($n = 11$) or commercial ($n = 4$) in nature (Table 2). Most studies used a multimodal device ($n = 8$, Table 2), but primarily reported data from the included accelerometer for mobility outcomes.

Device Number. Table 2 shows 14 reviewed studies used a single device to measure mobility outcomes in PAH. Two studies used more than one device[20,28] and compared data reported from the two devices or interchangeably used different devices at different locations, and then combined outcomes.

Sensor Sampling Rate. Temporal resolution of instruments (i.e. sampling rate; Hz) was not reported in most of the reviewed studies. Where it was reported, the temporal

Table 1. Participants, inclusion/exclusion criteria, and study design.

Author	Participants	Inclusion Criteria	Exclusion Criteria	Study Design
Hemnes et al. (2021)	*N* = 42 PAH *N* = 20 in control arm Age: 47 (36–58) years Gender: *n* = 21 (95%) female WHO FC I (7), II (12), III (3), IV (0) 6MWD: 442 (362–494) m *N* = 22 in intervention group Age: 47 (41–54) years Gender: *n* = 15 (75%) female WHO FC I (3), II (15), III (2), IV (0) 6MWD: 431 (396–456) m	• Adults (>18 years old) • Diagnosis of idiopathic, heritable, drug/toxin-associated, or connective tissue disease-associated PAH • World Health Organization (WHO) functional class I, II, or III participants were ambulatory and receiving a stable PAH medical regimen for at least 3 months, A single diuretic adjustment in the prior 3 months was permitted	• Prohibited from normal activity due to wheelchair bound status, bed bound status, reliance on a cane/walker, activity-limiting angina, activity-limiting osteoarthritis, or other condition • Pregnancy • Diagnosis of PAH etiology other than idiopathic, heritable, or associated • Forced vital capacity <70% predicted • Functional class IV heart failure • Requirement of >1 diuretic adjustment in the prior 3 months • Preferred form of activity is not measured by an activity tracker (swimming, yoga, ice skating, stair master, or activities on wheels such as bicycling or rollerblading)	*Free-living mobility* Randomized, single-blind, controlled pilot trial of a text-based mobile health intervention in PAH
Howard et al. (2023)	*n* = 108 PAH *N* = 55 in placebo group Age: 42 (76.2) years Gender: *n* = 42 (76%) female WHO FC II (41), III (14), IV (0) 6MWD: 449.5 (98.9) m *N* = 53 in intervention group Age: 35 (66.0) years Gender: *n* = 35 (66%) female WHO FC II (33), III (20), IV (0) 6MWD: 453.1 (129.7) m	• Aged 18–75 years with PAH (idiopathic, heritable, drug and toxin induced, or associated with connective tissue disease, HIV infection, or corrected congenital heart disease [simple systemic-to pulmonary shunts >1 year after repair]) diagnosed by right heart catheterization • Patients were required to have a 6 min walk distance (6MWD) > 100 m • WHO FC II to III, without hospitalization or worsening WHO FC in the 30 days prior to screening. • Patients had to be receiving an endothelin receptor antagonist alone or in combination	Patients on a PAH-specific monotherapy targeting the nitric oxide pathway (i.e. PDE-5 inhibitor or sGC stimulator) Patients treated with prostacyclin, prostacyclin analog or selexipag within 3 months prior to screening Any hospitalization during the last 30 days prior to screening Severe coronary heart disease or unstable angina Documented severe hepatic impairment or severe renal insufficiency at screening Participation in a cardio-pulmonary rehabilitation program based on exercise training within 8 weeks prior to screening Any factor or condition	*Free-living mobility* Prospective, multicentre, randomized, placebo controlled, double-blind exploratory phase 4 study

(continued)

Table 1. Continued.

Author	Participants	Inclusion Criteria	Exclusion Criteria	Study Design
		with a phosphodiesterase type 5 inhibitor or soluble guanylate cyclase stimulator for >90 days and at a stable dose for >30 days prior to randomization. • Participation in an exercise-based rehabilitation program was not permitted in the 8 weeks prior to study start or at any point during the study.	likely to affect full participation in the study or compliance with the protocol (such as adherence to protocol mandated procedures), as judged by the investigator	
Lachant et al. (2022a)	*N* = 20 PAH Age: 59 (44–67) years Gender: *n* = 16 (80%) female WHO FC I (2), II (18), III (0), IV (0) 6MWD: 405 (330–464) m	Stable in New York Heart Association Functional class I-III without adjustment to vasodilator therapy for >90 days; in addition, required that participants complete the 6MWT without stopping in an effort to decrease variability between clinic and remote 6MWT.	Not Reported (NR)	*Clinic and free-living mobility* Single-center, prospective, observational study
Lachant et al. (2022b)	*N* = 22 PAH Treatment naive (*n* = 6) Age: 61 (13) years Gender: *n* = 5 (83%) female WHO FC I (0), II (3), III (3) 6MWD: 395 (229–429) m Treatment intensification (*n* = 6) Age: 53 (17) years Gender: *n* = 3 (50%) female WHO FC I (0), II (1), III (5) 6MWD: 377 (152–498) m Stable (*n* = 10) Age: 53 (15) years Gender: *n* = 7	Patients were not required to have a smart device or internet.	Those who had severe immobility unrelated to PAH	*Free-living mobility* Single-centre prospective observational study

(continued)

Table 1. Continued.

Author	Participants	Inclusion Criteria	Exclusion Criteria	Study Design
	(70%) female WHO FC I (0), II (10), III (0) 6MWD: 381 (352–459) m			
Mainguy et al. (2011)	*N* = 15 iPAH Age: 47 (15) years Gender: *n* = 10 (67%) female WHO FC I (0), II (11), III (4) 6MWD: 401 (89) m *N* = 10 PAH + SSc Age: 58 (10) years Gender: *n* = 9 (90%) female WHO FC I (0), II (5), III (5) 6MWD: 349 (129) m *N* = 10 SSc Age: 58 (9) years Gender: *n* = 9 (90%) female 6MWD: 502 (55) m *N* = 15 controls Age: 46 (16) years Gender: *n* = 10 (67%) female 6MWD: 670 (64) m	Idiopathic pulmonary arterial hypertension (IPAH, n= 15) and with pulmonary arterial hypertension associated with limited systemic sclerosis (PAH-SSc, n= 10) The PAH diagnosis was made according to recent guidelines All patients displayed significant PAH, defined as a mean pulmonary artery pressure .25 mmHg at rest with a pulmonary capillary wedge pressure, 15 mmHg Recent right heart catheterization (12 months) was used to described hemodynamic severity. Only patients with no change in their PAH therapy, in stable clinical condition over the last 4 months and belonging to functional classes II or III defined by the New York Heart Association (NYHA) functional classification were eligible.	1. Unstable PAH defined as recent syncope or NYHA functional class IV 2. left ventricular ejection fraction, 40% of predicted 3. significant restrictive (more than minimal lung fibrosis on CT scan or total lung capacity, 70% of predicted) or obstructive (FEV1/FVC, 70%) lung disease	*Free-living mobility* Observational study
Matura et al. (2016)	*N* = 15 PAH Age: 50.5 (15.9) years Gender: *n* = 15 (100%) female WHO FC I (0), II (12), III (3) 6MWD: 412.9 (66.1) m	18 years or older with PAH (idiopathic, heritable, or associated with connective tissue disease, congenital heart disease, drug/toxin use, or HIV) who were receiving targeted PAH therapy at a stable dose for at least 3 months.	Chronic fatigue syndrome, sleep disorders, or major depression, or who were hospitalized or acutely ill Gait limitations, such as significant arthritis or excessive pain in joints, an orthopedic injury that limited mobility in the hip or knee, or neurologic conditions that affected balance	*Free-living mobility* Prospective cohort study

(continued)

Table 1. Continued.

Author	Participants	Inclusion Criteria	Exclusion Criteria	Study Design
Minhas et al. (2022)	*N* = 55 PAH Age: 61 (10.3) years Gender: *n* = 37 (67%) female WHO FC I (4), II (35), III (16) 6MWD: 424 (113) m	Adult men and postmenopausal women with PAH on stable therapy	Hospitalized, acutely ill, with World Health Organization (WHO) functional class IV or those limited by musculoskeletal function or coordination Contraindications to anastrozole, such as osteoporosis, ongoing treatment with hormone replacement therapy, and a history of breast cancer were excluded	*Free-living mobility* Cross-sectional analysis of the baseline (pre-randomization) data from the Phase 2 PHANTOM (Pulmonary Hypertension and Anastrozole) trial, an ongoing multi-centre placebo-controlled trial
Nakazato et al. (2021)	*N* = 20 PAH Age: 44.3 (13.2) years Gender: *n* = 16 (80%) female WHO FC I (7), II (10), III (3) 6MWD: 451.5 (96.4) m	Over 18 years old diagnosed with PAH right catheterization and a diagnosis according to PAH guidelines receiving targeted PAH therapy at a stable dose for at least 8 weeks and categorized as functional class (FC) I, II, or III for dyspnea New York Heart Association (NYHA)	Those diagnosed with depression, receiving medication for this condition, those with cognitive impairment who might have difficulty completing the questionnaires, and subjects with mobility limitations or any muscular or neurological condition that could compromise walking or PA	*Free-living mobility* Cross-sectional, observational study
Pugh et al. (2012)	*N* = 20 PAH Age: 53.7 (14.3) years Gender: *n* = 15 (75%) female WHO FC I (1), II (10), III (7), IV (2) 6MWD: not reported *N* = 30 controls Age: 51.1 (15.4) years Gender: *n* = 22 (73%) female 6MWD: not reported	Aged 18 years with established World Health Organization (WHO) functional class I PAH stable PAH (defi ned as no hospitalization for PAH and no escalation in dose or addition of PAH therapy or diuretics within 2 months prior to enrolment or during the study)	Pulmonary artery occlusion pressure of 15 mm Hg, mixed pulmonary hypertension, more than one etiology for pulmonary hypertension, portopulmonary hypertension, significant arthritis or conditions other than pulmonary vascular disease limiting ambulatory activities (e.g. orthopedic injury, neurologic disease), or significant obstructive or restrictive lung disease (FEV 1/FVC, 70%, total lung capacity, 70% predicted). Patients with PAH who initiated a structured physical rehabilitation program within 2 months of study enrollment were not eligible to participate.	*Free-living mobility* Observational study
	N = 39 incident	All patients had invasive	Patients with other forms of	

(continued)

Table 1. Continued.

Author	Participants	Inclusion Criteria	Exclusion Criteria	Study Design
Saxer et al. (2019)	PAH Age: 65 (54–73) years Gender: *n* = 23 (59%) female WHO FC I (1), II (13), III (21), IV (4) 6MWD: 458 (300–593) m	hemodynamic assessment by right heart catheterization (RHC) to diagnose precapillary PH and a full assessment to diagnose PAH or CTEPH according to current guidelines	PH, especially those with PH due to lung or left heart disease were excluded.	*Free-living mobility* Cross-sectional study
Sehgal et al. (2019)	*N* = 30 PAH Age: 50.5 (13.0) years Gender: *n* = 26 (87%) female WHO FC I (3), II (14), III (11), IV (2) 6MWD: 401.3 (101.9) m	Subjects with hemodynamically confirmed WSPH group one PAH, who could ambulate were enrolled	NR	*Free-living mobility* Pilot, prospective, observational study
Sood et al. (2019)	*N* = 58 PAH Age: 61.7 (11.4) years Gender: *n* = 66 (88%) female WHO FC I (7), II (23), III (44), IV (1) 6MWD: 361.4 (95.4) m	aged 18–80 years with the diagnosis of symptomatic PAH (WHO Group 1) with PVR >300 dynscm5, mean pulmonary artery pressure >25 mmHg, pulmonary capillary wedge pressure <15 mmHg as assessed by right heart catheterization within six months before screening (Visit 0), and 6MWD of 150–450 m with relative difference (i.e. absolute difference/ mean) 15% between the screening and the baseline test. Idiopathic and familial PAH were included, as well as PAH associated with connective tissue disease, congenital heart disease >1 year after surgical repair, anorexigen or amphetamine use, and portal hypertension with liver cirrhosis.	Concomitant treatment with nitrate or nitric oxide donor therapy, phosphodiesterase (PDE) type 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil), and non-specific PDE inhibitors (e.g. theophylline, dipyridamole) was not allowed. Patients unable to perform a valid 6MWD were excluded.	*Clinic mobility* Clinical trial (Phase 4)–prospective, multicentre, single-arm, open-label
	N = 18 PAH	Patients aged ≥18 years	Allergic to nickel and	*Clinic and free-living mobility*

(continued)

Table 1. Continued.

Author	Participants	Inclusion Criteria	Exclusion Criteria	Study Design
Stollfuss et al. (2021)	Age: not reported Gender: $n = 12$ (67%) female WHO FC: not reported 6MWD: 339 (250–420) m	with pulmonary arterial hypertension in WHO functional class III despite treatment were eligible for enrolment if they were willing to wear a smartwatch for the duration of the study, had no previous treatment with inhaled iloprost, and they and their treating physician had decided to initiate treatment with inhaled iloprost using a Breelib nebulizer	methacrylates or if they were already participating in an investigational program that included an intervention outside of routine clinical practice	National, prospective, observational, multicentre, single-arm cohort study
Wieteska-Miłek et al. (2022)	$N = 40$ PAH Age: 45.5 (24.7–64.4) years Gender: $n = 32$ (80%) female WHO FC: I (2), II (33), III (5), IV (0) 6MWD: 527.1 (68.7) m	18 years old or older and had a diagnosis of PAH confirmed by right heart catheterization and additional necessary compulsory tests according to the current guidelines	Cognitive impairment to completing the questionnaire, mobility impairment due to musculoskeletal or neurological disease, and lack of consent to participate in the study	*Free-living mobility* Prospective cross-sectional study
Xu et al. (2022)	$N = 22$ PAH Age: 50.6 (13.4) years Gender: $n = 19$ (86%) female WHO FC: not reported 6MWD: not reported	NR	NR	*Free-living mobility* Prospective, observational study
Zijlstra et al. (2017)	$N = 29$ PAH Age: 12 (7.5–14.7) years Gender: $n = 19$ (66%) female WHO FC: I (4), II (15), III (9), IV (1) 6MWD: 411 (68) m $N = 60$ controls Age: 11.8 (9.0–15.1) years Gender: $n = 38$ (63%) female 6MWD: not reported	PAH had been confirmed with cardiac catheterization, and patients were classified according to the Updated Clinical Classification of PAH	NR	*Free-living mobility* Prospective, observational study

resolution was inconsistent and relatively low (i.e. 30–60 Hz) (Table 2).

Sensor Location and Attachment. Digital sensors were primarily placed on the wrist ($n = 8$), but provided limited information on dominant or non-dominant hand side (Table 2). Other placements included the hip,[20,24,25,27] upper arm,[26,29] thigh,[28]or chest,[28,30] as well as multiple locations (i.e. shirt or pants' pocket, waist on belt, in a bag, etc.).[30,31] Most devices were attached via a strap or belt, with few being clipped to clothing[31] or stuck to the skin.[30]

Environment. Only five studies recorded mobility with a wearable in a clinic/lab setting[22,28,30,32,33] to record the 6MWT, with one study also conducting a free-living 6MWT.[33] All other studies examined mobility in a free-living habitual environment (Table 2).

Duration. Most studies recorded mobility over a 7-day period ($n = 7$), but some studies collected data for longer (i.e. 2–65 weeks) (Table 2). Several studies that did record data for long periods (>2 weeks) reduced the data being analysed. For example, one study took a 4-week period from a longer wear time (i.e. 7–65 weeks),[33] and another study recorded data for up to 133 days, but cut out 2-week periods prior to assessment sessions and discarded other recorded data.[34] Although not consistently reported in all studies, there were differences across studies for the reported number of valid days required and hours that needed to be recorded each day for a day to be valid for data processing/analysis (i.e. requirements across studies were a minimum of 3–5 days or 4 weeks, with data from >4.8 h to >12 h per day) (Table 2).

Algorithm. There was a lack of detailed reporting for the data processing methods involved in deriving mobility outcomes from the instrumentation, with most studies reporting that they used a manufacturer proprietary algorithm. Two studies reported using custom-made algorithms created specifically for their study (i.e. one Python-based code and one mobile application).[30,32] Only one of the studies provided the version of the software used for data processing.[26] Within studies that used the same device or data processing platform there was inconsistency in the data processing procedure, with different data epochs used to filter data (i.e. 15 or 60 s epochs) (Table 2).

Reliability and validity. No studies provided information on the validity or reliability of the instrumentation used specifically in PAH. Several studies commented that the instrument used to examine mobility had been validated in other populations. For example, Matura et al.[24] noted that the actigraphy device that they used has had validation performed for physical activity measures, but this was not specific to PAH as they referenced a verification study of the device[35] and a study in healthy adults within a laboratory setting.[36] Similarly, Pugh et al.[27] stated the device had been validated in other studies in healthy adults and was included in a large-scale US-based study of mobility in healthy adults (>20 years old).[37]

Outcome measures

Mobility was solely reported in terms of quantity, rather than quality. For example, the number of daily steps (step count) was most reported ($n = 12$) (Table 2). Quantity measures largely related to duration, such as volume/time of daily mobility ($n = 4$), or intensity, such as step count/rate ($n = 12$), time spent in sedentary, light, moderate, or vigorous activity ($n = 9$), activity count/vector magnitude units ($n = 4$), or energy expenditure ($n = 2$) of mobility (Table 2). Total wear time (or not worn time) was reported in three studies,[20,24,25] although most reported details on time for a valid day (Table 2).

No studies objectively examined mobility quality (i.e. gait) outcomes (e.g. gait speed, stride length, etc.). Studies that digitised a mobility capacity test (i.e. 6MWT) within a clinic/lab[22,28,30,32] or free-living[33] setting reported several additional quantity outcomes, such as the distance walked over 6-min or novel metrics that combined signals or outcomes. For example, multi-modal sensors were used to derive outcomes that combined mobility outcomes with physiological outcomes, such as combinations of step counts per minute and heart beats per minute.[33]

Interpretation of outcomes

Influence of PAH on mobility compared to healthy controls was consistent, with studies generally reporting reduced quantity of mobility (e.g. reduced number of steps,[23,25,26] energy expenditure,[26] and activity duration/intensity[26,27] in PAH. Additionally, mobility quantity outcomes were shown to correlate with clinical rating scales (e.g. 6-min walk distance (6MWD),[20–22,25–30,32–34,38,39] fatigue levels,[24] quality of life,[20,24,34,38] and self-reported or clinician rated physical activity[25,28,38]). However, mobility quantity outcomes (e.g. step count, time spent in activity intensities) were also found to poorly correlate with objectively measured physiological outcomes (i.e. haemodynamic function at rest, stroke volume, cardiac effort, etc.).[28,29,39,40] Alternatively, physiological outcomes recorded during mobility (e.g. fitness slope) correlated with clinical physiological outcomes (e.g. NT-pro BNP).[25,28,33]

Not all findings were consistent across studies in PAH. Two intervention studies reported different findings, with one reporting that there was an improvement in mobility quantity outcomes with intervention in PAH,[23] whereas the other reported small and variables changes in mobility quantity outcomes with intervention in PAH.[21] Another

Table 2. Mobility instrument, outcome measures and findings.

Author	Mobility Instrument	Mobility Outcome Measure(s)	Algorithm	Key Findings
Hemnes et al. (2021)	*Multi-modal wearable*–commercial *Device:* FitBit Charge HR–Triaxial accelerometer and PPG sensors *Placement and attachment:* Wrist-worn • On strap *Duration:* • Worn every-day for 12 weeks • Greater than 10 h per day • Had to detect at least 100 steps per day to be included	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Step count	FitBit proprietary algorithm	Change in step count was greater in the PAH group that received a text-message based step-count intervention
Howard et al. (2023)	*Unimodal wearable*–research-grade *Device:* ActiGraph GT9X Link–Triaxial accelerometer *Placement and attachment:* Wrist-worn (non-dominant) • On strap *Duration:* • 7 days, 24 h per day (within a 14-day period) • 60 s epochs	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Step count • Time spent in non-sedentary physical activity (NSPA) • Time spent in moderate to vigorous physical activity (MVPA) • Average daily activity time	ActiGraph proprietary algorithm	Small and variable changes in mobility that were not significantly different between PAH treatment groups • Step count correlated strongly with 6MWD at baseline, week 16 and week 24 • NSPA and MVPA only correlated moderately with 6MWD at week 16 *Non-significant findings:* • High compliance with wearable at home • Daily step count decreased by 0.3 steps in the intervention arm and by 201.9 steps in placebo arm • NSPA increased by 1.1 min in intervention arm and reduced by 16.7 min in placebo group • MVPA increased by 0.3 min in intervention arm and reduced by 2 min in placebo group • Large confidence intervals (variance) were observed for all mobility quantity metrics
Lachant et al. (2022a)	*Multi-modal wearable*–research-grade *Device:* BioStamp nPoint sensor (MC10)–Triaxial accelerometer (31.25 Hz) and ECG sensors	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Vector magnitude units • 6MWT distance	Custom Python algorithm	MC10 nPoint accelerometer and HR data provided a relatively easy, safe, and reproducible way to perform an indoor, remote 6MWT. • 6MWD from wearable

(continued)

Table 2. Continued.

Author	Mobility Instrument	Mobility Outcome Measure(s)	Algorithm	Key Findings
	Placement and attachment: Chest worn • Stuck to skin on patch *Duration:* • Worn during the 6MWT • At home for 2 weeks, with recorded remote 6MWT (2–4 times)	• 6MWT walking course distance *Other relevant outcomes:* • Peak HR • HR at end of 6MWT • HR expenditure • Cardiac effort (beats/m)		correlated strongly with clinical rated 6MWD • Remote 6MWD were shorter than clinic 6MWD • No significant difference between clinic or remote cardiac effort
Lachant et al. (2022b)	*Unimodal and Multi-modal wearables*–research-grade *Devices:* 1. ActiGraph GT9X Link–Triaxial accelerometer 2. MC10 Biostamp nPoint–Triaxial accelerometer and ECG sensors *Placement and attachment:* 1. Wrist (non-dominant) • On strap 2. On chest and thigh • Stuck to skin on patch *Duration:* • 5–10 days • 12 h/day	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Step count • Average daily activity time • Light activity time (GT9X only) • Moderate activity time (GT9X only) *Other relevant outcomes:* • Cardiac effort (beats/m) (MC10 only)	Proprietary algorithms	Different sensors in different locations yielded different mobility outcomes in PAH • Wrist-worn device overestimated step count compared to other locations, especially when in sedentary range • ActiGraph proprietary algorithm classed 6MWT as 'light activity' even in those performing distance over 500 m, patients reported as moderate or vigorous activity • Outcomes from both sensors correlated with clinical scale of daily activity • Activity time correlated better than step count with REVEAL 2.0, functional class, 6MWD and NT-pro-BNP • No mobility outcomes correlated with physiological outcomes (stroke volume, cardiac effort)
Mainguy et al. (2011)	*Multi-modal wearable* – research-grade *Device:* SenseWear Pro armband–biaxial accelerometer, galvanic skin response, heat flux, skin temperature and near-body ambient temperature *Placement and attachment:* Right upper arm on skin (triceps brachii) at midpoint between the acromion and the olecranon. • On strap *Duration:*	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Step count • Time spent in (minutes) of physical activities above a pre-determined intensity level (e.g. metabolic equivalents [METs]); >3 METs • Energy expenditure	SenseWear Pro software version 6.1.0.1523	Mobility quantity outcomes (step count, energy expenditure and duration of activity) were reduced in PAH compared to controls. • Step count correlated to 6MWD in PAH

(continued)

Table 2. Continued.

Author	Mobility Instrument	Mobility Outcome Measure(s)	Algorithm	Key Findings
	• 7 days • Worn entire day (except sleep and showering)			
Matura et al. (2016)	*Unimodal wearable*–research-grade *Device:* ActiGraph wGT3X-BT–Triaxial accelerometer (30 Hz) *Placement and attachment:* Hip worn (dominant) • On belt • *Duration:* • 7 days (entire day) • At least 2 h per day	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Activity count; a composite of vector magnitude (VM) unit–counts/min all axes and axis 1 • Average intensity (% time and min in sedentary, low, moderate, vigorous, or very vigorous) • Bouts of being active: defined as episodes of continuous activity with VM levels greater than 40 (90th percentile) • Total wear time	ActiGraph proprietary algorithm	People with PAH were mostly sedentary (85% of time), with 10% of time performing low-level activity • Mobility quantity outcomes correlated to self-reported fatigue levels and health related quality of life in women with PAH • Mobility quantity outcomes were consistent across weeks (week 1–week 3) in women with PAH
Minhas et al. (2022)	*Unimodal wearable*–research-grade *Devices:* 1. ActiGraph GT9X–Triaxial accelerometer (30 Hz) 2. ActiGraph GT3X–Triaxial accelerometer (30 Hz) *Placement and attachment:* 1. Hip worn (non-dominant) • On belt (removed for water activities) 2. Wrist worn (non-dominant) • On strap (removed for water activities) *Duration:* Both devices–7 days (24 h per day) • Minimum of 5 h per day processed at 60 s epochs	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Step count • Vector magnitude units • Time (minutes) spent in sedentary activity (1.0–1.5 METs), light activity (1.6–3.0 METs), moderate activity (3.1–6.0 METs), or vigorous activity (6.1 metabolic equivalent of tasks [METs]) • Total wear time	ActiLife Software: ActiGraph proprietary algorithm	Wrist worn device overestimated mobility quantity outcomes compared to the hip worn device • Vector magnitude units related to 6MWD and HRQoL • Three mobility quantity (activity) phenotypes were identified; low, medium and high • The most active phenotype (high) had greater 6MWD • Results were adjusted for confounders of age, sex, body mass index, wear time, and disease severity
Nakazato et al. (2021)	*Unimodal wearable*–research-grade *Device:* Power Walker, Yamax–Accelerometer *Placement and attachment:* Shirt pocket, clipped to pants,	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Step count • Activity time	Not Reported (NR)	Mobility monitoring with accelerometer in PAH is feasible, with no adverse events or notes of discomfort • Mobility quantity outcomes (step count and activity time) significantly correlated with 6MWD, sit to stand test,

(continued)

Table 2. Continued.

Author	Mobility Instrument	Mobility Outcome Measure(s)	Algorithm	Key Findings
	or strapped to their belt *Duration:* • Waking hours for 7 days			anxiety/depression, HRQoL, and self-reported physical capacity for daily activities
Pugh et al. (2012)	*Unimodal wearable*–research-grade *Device:* ActiGraph GT3X–Triaxial accelerometer *Placement and attachment:* Hip or wrist (dominant) • Belt or strap *Duration:* • 7 days, except sleep and showering/bathing • At least four valid days • Processed in 60 s epochs	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Activity count • Activity intensity levels (METs)	ActiLife software: ActiGraph proprietary algorithm	Mobility quantity outcomes were all significantly reduced in PAH compared to controls • Sedentary time was significantly greater in PAH than controls • MVPA was significantly reduced in PAH compared to controls • Activity counts correlated to 6MWD in the PAH group
Saxer et al. (2019)	*Multi-modal wearable*–Research-grade Device: SenseWear armband–Biaxial accelerometer, galvanic skin response, heat flux, skin temperature and near-body ambient temperature *Placement and attachment:* Upper arm (non-dominant) • On strap *Duration:* • 7 days • at least 3 days weekly	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Step count • Time spent in minutes of physical activities above a pre-determined intensity level (e.g. metabolic equivalents [METs]) • Energy expenditure	SenseWear Pro software	People with incident PAH were primarily sedentary as 65% had <5000 steps per day, with only 26% moderately active (5000–9999 steps/day) and 10% active (>10,000 steps/day) • Step count poorly correlated with haemodynamic at rest and during exercise in incident PAH • Step count correlated significantly with 6MWD in incident PAH
Sehgal et al. (2019)	*Multi-modal wearable*–Commercial *Device:* FitBit Charge HR *Placement and attachment:* Wrist worn • On strap *Duration:* • collected for 135.4 ± 47.3 days on average, but only processed first 2 weeks for correlations and looked at full time for change in outcomes over time	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Step count • Time spent in light, moderate and vigorous activity	FitBit proprietary algorithm	Mobility quantity outcomes of step count and time spent active descriptively reduced over time, and sedentary time increased in PAH • Only 20 out of 30 patients had adequate accelerometer data over the study duration to be included in analysis; compliance reduced with greater recording duration • All recorded changes in mobility outcomes correlated with 6MWD and HRQoL in PAH • Changes in mobility quantity outcomes did not correlate with physiological outcomes (echocardiographic measures or NT-pro BNP)

(continued)

Table 2. Continued.

Author	Mobility Instrument	Mobility Outcome Measure(s)	Algorithm	Key Findings
Sood et al. (2019)	*Multi-modal wearable–* ommercial *Device:* FitBit One *Placement and attachment:* Wrist worn • On strap *Duration:* • Recorded during 6MWT at baseline, week 16 and week 24 clinic visits	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Step count during 6MWT	FitBit proprietary algorithm	Clinical rated/measured 6MWD correlated with step count during 6MWT in each clinic visit in PAH
Stollfuss et al. (2021)	*Multi-modal wearable–* Commercial *Device:* Apple Smart Watch Series 2 with iPhone 6S; app xbird GmbH *Placement and attachment:* Wrist worn • On strap *Duration:* • Greater than 3 valid days within past 2 weeks of recording • 4–14-day period at baseline and observation periods • worn 30–113 days overall • worn 4.8 to 11.5 h per day	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • 6MWD • Distance walked • Step count *Other relevant outcomes:* • Number of standing up events • HR at rest and during 6MWT	Mobile application	Parallel monitoring of mobility quantity and heart rate in PAH is feasible • Clinically rated and digital 6MWD were moderately correlated in PAH • Mobility quantity outcomes (daily distance walked and step count) showed short-term increases with standard care medication • Digital 6MWD did not substantially change from baseline to study end, but traditional clinical rated 6MWD did change • Free-living mobility quantity outcomes (daily distance walked and step count) changed over the observation period in PAH
Wieteska-Miłek et al. (2022)	*Unimodal wearable–* Research-grade *Device:* Pedometer (Omron HJ-321-E) –Tri-axial Accelerometer *Placement and attachment:* On belt or clipped to pants, in a pocket of clothing, or in a bag *Duration:* • worn for 4 weeks	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Step count (stored on sensor for 7 days, but written down each day by participant over 4 weeks)	NR	People with PAH had low activity during the pandemic, which was not impacted by mental factors. • A threshold of 5000 steps per day was used to differentiate low and high activity groups in PAH • Mobility (steps per day) correlated with 6MWD in PAH, but not QoL, fear of COVID-19 or anxiety/ depression
Xu et al. (2022)	*Multi-modal wearable–* Commercial *Device:* FitBit Charge HR *Placement and attachment:*	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Step rate	FitBit proprietary algorithm	Mobility quantity outcomes can be used to sub-group patients with PAH and compare clinical parameters.

(continued)

Table 2. Continued.

Author	Mobility Instrument	Mobility Outcome Measure(s)	Algorithm	Key Findings
	Wrist worn *Duration:* • At least 4 weeks (ranged from 7 to 65 weeks) • Classed as worn if average HR was >20 BPM and less than or equal to age predicted maximal HR	• Ambulation (endurance, intensity, frequency)–step rate >60 steps per minute for at least 2 min • Free living 6MWD–6 min window with maximum accumulative number of steps during a given week Physical Health State–healthy individual predicted 6MWD divided by free-living 6MWD *Other relevant outcomes:* • HR at step count equal zero (i.e. no activity) • HR at step count greater than zero (i.e. activity) • Fitness–power output at an extrapolated heart rate of 170 bpm is then considered a proxy of VO_2max		• Use of minute-to-minute mobility quantity outcomes can provide useful metrics in PAH • Mobility quantity outcomes (ambulation and FL6MWD) correlated with clinical outcomes (6MWD) in PAH • Fitness slope correlated with physiological outcomes (NT-proBNP)
Zijlstra et al. (2017)	*Unimodal wearable*–Research-grade *Device:* ActiGraph wGT3X–Triaxial accelerometer (60 Hz) *Placement and attachment:* Right hip *Duration:* • 7 days, continuously • At least four valid days • At least 8 h wear time overall was valid • In infants that slept during the day at least 6 h wear time was valid • 15 s epochs • Taken off for water-related activities	*Mobility quality outcomes:* None *Mobility quantity outcomes:* • Vector magnitude units • Average intensity (time in min and hour for sedentary, light, moderate, vigorous, or MVPA) • Non-wear time–consecutive zeroes > 90 min, with a two spike tolerance	ActiLife software: ActiGraph proprietary algorithm	Mobility quantity (vector magnitude units, moderate, vigorous and MVPA) was significantly reduced in children with PAH: • Mobility outcomes correlated with disease severity markers (WHO FC and 6MWD) • Lower vector magnitude units and less time spent in MVPA were associated with poor outcome (hospitalisation) over 2.2 years

two studies showed the opposite relationships for correlations between mobility quantity outcomes and clinical rating scales or tests, such as health related quality of life or anxiety scales.[38,39]

Usability

Very few studies reported any usability evidence for the digital instruments used. One reported that there was high compliance with use of a wearable at home,[21] and another suggested that use of a wearable was easy, safe, and repeatable within clinic or remote settings in PAH.[30] Another study reported that patient feedback on the intensity of their activity did not align with the digital sensor reported intensity zones (e.g. patients reported being in moderate to vigorous activity levels, but the sensor reported that they were only performing light activity intensity).[28]

Discussion

This is the first study, to our knowledge, to review existing evidence around the digital measurement of mobility in PAH. The review has demonstrated that evidence for the measurement of mobility in PAH is currently limited and poorly reported or performed, with a lack of standardisation in approach. Methodological limitations of previous studies impact the ability to understand and implement previously used mobility measurement approaches in future PAH studies. Further work is warranted to establish the validity and reliability (and usability) of the mobility instrumentation, and the nature of the mobility impairment in PAH. Specific recommendations for future digital mobility measurement in PAH are provided in Table 3.

Study design

This review found that of the 16 studies selected for data extraction, the study designs were mostly observational with only four studies, including objective digital measurement of mobility in PAH on a clinical trial. This is perhaps reflective of the recent novel deployment of digital (wearable) sensors within clinical trials and growing evidence base within PAH. Progression toward capture of mobility outcomes in free-living ("real-world," remote) settings was made in most of the reviewed studies. Home-based testing of mobility in PAH may be beneficial to cater for patients who are limited geographically or practically from attending frequent clinic assessments at site. This may potentially reduce patient burden, save costs, and also achieve more ecologically valid assessment of mobility in PAH, which is not possible within infrequent 'snap-shot' mobility capacity or perception assessments within clinic or laboratory visits (typically used in clinical trials).

The sample sizes used ranged widely from 15 to 108 people with PAH, with larger samples sizes used within clinical trials compared to observational studies. The ideal sample size for studies depends on the intent of the research, with smaller samples possibly being enough for initial feasibility of instrument use within the clinical cohort, but not being enough to ensure that instruments and outcomes are accurate and generalisable in heterogeneous or rare clinical conditions like PAH. The larger sample sizes seen in the clinical trials are good indicators of scalability of using wearable digital technology in PAH for mobility measurement and may provide useful data for future power calculations for sample size justifications to ensure adequately powered trials (Table 3).

Table 3. Recommendations for future mobility measurement in PAH.

Recommendations for Future Studies
Study design and reporting: • Use an adequately justified and powered sample size to achieve study aims. • Comprehensive reporting of technical specifications of wearable sensors, including hardware and software type and version, sampling frequency, placement location, attachment type, and number of sensors • Measure and report mobility comprehensively, including both quantity (e.g. step count) and quality (e.g. gait speed) performance outcomes. **Technology specific:** • Conduct and report analytical and clinical validation (including reliability and usability testing) of mobility measurement methods in PAH (i.e. representative sample that may also include sub-group analysis) within relevant environment (e.g. laboratory, free-living, etc.) • Place sensor in region that can obtain comprehensive (quality and quantity) and accurate mobility outcomes (e.g. lumbar region). • Adequate sampling frequency (e.g. > 100 Hz) for comprehensive mobility measurement • Use an inertial measurement unit (combined accelerometer, gyroscope, and magnetometer) to provide comprehensive raw data on mobility/movement. • Record for an adequate duration for reliable data for mobility performance outcomes (quantity and quality) (i.e. 5–7 days continuously with minimum of 3 days) (>5 h per day) for valid analysis.

Instruments

There was poor reporting and a lack of standardisation across reviewed studies for the instrument type, sampling frequency, placement location, recording duration, environment of use, and algorithm used for mobility data processing. To ensure digital mobility outcomes are generalisable across studies and implementation is standardised for direct comparison across studies, future studies need to provide comprehensive reporting of technical details of the digital devices used (Table 3).

A single research-grade wearable device was used in most of the reviewed studies, with fewer studies using more than one device or commercial devices (e.g. FitBit or Apple Watch). The preference for research-grade devices to measure mobility in PAH likely stems from the need for accurate data to inform clinical decisions, as such devices are specifically designed for clinical assessment rather than wellness.[41] Most studies also deployed multi-modal (e.g. inertial sensor with a physiological sensor) rather than unimodal wearable devices (e.g. inertial sensor only), but there were insufficient details on the technical specifications set for the instruments provided in the reviewed studies. For example, the temporal resolution of the sensors was not provided in many of the studies, and it varied in those that did provide this specification. Additional factors may have also influenced the decision to use a commercial device, such as the desired duration

of recording, as instruments that were used for recording over long durations (>2 weeks) were primarily commercial. From the reviewed evidence, an IMU is recommended for digital mobility measurement in PAH to provide comprehensive assessment (Table 3).

There was a lack of consistency for days and hours that mobility was recorded in PAH. Across free-living studies, 7 days of mobility recording at home was the most consistent duration of recording, but duration ranged from 5 days to >1 year. However, despite set durations of recording, the studies analysed selective data from 'valid days' (i.e. a minimum number of required days and daily hours of recording) or cropped large datasets (i.e. data from months of recording) to more manageable and interpretable durations (i.e. instead of processing 65 weeks, researchers reduced this to 4 weeks). In line with the reviewed studies, evidence suggests that short durations of 2–3 days could provide enough data for accurate mobility outcome measurement in clinical populations,[42] but to ensure enough valid days are captured studies may record a few more days (i.e. 5–7 days) to account for potential missing data (i.e. non-wear time) (recommended in Table 3). Reviewed evidence suggests that mobility measurement over longer periods (i.e. months) may not be necessary to determine clinical deficits (or intervention improvements) in mobility in PAH, which reduces the burden on patients and the complexity of data collection, analysis, or interpretation.

Despite nine studies examining mobility outcomes from a wrist worn device, the instrument placement location was inconsistent across studies. Studies included a range of locations (e.g. wrist, hip, pocket, chest, upper arm, on belt, in a bag, etc.) between and within studies, and there was limited report of placement on dominant or non-dominant sides, with no consensus across studies that did report this. Consistent sensor placement location is vital to accuracy of the data collected, especially for clinical conditions where increased mobility variability may impact outcomes. This was directly shown in two of the reviewed studies that demonstrated that a wrist worn wearable device overestimated mobility outcomes compared to a hip worn device in people with PAH.[20,28] Similarly, two different sensors worn in different locations (i.e. chest or hip) on the same people provided different mobility outcomes in PAH,[28] in line with other research.[31,43] Large expert consensus and evidence from varied clinical cohorts have demonstrated that use of a single sensor for mobility measurement may be best located at the lumbar (over the ~L5 vertebrae) region,[7,44–48] as this has been shown to be acceptable and comfortable for patients,[49] as well as comparable in accuracy to two sensors on the feet/shank[50,51] and the central location (as opposed to the hip) allows for more accurate gait characteristics to be derived.[52] Therefore, future studies should consider sensor placement in terms of accuracy of mobility outcome of interest in PAH (i.e. if accuracy of mobility quantity and quality outcomes are desired from a single sensor, then lumbar placement could be deployed) (Table 3).

Sampling frequency (or sampling error) influences the accurate detection and derivation of mobility outcomes from wearable sensors.[53,54] Sampling frequencies in the reviewed studies were either not reported or were relatively low (~30–60 Hz), which may be why studies did not examine mobility quality (i.e. gait) outcomes. Low sampling rate (<60 Hz) reduces the accuracy of gait event detection.[55] Therefore, most IMU-based gait systems use higher sampling rates (>100 Hz),[56,57] which are particularly required for derivation of characteristics, such as gait variability.[58] Lower sampling frequency has the benefit of a longer duration recording as the battery does not drain as quickly and memory storage may last longer, but this comes at the cost of data quality that may limit outcomes that can be derived from the obtained signal.[57] Therefore, studies should consider whether they want to examine specific (e.g. only mobility quantity, counts, durations, intensity, etc.) or comprehensive (i.e. mobility quantity and quality) mobility outcomes in PAH, as this will inform the choice of sensor sampling frequency (Table 3).

Outcome measures

There are currently no "gold-standard" or comprehensive algorithms for mobility measurement from wearable devices, although there are currently large-scale consensus studies underway to potentially provide this (e.g. IMI Mobilise-D, IDEAFAST).[7,45,46,59] This likely explains why the reviewed studies primarily used proprietary ("Black-box") algorithms from device companies to derive mobility outcomes in PAH. Different underlying algorithms can lead to differences in mobility outcomes obtained from sensors,[28] which is why the field of mobility research is moving toward open-source algorithms that can be used consistently across instruments with minor adjustment for use in specific clinical cohorts (i.e. device agnostic algorithms).[7,60–62] Algorithms that have different thresholds could provide different outcomes as they may include or exclude relevant data. For example, within the reviewed studies, time epochs for data processing were not consistent (e.g. 15–60 s), even between studies that were using the same proprietary analysis software (and instrument). This may be why some mobility metrics (i.e. vector magnitude units) did not consistently relate to relevant clinical outcomes (i.e. 6MWD) in PAH.[20,25] Lack of consistency in the underlying algorithms used to derive outcomes across studies makes direct comparison difficult; therefore, establishing consistent approaches is necessary in future studies.

There are currently no universally accepted protocols or outcome measures of mobility in PAH. This was shown through both mobility capacity and performance protocols/outcomes being reported in the reviewed studies. Mobility performance outcomes, more specifically quantity

outcomes (i.e. counts, movement bout duration and intensity), were the most reported outcomes in PAH. Unsurprisingly, step count was the most reported individual outcome likely due to being a potential prognostic biomarker in PAH,[8] as well as other cardio-pulmonary conditions.[63,64] However, one reviewed study also demonstrated that other mobility quantity outcomes of vector magnitude units or time spent in moderate to vigorous intensity physical activity (MVPA) may also be prognostic biomarkers of outcome (hospitalisation within 2 years) in children with PAH,[25] but these outcomes were not consistently included across studies. Other studies showed that there may still be valuable information to be gleaned from mobility capacity assessment in PAH. For example, several of the reviewed studies examined mobility capacity testing (i.e. 6MWT) both within the clinic and remote settings with digital technology[22,28,30,32,33] and demonstrated differences between groups and correlations with clinical scales. The reviewed evidence suggests that objective digital mobility assessment in PAH is currently limited and needs standardization and establishment.

To date, there are no instruments on the market ("off-the-shelf") that provide fully validated free-living mobility quality (i.e. gait) outcomes, which is likely why the reviewed studies limited their focus to mobility quantity outcomes, such as step detection. Detection of steps is a core element of gait cycle measurement within free-living settings (i.e. initial and final contact of the foot to the ground),[48] which is a requirement for accurate algorithms that examine the quality of mobility (e.g. specific gait characteristics such as speed, stride length, etc.). However, despite the clinical use of gait speed as a measure of mobility quality in PAH and wider cardio-pulmonary cohorts,[65–70] this review has highlighted that objective digital measurement of mobility quality has yet to be performed in PAH. The measurement of mobility quality in PAH may be important in future studies. For example, gait speed has been noted to be a potential prognostic biomarker of mortality or hospitalisation in chronic cardiopulmonary conditions.[2,15,69,71–76] Additionally, mobility quantity outcomes (counts, durations, intensities) are global performance outcomes that are not specific to disease,[77] whereas mobility quality outcomes may reflect disease-specific impairment in musculoskeletal, cardio-pulmonary, or neural processes.[78] For example, the quality of mobility could be a useful indicator of underlying sarcopenia in PAH.[79] Future studies are needed to examine mobility quality in PAH to derive valid outcomes that are clinically meaningful.

Evidence for validity and reliability of mobility outcomes in PAH

There was generally a lack of specific validity and reliability evidence reported regarding the instrumentation, algorithms, and outcomes used within the reviewed studies, with only reference to generic sensor verification or healthy adult analytical validity studies. As mobility outcomes are investigated and refined in PAH clinical trials, there will be a need to establish fit-for-purpose mobility performance endpoints for trials in PAH populations (e.g. proof-of-concept endpoints, registrational endpoints). Endpoint variability, natural history, and reliability in specific PAH populations (e.g. defined by WHO Functional Class, risk score category, or background therapy) should be established. Analytical and clinical validation of mobility endpoints and assessment of meeting surrogate endpoint criteria should be performed in the future (Table 3).

Significant challenges face researchers that wish to validate free-living mobility outcomes for clinical application, as ground truth references are primarily laboratory-based and may not reflect the contextual information that influences real-world mobilisation.[80] Indeed, studies have shown that IMUs may provide accurate mobility data during continuous walking in controlled laboratory tasks, but can be less accurate during intermittent walks that may lead to inaccurate outcomes in free-living environments where both continuous and intermittent mobility bouts are common.[81–84] Validation is further complicated, as even healthy individual use of different sensors (even different versions of sensor hardware from the same company) may provide varied results in free-living,[85,86] which makes defining robust cut-offs or thresholds for mobility as a biomarker difficult.

Basic analytical validity evidence, such as comparison of outcome measures from wearables to an accepted reference standard (e.g. 2D video, 3D motion capture, etc.) within PAH, is required to ensure that outcomes are accurately being measured within the specific clinical population in line with industry accepted guidelines.[7,87,88] Mobility outcome validation procedures should be carried out within the clinical cohort of interest, as results in healthy or other clinical cohorts may not adequately capture the mobility patterns or deficits present in PAH,[7,44,87,88] which may require changes in underlying algorithm thresholds, settings or device placement to accurately capture (i.e. adjustment for slow walking speeds).[89] Indeed, one previous study has suggested that cut-off thresholds for some physical activity outcomes (i.e. activity intensity) that have largely been developed with healthy adults are not accurate for people with PAH (i.e. patients report working in moderate or vigorous activity when the sensor classes their activity as light).[28]

The reviewed studies did provide some initial clinical validity evidence on the use of wearables in PAH for mobility measurement. For example, mobility outcomes were reduced in PAH compared to controls, correlated with clinical tests/rating scales (e.g. 6MWD, WHO FC, healthrelated quality of life (HRQoL), self-reported physical activity, anxiety/depression, and fatigue levels), and some improved with interventions. However, findings were not consistent across studies, as two studies found the opposite

relationships for mobility outcomes (i.e. step count) and clinical scales (anxiety/depression, HRQoL),[38,39] and another study found small/variable change in mobility outcomes with intervention.[21] Additionally, reliability (repeatability) of mobility outcome measurement with a wearable in PAH was also reported in one study, finding consistent outcomes across separate weeks.[24] Initial usability of wearables for mobility outcomes measurement in PAH was also provided in several studies, with no adverse events or discomfort reported,[21,30] but there was generally a lack of thorough usability evidence provided in reviewed studies. Findings suggest that mobility outcomes have promise in being digital biomarkers in PAH, but further work is needed to robustly establish analytical and clinical validity, as well as usability, before deployment within clinical trials or healthcare settings as pivotal outcomes.

Literature review limitations

While there was a sufficient body of evidence to provide a structured review of digital mobility assessment in PAH, this review did not perform any risk of bias assessments or other subjective quality checks on the reviewed articles due to the limited number of studies and generally poor reporting within studies for this relatively rare clinical condition. The aim of this review was to understand the methodologies employed to measure mobility in PAH rather than specific impacts of PAH on mobility; therefore, we did not perform specific data analysis for effects (e.g. meta-analysis). We recommend that future systematic reviews and meta-analysis are conducted in future when there is sufficient evidence to support this endeavour.

Recommendations

Based on the specific findings of this review and discussed alignment with the wider field of digital mobility measurement in clinical populations we provide specific recommendations for future studies (or use in healthcare settings) in Table 3 to aid more accurate and standardisation of methods across PAH studies.

Conclusion

The impact of PAH on specific mobility outcomes remains unclear, but research is emerging in this area that suggests mobility impairment or reduction. Precise quantitative measures of mobility are essential for characterising mobility impairments involved in PAH. Mobility quantity measures were the most reported outcomes, particularly step count, but despite this, no single or combination of mobility outcomes has been established as the most informative indictor of pathogenic (or interventional) responses in PAH. Similarly, multi-modal wearable devices have been most used, but the validity and reliability of digital mobility instruments and the outcomes (or underlying algorithms) they can provide during free-living monitoring in PAH are yet to be fully determined. Further research is required to establish standardised methods for mobility assessment in PAH, which will help to determine mobility outcomes (e.g. quality and quantity of movement) that are most accurate and clinically meaningful.

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