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Physical Activity, Sleep, and Quality of Life in Pulmonary Arterial Hypertension: Novel Insights From Wearable Devices

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ABSTRACT

Reduced functional capacity and poor sleep quality are common in pulmonary arterial hypertension (PAH). Wearable devices are an emerging, user-friendly tool to capture activity and sleep information. We aimed to determine whether Fitbit-derived activity and sleep trends provide clinically meaningful information in patients with PAH. Our prospective observational study recruited patients with PAH from across the United States using remote enrollment strategies and in-person efforts. Participants wore a Fitbit device for 12 weeks at baseline and a subgroup with 1-year follow-up. A matched control cohort was generated from the *All of Us* Research Program and we evaluated changes in patients with PAH compared to matched controls. Among 110 patients with baseline monitoring, average daily steps correlated with 6MWD ($r = 0.61$, $p < 0.001$) and percent rapid eye movement (REM) sleep ($r = 0.28$, $p = 0.008$). In 44 PAH participants who completed baseline and 1-year monitoring, there was a group-time interaction for percent light sleep ($p = 0.024$) and percent REM sleep ($p = 0.034$), which demonstrated that sleep quality worsened in patients with PAH over 1 year compared to matched controls. Average daily steps decreased in patients with PAH from 5200 [IQR 3212–7458] at baseline to 4651 [IQR 2912–6827] at 1 year ($p = 0.008$). In conclusion, our study demonstrated the potential clinical value of wearable devices by showing that activity and sleep quality are reduced in PAH compared to matched controls and these measures decline over time. Future studies should investigate if monitoring these health behaviors detects early functional decline and whether targeted interventions may improve outcomes.

Pulmonary arterial hypertension (PAH) is characterized clinically by dyspnea, exercise intolerance, and reduced quality of life (QOL) [1, 2]. The 6 min walk test (6MWT) is the most common metric for assessing functional capacity but it has important limitations as a prognostic tool and trial endpoint [3]. Wearable devices, such as activity trackers and smartwatches, are popular among patients and report real-world physical activity and sleep behaviors. Unlike the 6MWT, daily activity integrates physical, environmental, and behavioral inputs of capacity. Remote activity monitoring captures activity over weeks to months, which mitigates the temporary influences of clinic-based assessments. Changes in wearables-derived activity levels correlate with changes in 6-min walk distance (6MWD) and health-related QOL in short-term studies of patients with PAH [4, 5].

Poor sleep quality is common and associated with mood disorders and impaired QOL in patients with pulmonary hypertension [6, 7], though prior studies have largely assessed sleep quality through self-reported qualitative surveys. Studies with objective, longitudinal sleep metrics are lacking in PAH. Wearable devices represent an emerging low-cost, user-friendly tool to assess sleep duration and quality by capturing the amount of time that individuals spend in different sleep stages [8, 9].

We aimed to study the objective, free-living data from commercially available wearables to understand the relationship between sleep, physical activity, and QOL in patients with PAH over the course of 1 year. Our study is the first in the PAH population to describe longitudinal trajectories of sleep quality with sleep-stage data, provide novel insights regarding longitudinal changes in physical activity, and directly correlate sleep and activity in PAH and matched controls.

1 | Methods

1.1 | Study Design

This is a prospective observational study of patients with PAH between October 2019 and December 2023. This study was approved by our Institutional Review Board. Matched controls were identified from the All of Us Research Program (AoURP) [10]. Only authors who completed the AoURP Responsible Conduct of Research Training handled the data on the secured cloud platform—Researcher Workbench, according to AoURP policy.

1.2 | Study Population

The study enrolled adults in the United States with PAH confirmed by hemodynamics and expert clinical diagnosis. We utilized several recruitment sources. Forty-three participants were recruited from the NHLBI-funded Longitudinal Pulmonary Vascular Disease Phenomics Program (L-PVDOMICS), a substudy of the Pulmonary Vascular Disease Phenomics Program [11]. Twenty-two participants from a previously published trial [12] with a similar 12 weeks of observational monitoring were included in the baseline correlation analyses, but this trial design did not have follow-up. Additional enrollment sources included patients treated in our clinic and patients who attended the Pulmonary Hypertension Association Research Room, the latter of which captures patients throughout the United States. Medical records for these participants were reviewed by study investigators to confirm PAH diagnosis. Our ability to enroll participants from several sources led to a diverse, "multicenter" cohort of patients with PAH. Participants were excluded if they were hospitalized within the last 3 months, pregnant, or had orthopedic limitations that precluded 6MWD testing.

The matched control cohort was derived from AoURP participants in the "Bring Your Own Device" Program who linked their personally owned Fitbit devices with their electronic health record. Mahalanobis distance matching created the controls in a 3:1 fashion based on age, sex, body mass index (BMI), and Fitbit monitoring dates. Controls were matched with the 44 patients with PAH who completed both the baseline and 1-year follow-up. The study used the Controlled Tier Data Set (version 7). The AoURP and Fitbit data have been described previously [13].

1.3 | Baseline Assessment

The baseline assessment included 12 weeks of activity and sleep monitoring with a Fitbit device, 6MWD, World Health Organization (WHO) functional class assessment, PAH medications, and QOL surveys. Participants wore the Fitbit device 24 h/day for 12 weeks except for charging the device or while bathing. 6MWD and functional class assessment were completed as part of the L-PVDOMICS enrollment protocol. For participants enrolled outside of L-PVDOMICS, the 6MWD and functional class were included if they were completed during a clinic visit within 6 months of the baseline activity monitoring. In a minority of patients enrolled outside L-PVDOMICS, the WHO Functional Class was not stated in the available medical records, so these individuals were characterized as unspecified. QOL was assessed through the Minnesota Living with Heart Failure (MLHF) questionnaire [14, 15]. The MLHF questionnaire is a 21-item survey scored on a Likert scale (0–5), which calculates a total score (21 questions, range 0–105), a physical score (8 questions, range 0–40), and an emotional score (5 questions, range 0–25). Higher scores indicate greater impairment.

1.4 | Follow-Up Assessment

At 1-year follow-up, participants wore the Fitbit device for an additional 12 weeks and completed online surveys to capture MLHF scores and PAH medications. 6MWD and functional class were not reassessed.

1.5 | Devices and Activity/Sleep Data Capture

Fitbit devices collected activity and sleep data in all participants. Multiple models were used, including Charge 3, Charge 5, and Versa. The same Fitbit model was used for the entire duration of a 12-week monitoring period. The Fitbit device was mailed to

the participant and a coordinator assisted the participant with set-up over the phone.

The Fitbit device collects several activity metrics, including steps per day and total minutes of activity intensities per day (sedentary, lightly active, fairly active, and very active), which are based on calculated metabolic equivalents through proprietary algorithms. Fairly active minutes are widely considered to reflect moderate intensity in the wearables community. A valid day of activity monitoring required at least 100 steps and 10 h of wear time. Fitbit activity metrics were measured daily for ~12 weeks and averaged over the entire monitoring period. Sleep variables included total minutes asleep and percent of time in each sleep stage, which was calculated as minutes in each stage divided by total sleep duration. Fitbit devices use accelerometers and photoplethysmography to capture the sleep variables via proprietary algorithms. Participants with fewer than 15 total days of sleep tracking in a monitoring period were removed from analyses.

Activity and sleep data were collected in real time. Automated text message reminders were sent to participants if there was no data transmitted to the data collection program (Fitabase) after 24 h. Coordinators contacted participants via telephone if more than 72 h elapsed since their last data transmission. Participants were unblinded to their activity and sleep levels.

1.6 | Outcome Measures

We investigated associations between Fitbit-derived activity and sleep measures, 6MWD, and QOL and studied how these metrics changed over 1 year. We directly compared activity and sleep levels in patients with PAH to matched controls at baseline and 1-year follow-up. We combined fairly active and very active minutes to capture moderate-to-vigorous physical activity (MVPA).

1.7 | Statistical Analyses

Continuous variables are expressed as median with interquartile range (IQR) and categorical variables as counts with proportions. The Wilcoxon signed-rank test compared continuous variables at baseline and 1-year follow-up in the PAH cohort. The Wilcoxon rank-sum test compared continuous variables between PAH patients and matched controls. X^2 tests compared categorical variables. To evaluate for any potential Hawthorne effect, a generalized least squares regression model was fit to the average activity and sleep metrics with month of monitoring serving as the predictor variable. Associations between activity and sleep were analyzed with Spearman's rank correlation test. Generalized least squares models, adjusted for age, sex, and BMI, with linear interaction terms evaluated changes in sleep variables from baseline to Year 1 in patients with PAH compared to matched controls. All analyses were conducted in the R programming language (version 4.3). Matched case control analyses specifically utilized the Researcher Workbench within the same R environment. Generalized least squares models were fit using the rms R package. Mahalanobis distance matching was performed in the MatchIt R package.

2 | Results

2.1 | Patient Characteristics

A total of 110 participants completed the 12-week baseline monitoring period. The cohort was median age 52.7 years (IQR: 40.9–60.5), female predominant (84% female), and majority WHO Functional Class II. The most common PAH etiology was idiopathic (60%) (Table 1).

2.2 | Activity and Sleep Levels

In the PAH cohort who completed the 12-week baseline monitoring period ($n = 110$), the average daily steps were 5120 (IQR 3306–6687). The average sedentary minutes per day were 823 (IQR 724–958), lightly active minutes 194 (152–247), and MVPA minutes 7.8 (2.4–16.9). Average total minutes asleep per day were 391 (IQR 340–432). The percentage of time spent in light sleep was 62.8% (59.0–66.2), deep sleep 15.1% (12.4–17.1), and REM sleep 18.0% (15.4–21.5). There was no Hawthorne effect observed in activity or sleep metrics as month of monitoring was not significant for any measure.

2.3 | Baseline Activity and 6MWD Correlations

6MWD correlated with average daily steps ($r = 0.61$, $p < 0.001$, Figure 1), daily sedentary minutes ($r = -0.25$, $p = 0.017$), daily lightly active minutes ($r = 0.35$, $p < 0.001$), and daily MVPA minutes ($r = 0.48$, $p < 0.001$).

2.4 | Baseline Activity and Sleep Correlations

We observed a positive correlation between the percent of time in restorative sleep stages (deep and REM sleep) and average daily steps, 6MWD, and lightly active minutes. There was an inverse relationship between high-quality sleep stages and sedentary minutes (Table 1 and Figure 1). MVPA minutes were associated with % REM sleep ($r = 0.24$, $p = 0.034$), but not % deep sleep ($r = 0.20$, $p = 0.080$).

2.5 | Baseline Activity and QOL Correlations

Average daily steps were negatively correlated with MLHF total score ($r = -0.36$, $p = 0.014$), MLHF physical score ($r = -0.40$, $p = 0.005$), and MLHF emotional score ($r = -0.33$, $p = 0.024$) (Table 2). Since higher MLHF scores indicate greater impairment, this shows that steps are lower in patients with worse QOL. Sedentary and lightly active minutes were not correlated with any MLHF scores. MVPA minutes were associated with MLHF total score ($r = -0.43$, $p = 0.003$) and physical score ($r = -0.46$, $p = 0.001$), but not MLHF emotional score ($r = -0.25$, $p = 0.10$).

2.6 | Baseline Sleep and QOL Correlations

There were no significant associations between sleep metrics and MLHF scores (Table 2).

TABLE 1 | Correlations between sleep and activity measures in patients with PAH ($n = 110$).

Baseline characteristics		
Age (years)	52.7 (40.9–60.5)	
Sex, % female	84%	
Body mass index (kg/m^2)	29.8 (24.3–34.8)	
Geographic region, *n* (%)		
Midwest	7 (6%)	
Northeast	18 (17%)	
South	72 (66%)	
West	12 (11%)	
PAH etiology, *n* (%)		
Idiopathic	66 (60%)	
Connective tissue disease	17 (15%)	
Familial	9 (8%)	
Congenital heart disease	7 (6%)	
Other	11 (10%)	
WHO Functional Class, *n* (%)		
Class I	21 (19%)	
Class II	58 (53%)	
Class III	18 (16%)	
Unspecified	13 (12%)	
	Spearman's rank correlation (*r*)	***p***
Correlation of total minutes asleep with:		
6 min walk distance	−0.02	0.885
Daily steps	−0.17	0.070
Sedentary minutes	−0.48	< 0.001
Lightly active minutes	−0.11	0.273
MVPA minutes	0.03	0.785
Correlation of % light sleep with:		
6 min walk distance	−0.24	0.048
Daily steps	−0.22	0.040
Sedentary minutes	0.15	0.152
Lightly active minutes	−0.34	0.001
MVPA minutes	−0.07	0.524
Correlation of % deep sleep with:		
6 min walk distance	0.37	0.002
Daily steps	0.32	0.003
Sedentary minutes	−0.32	0.003
Lightly active minutes	0.36	< 0.001
MVPA minutes	0.20	0.080
Correlation of % REM sleep with:		
6 min walk distance	0.30	0.010
Daily steps	0.28	0.008
Sedentary minutes	−0.24	0.026

(Continues)

TABLE 1 | (Continued)

	Spearman's rank correlation (*r*)	*p*
Lightly active minutes	0.31	0.004
MVPA minutes	0.24	0.034

Abbreviations: MVPA = moderate-to-vigorous physical activity, PAH = pulmonary arterial hypertension, WHO = World Health Organization.

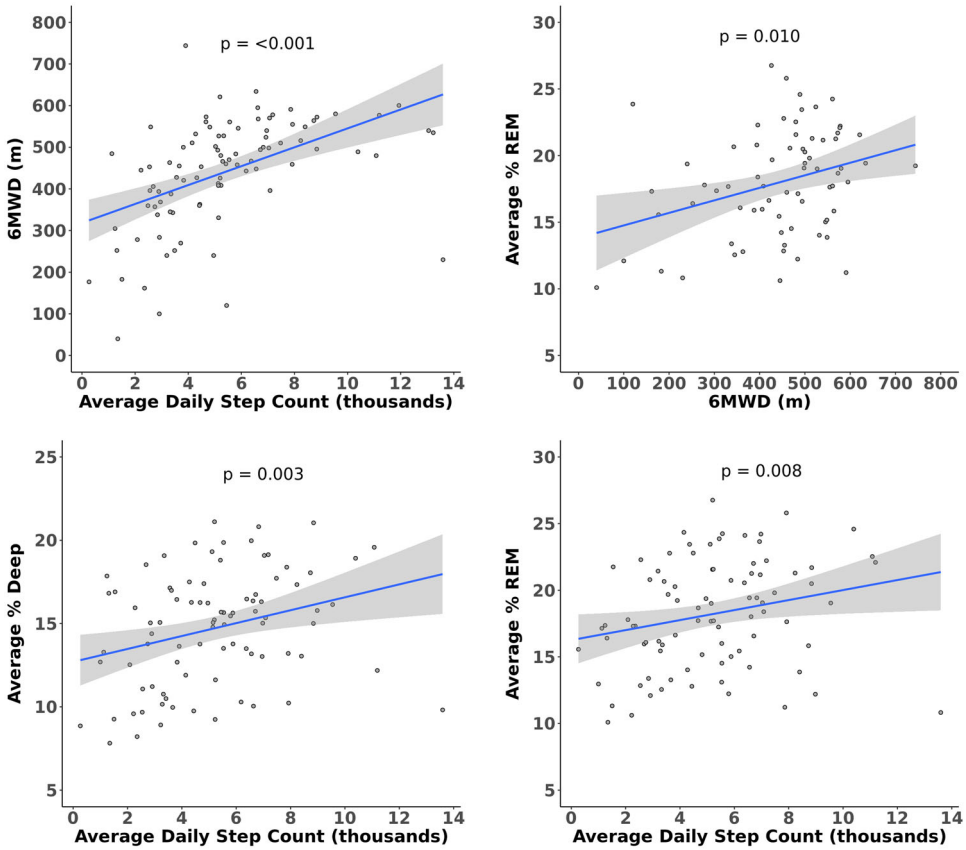

FIGURE 1 | Correlation plots for baseline sleep and activity measures. In the cohort of patients with PAH who completed a 12-week baseline monitoring period ($n = 110$), correlation plots demonstrated significant associations between several sleep and activity metrics.

2.7 | Longitudinal Trends in PAH Patients

A total of 44 participants completed a 12-week monitoring period at baseline and 1-year follow-up. The median time between the start of the baseline and the follow-up monitoring period was 1.03 years (IQR 0.96–1.34 years). The cohort was similar with a median age of 55.2 years old (43.3–62.1), 80% female, 59% WHO Functional Class II, and 59% idiopathic PAH (Table 3).

Daily steps decreased from 5200 [IQR 3212–7458] at baseline to 4651 [IQR 2912–6827] at 1 year, ($p = 0.008$), but the active minutes did not change significantly (Table 3). The percent of time in light sleep increased from 63.0% [59.1%–68.0%] at baseline to 65.0% [61.3–69.3%] at 1 year, ($p = 0.004$), and the percent of time in REM sleep decreased from 17.3% [14.1–21.0] to 16.0% [13.4–20.4] ($p = 0.001$) (Table 3 and Figure 2). MLHF scores did not change significantly. The number of participants on prostanoids increased from 16% at baseline to 32% at 1-year follow-up, ($p = 0.046$). The average number of PAH medications at baseline was 1.48 ± 1.32 and 1.86 ± 1.27 at 1 year ($p = 0.095$). Subgroup analyses were performed for patients who were started on prostanoids between baseline and 1-year follow-up, but there were no significant differences in their activity or sleep patterns.

2.8 | Longitudinal Activity, Sleep, and QOL Correlations

In the patients with PAH who completed baseline and 1-year follow-up, we analyzed correlations between changes in all activity, sleep, and QOL metrics. Most of the correlations were non-significant. The only significant correlations were Δ sedentary minutes and Δ total minutes asleep ($r = -0.47$, $p = 0.002$), and Δ daily steps and Δ % REM sleep ($r = -0.33$, $p = 0.035$).

2.9 | Activity Levels in PAH and Matched Controls

Average daily steps and active minutes were significantly lower in patients with PAH than matched controls at baseline and 1-year follow-up. Average sedentary minutes were significantly

TABLE 2 | Quality of life correlations in patients with PAH ($n = 110$).

	Spearman's rank correlation (r)	p
Quality of life and activity metrics:		
Correlation of MLHF total score with:[1]		
Daily steps	−0.36	0.014
Sedentary minutes	0.19	0.215
Lightly active minutes	−0.13	0.390
MVPA minutes	−0.43	0.003
Correlation of MLHF physical score with:		
Daily steps	−0.40	0.005
Sedentary minutes	0.26	0.083
Lightly active minutes	−0.15	0.311
MVPA minutes	−0.46	0.001
Correlation of MLHF emotional score with:		
Daily steps	−0.33	0.024
Sedentary minutes	0.12	0.414
Lightly active minutes	−0.20	0.182
MVPA minutes	−0.25	0.099
Quality of life and sleep metrics:		
Correlation of MLHF total score with:		
Total minutes asleep	0.10	0.522
% light sleep	0.13	0.389
% deep sleep	−0.07	0.662
% REM sleep	−0.03	0.848
Correlation of MLHF physical score with:		
Total minutes asleep	0.06	0.691
% light sleep	0.11	0.457
% deep sleep	−0.13	0.383
% REM sleep	−0.06	0.676
Correlation of MLHF emotional score with:		
Total minutes asleep	0.13	0.394
% light sleep	0.17	0.253
% deep sleep	−0.09	0.548
% REM sleep	−0.05	0.755

Abbreviations: MLHF = Minnesota Living with Heart Failure Questionnaire, MVPA = moderate-to-vigorous physical activity, PAH = pulmonary arterial hypertension, REM = rapid eye movement.
[1]Higher MLHF scores indicate greater impairment.

higher in patients with PAH compared to matched controls at both time points (Table 4).

2.10 | Sleep Patterns in PAH and Matched Controls

Patients with PAH had shorter sleep duration at 1 year compared to controls (385 min (322–409) vs. 397 min (370–425), $p = 0.039$; Table 4). In adjusted models, patients with PAH had, on average, 36 (14–57) fewer minutes of sleep at 1 year compared to controls ($p = 0.001$; Figure 3). Percent light sleep was similar in patients with PAH and matched controls at baseline and 1-year follow-up. In adjusted models, there was a significant increase in % light sleep in patients with PAH from baseline to Year 1 ($p = 0.004$), but no significant change in controls ($p = 0.534$). We also observed a group–time interaction ($p = 0.024$), which shows that % light sleep increased significantly over the course of 1 year in patients with PAH compared to controls. Average % REM sleep was significantly lower in patients with PAH compared to controls at baseline and Year 1. The adjusted models showed that % REM decreased in patients with PAH from baseline to Year 1 ($p = 0.002$), it did not decline significantly in controls, and there was a significant group–time interaction confirming that relationship over 1 year ($p = 0.034$).

3 | Discussion

In this study, we demonstrate that daily activity and sleep quality are correlated, activity levels and sleep quality are significantly worse in patients with PAH compared to matched controls, and these measures decline over 1 year in patients with PAH. These reflect important health behaviors that are not captured in routine clinic-based measurements. Our study provides novel insights into sleep quality as it is the first to report longitudinal sleep-stage patterns in PAH and the first to investigate sleep and activity in the context of rigorously matched controls.

Functional capacity is a strong prognostic marker in PAH [16, 17]. 6MWD is the most common measure of functional capacity but it has important limitations as a clinical surveillance measure [3] with a narrow range of values, ceiling and floor effects [18, 19], and is vulnerable to transient influences at the moment of testing. Free-living activity monitoring with commercial wearables may overcome these limitations. These devices are popular with consumers and step counts are easier to understand than actigraphy vector counts. Activity levels from commercial wearables can provide valuable insight into the risk of chronic disease [13], measure the response to a therapeutic intervention in PAH [12], serve as an objective longitudinal measure in PAH [4, 5], and have prognostic significance in PAH [20]. We found that all Fitbit-derived activity metrics correlated with the 6MWD, but the R^2 was between 0.1 and 0.35. This shows that, at best, the 6MWD accounts for a third of the variability in daily activity. 6MWD and wearable devices provide different, complementary information as real-world activity monitoring incorporates behavioral choices as well as social and environmental influences. Daily steps in PAH appear to represent a modifiable health behavior as a text-based mobile health intervention increased daily steps by 1400 and these participants reported improved QOL without any difference in 6MWD [12]. This supports the notion that steps are a clinically meaningful measure that captures complementary information to clinic-based measurements, but future studies are needed to investigate whether declining steps precede clinically significant outcomes.

To our knowledge, this is the first study to evaluate long-term sleep patterns in patients with PAH using wearable devices that capture sleep stages. Prior PAH studies were limited by self-

TABLE 3 | Changes in activity, sleep, quality of life, and medications in patients with PAH.

	Baseline ($n = 44$)	Year 1 ($n = 44$)	p
Baseline characteristics			
Age (years)	55.2 (43.3–62.1)		
Sex, % female	80%		
Body mass index (kg/m^2)	29.7 (24.7–33.3)		
PAH etiology, *n* (%)			
Idiopathic	26 (59%)		
Connective tissue disease	6 (14%)		
Congenital heart disease	3 (7%)		
Familial	3 (7%)		
Other	6 (14%)		
WHO Functional Class, *n* (%)			
Class I	7 (16%)		
Class II	26 (59%)		
Class III	6 (14%)		
Unspecified	5 (11%)		
6MWD (m)	459 (343–546)		
Fitbit activity measures (daily)			
Steps	5200 (3212–7458)	4651 (2912–6827)	0.008
Sedentary minutes	800 (748–919)	828 (748–953)	0.401
Lightly active minutes	191.7 (163.5–236)	189 (144.2–236.1)	0.986
MVPA minutes	8.9 (3.3–29.1)	12.5 (3.9–21.0)	0.376
Fitbit sleep measures (daily)			
Total minutes asleep	386 (341–433)	385 (322–409)	0.114
% light sleep	63.0 (59.1–68.0)	65.0 (61.3–69.3)	0.004
% deep sleep	13.6 (11.3–16.5)	14.4 (11.2–15.7)	0.117
% REM sleep	17.3 (14.1–21.0)	16.0 (13.4–20.4)	0.001
Quality of life measures[a]			
MLHF total score	11.0 (1.5–55.5)	24.0 (13.0–45.0)	0.244
MLHF physical	6.0 (0–26.0)	10.0 (5.0–22.0)	0.528
MLHF emotional	2.0 (0–11.0)	5.0 (1.0–10.0)	0.212
PAH medications, *n* (%)			
Prostanoids	7 (16%)	14 (32%)	0.046
PDE inhibitor	22 (50%)	25 (57%)	0.546
ERA	26 (59%)	30 (68%)	0.343
CCB	9 (20%)	11 (25%)	0.617
Total no. of PAH medications	1.48 ± 1.32	1.86 ± 1.27	0.095

Abbreviations: CCB = calcium channel blocker, ERA = endothelin receptor antagonist; MLHF = Minnesota Living with Heart Failure Questionnaire, MVPA = moderate-to-vigorous physical activity, PAH = pulmonary arterial hypertension, PDE = phosphodiesterase, REM = rapid eye movement, WHO = World Health Organization, 6MWD = 6-min walk distance.
[a]Higher MLHF scores indicate greater impairment.

report qualitative surveys or single-night sleep studies [6, 7, 21]. Fitbits measure real-world sleep patterns with good performance compared to polysomnograms or actigraphy in the general population [8, 22]. We observed that patients with PAH had reduced sleep quality compared to matched controls and the quality of sleep declined over time. Patients with PAH spent significantly less time in REM sleep than matched controls (i.e., 16.0% REM sleep per night vs. 21.3%, $p < 0.001$.) and the % REM sleep decreased by 1.3% in patients with PAH over 1 year. In the general population, decreased REM sleep has been associated with a higher risk of all-cause and cardiovascular mortality [23] and more REM sleep may be protective against incident heart

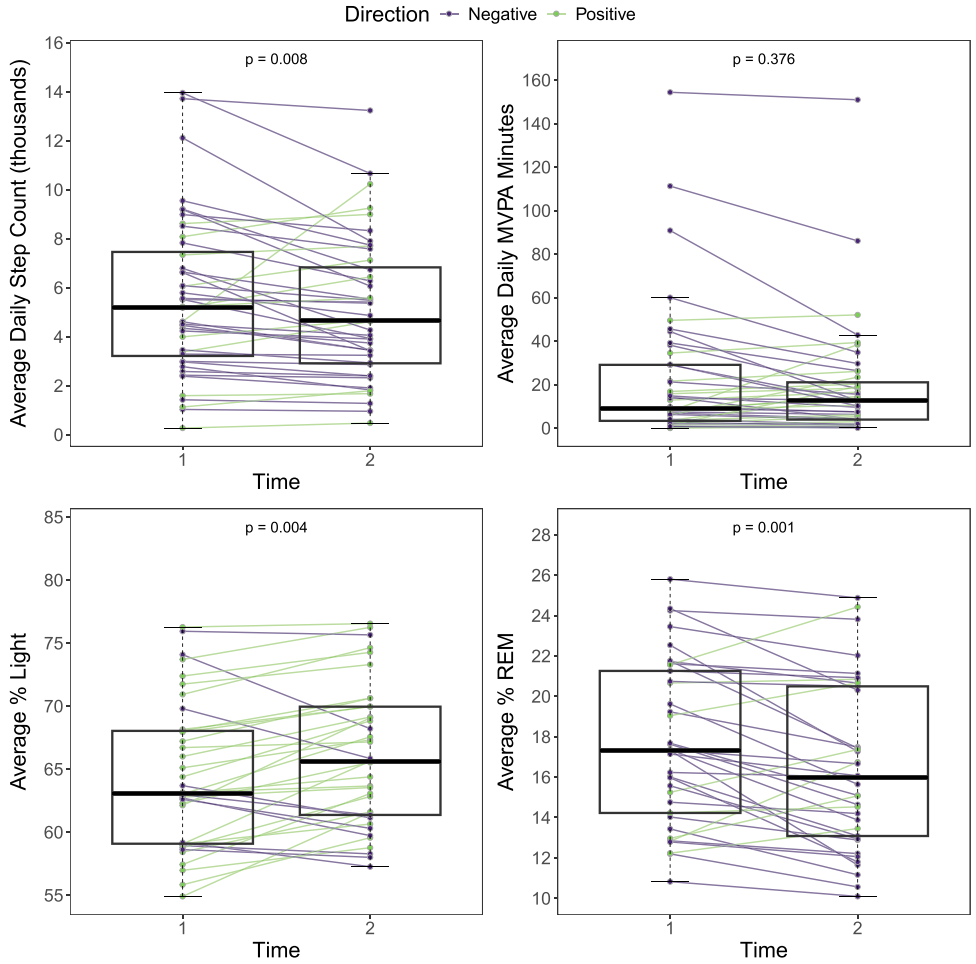

FIGURE 2 | Longitudinal activity and sleep metrics. In the PAH cohort with baseline and 1-year follow-up ($n = 44$), spaghetti plots demonstrate an overall decrease in average daily steps, an increase in the percent light sleep per night, and a decrease in the percent REM sleep per night. There is no significant change in the amount of moderate-to-vigorous physical activity (MVPA) per day. Green lines denote individuals with an increased value from baseline to Year 1 while purple lines denote individuals with a decreased value from baseline to Year 1.

failure [24]. Recently published work showed that a 1% difference in REM sleep, as measured by Fitbit devices, was associated with an increased incidence of several chronic conditions [25].

The main strength of our study is the use of objective "real-world" data from wearable devices to describe health behaviors over time in patients with PAH compared to matched controls. Our study's long-term and longitudinal monitoring overcomes some inherent limitations of previous studies where brief monitoring (i.e., 3–7 days) is associated with outcomes many years later. While activity and sleep have historically been examined separately, there is emerging evidence that these behaviors are interrelated and exist along one movement continuum [26, 27]. This is the first study to describe the interrelated nature of sleep and activity behaviors in PAH. The association between activity, sedentary behavior, and sleep suggests that interventions to improve one health behavior may positively impact the other health behaviors as well. Future studies are warranted to determine whether real-time, continuous monitoring of activity and sleep can detect a "digital prodrome" of functional decline that could improve outcomes by triggering medical contact. This is conceptually similar to CardioMEMS devices that detect and act on increases in filling pressure [28–30].

Our study should be viewed in the context of several limitations. We used commercial Fitbit devices which have reduced fidelity compared with research-grade actigraphy and have been studied less than actigraphy; however, the commercial wearables increase generalizability as patients use these devices in their daily lives [31, 32]. Our PAH cohort was quite functional at baseline as 70% were functional Classes I–II and they were only on an average of 1.5 PAH medications. Nevertheless, we demonstrated that step count and sleep quality decline over 1 year despite enrolling patients with more mild disease. Additionally, only 40% of participants completed the 1-year follow-up, which occurred for multiple reasons. Twenty-two participants were included in the baseline analyses from a trial that by design did not have a follow-up period. Additionally, the study is ongoing so many participants were recently enrolled and may complete their follow-up later. Most of the correlations for longitudinal changes were nonsignificant, but our study is likely underpowered and at risk of overinterpreting this data. We consider these results to be hypothesis-generating and worthy of investigation in future studies. The subgroup analyses

TABLE 4 | Activity levels and sleep metrics in patients with PAH and matched controls.

	PAH cohort ($n = 44$)	Matched controls ($n = 132$)	p
Baseline characteristics			
Age (years)	55.2 (43.3–62.1)	53.8 (41.4–61.9)	0.502
Sex, % female	80%	80%	1
Body mass index (kg/m^2)	29.7 (24.7–33.3)	29.3 (24.2–33.8)	1
Activity measurements			
Daily steps: baseline	5200 (3212–7458)	7369 (5225–10089)	< 0.001
Daily steps: Year 1	4651 (2912–6827)	7044 (5010–9834)	< 0.001
Sedentary mins: baseline	800 (748–919)	674 (623–745)	< 0.001
Sedentary mins: Year 1	828 (748–953)	690 (630–734)	< 0.001
Lightly active mins: baseline	191.7 (163.5–236.0)	219.6 (182.9–268.4)	0.009
Lightly active mins: Year 1	189.0 (144.2–236.1)	221.1 (186.8–255.0)	0.004
MVPA mins: baseline	8.9 (3.3–29.1)	31.7 (14.6–53.4)	< 0.001
MVPA mins: Year 1	12.5 (3.9–21.0)	25.9 (14.1–51.7)	< 0.001
Sleep measurements			
Mins asleep: baseline	386 (341–433)	395 (367–424)	0.518
Mins asleep: Year 1	385 (322–409)	397 (370–425)	0.039
% light sleep: baseline	63.0 (59.1–68.0)	63.3 (59.8–68.1)	0.921
% light sleep: Year 1	65.0 (61.3–69.3)	63.7 (60.2–67.9)	0.194
% deep sleep: baseline	13.6 (11.3–16.5)	15.2 (12.8–17.5)	0.095
% deep sleep: Year 1	14.4 (11.2–15.7)	15.2 (13.1–17.3)	0.02
% REM sleep: baseline	17.3 (14.1–21.0)	21.6 (18.7–23.8)	< 0.001
% REM sleep: Year 1	16.0 (13.4–20.4)	21.3 (17.9–23.8)	< 0.001

Abbreviations: mins = minutes, MVPA = moderate-to-vigorous physical activity, REM = rapid eye movement.

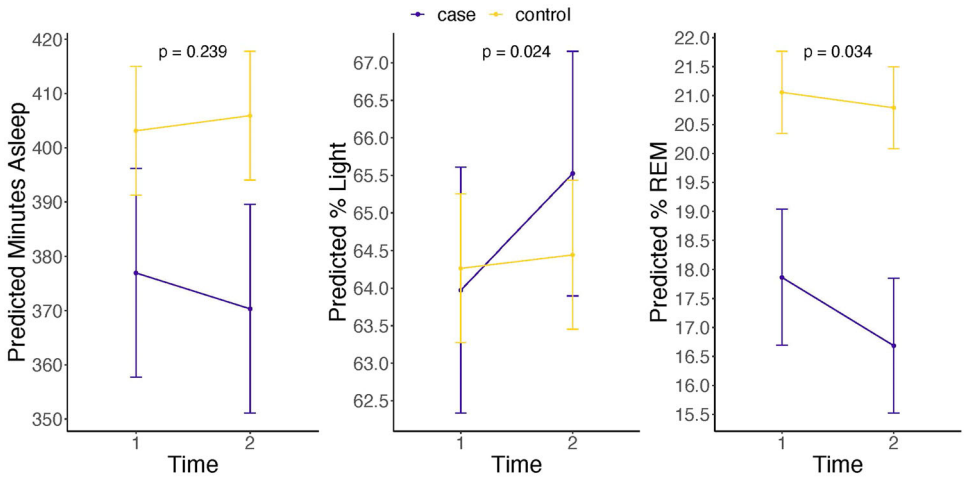

FIGURE 3 | Comparison of sleep duration and sleep quality in patients with PAH and matched controls. Generalized least squares models, adjusted for age, sex, and body mass index (BMI), with linear interaction analyses evaluated changes in total minutes asleep, percent light sleep, and percent REM sleep over the course of 1 year. The group-time interaction term was significant for percent light sleep ($p = 0.024$) and percent REM sleep ($p = 0.034$), which indicates that sleep quality worsened in patients with PAH over time compared to healthy controls. The interaction was not significant for total minutes asleep ($p = 0.239$).

of patients who were started on prostanoids between baseline and Year 1 were limited by a small cohort size so we may be underpowered to detect any clinically significant changes in this subgroup. However, it is also possible that the initiation of prostanoids may mitigate activity or sleep decline and this should be investigated in a future study with a larger cohort size. Given the geographic diversity of the PAH cohort, there may be some seasonal variation that we were unable to account

for with the matched controls. Lastly, some data were collected during the COVID-19 pandemic which may have impacted activity levels and changed sleep patterns. The matched monitoring dates in the controls mitigate the impact of the pandemic, but patients with chronic cardiopulmonary conditions may have been more adherent to social isolation guidelines, thereby decreasing their activity levels further.

In conclusion, this study illustrates the potential clinical value of activity and sleep monitoring with wearable devices and provides novel insights pertaining to health behaviors in patients with PAH. Activity and sleep quality are reduced in patients with PAH compared with matched controls and decline over 1 year. Sleep quality and physical activity are modifiable and may be underappreciated targets to improve how patients with PAH feel and function. Future studies are warranted to test whether interventions to improve sleep and activity lead to better outcomes and whether real-time continuous monitoring of sleep and activity behaviors can detect early functional decline.

Author Contributions

Guarantor statement: Evan L. Brittain takes responsibility for the data, analyses, and all content of the manuscript. Conception or design: Andrew M. Hughes, Jeffrey Annis, Anna R. Hemnes, and Evan L. Brittain. Data acquisition: Andrew M. Hughes, Alisha Lindsey, Kelly Burke, Jeffrey Annis, Luke G. Silverman-Lloyd, and Evan L. Brittain. Data analysis: Jeffrey Annis and Evan L. Brittain. Interpretation of the data: Andrew M. Hughes, Hiral Master, Jonah D. Garry, Michael J. Blaha, Erika S. Berman Rosenzweig, Robert P. Frantz, Paul M. Hassoun, Evelyn M. Horn, Jane A. Leopold, Franz P. Rischard, Brett Larive, Nicholas S. Hill, Serpil C. Erzurum, Gerald J. Beck, Anna R. Hemnes, and Evan L. Brittain. Drafting or revising the work: all of the authors. Final approval: all of the authors.

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Disclosure

The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Ethics Statement

The study was approved by the Vanderbilt University Medical Center Institutional Review Board (IRB). IRB Approval Number: 190357.

Conflicts of Interest

F.R. reports no direct conflicts related to this manuscript. His general disclosures include consulting relationships with Acceleron/Merck and United Therapeutics. A.R.H. has served as a consultant for GossamerBio, United Therapeutics, Merck, Janssen, and Tenax Therapeutics. She is a stockholder in Tenax Therapeutics. E.L.B. receives investigator-initiated grant funding from United Therapeutics. All other authors have no conflicts to disclose.

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