Step Count is Associated With Lower Nighttime Systolic Blood Pressure and Increased Dipping

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BACKGROUND

Higher nighttime blood pressure (BP) and the loss of nocturnal dipping of BP are associated with an increased risk for cardiovascular events. However, the determinants of the loss of nocturnal BP dipping are only beginning to be understood. We investigated whether different indicators of physical activity were associated with the loss of nocturnal dipping of BP.

METHODS

We conducted a cross-sectional study of 103 patients referred for 24-hour ambulatory monitoring of BP. We measured these patients' step count (SC), active energy expenditure (AEE), and total energy expenditure simultaneously, using actigraphs.

RESULTS

In our study population of 103 patients, most of whom were hypertensive, SC and AEE were associated with nighttime systolic BP in univariate (SC, r = -0.28, P < 0.01; AEE, r = -0.20, P = 0.046) and multivariate linear regression analyses (SC, coefficient beta = -5.37, P < 0.001; AEE, coefficient beta = -0.24, P < 0.01). Step count was associated with both systolic (r = 0.23, P = 0.018) and diastolic (r = 0.20, P = 0.045) BP dipping. Nighttime systolic BP decreased progressively across the categories of sedentary, moderately active, and active participants (125 mm Hg, 116 mm Hg, 112 mm Hg, respectively; P = 0.002). The degree of BP dipping of BP increased progressively across the same three categories of activity (respectively 8.9%, 14.6%, and 18.6%, P = 0.002, for systolic BP and respectively 12.8%, 18.1%, and 22.2%, P = 0.006, for diastolic BP).

CONCLUSIONS

Step count is continuously associated with nighttime systolic BP and with the degree of BP dipping independently of 24-hour mean BP. The combined use of an actigraph for measuring indicators of physical activity and a device for 24-hour measurement of ambulatory BP may help identify patients at increased risk for cardiovascular events in whom increased physical activity toward higher target levels may be recommended.

Keywords: physical activity; blood pressure; step count; ambulatory blood pressure monitoring; dipping; hypertension; night-time blood pressure.

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Twenty-four-hour ambulatory blood pressure monitoring (ABPM) is an indispensible complement to office blood pressure (BP) measurement in the management of hypertension. Ambulatory BP is a better prognostic marker of cardiovascular outcome than is office BP in patients with hypertension,¹ and for a given increase in BP, the associated risk of death is increased in both the general and the hypertensive population.^{2,3} Ambulatory BP monitoring also allows the detection of circadian variation of BP, which in healthy people is characterized by a lower BP at night. Three large-scale prospective studies have associated the absence of a nocturnal decline in BP with a poorer cardiovascular outcome.^{2–5}

Several mechanisms, such as daytime urinary sodium excretion,⁶ autonomic failure,⁷ and physical activity,⁸ have been associated with the loss of nocturnal dipping of BP, and may at least partly explain why the reproducibility of

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dipping is limited. Older age, female sex, African descent, body mass index (BMI), and treatment of hypertension and diseases such as chronic kidney disease have been associated with less nocturnal dipping of BP.⁹⁻¹¹

So far, clinical trials evaluating the relationship between BP dipping and physical activity have used questionnaires or actigraphs that quantify physical activity as dimensionless units that are difficult to interpret by physicians and patients.^{8,9,12,13} The development of new actigraphs allows the measurement of step count (SC), active energy expenditure (AEE), or metabolic equivalents (METS), which are measures that most patients find easy to understand. Relating these quantitative measures to the pattern of 24-hour BP could facilitate interactions between patients and physicians toward setting targets of physical activity and evaluating BP responses to various levels of activity. However, the

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association between these objective and quantitative markers of physical activity and circadian BP parameters such as nighttime BP or BP dipping has not been explored. We hypothesized that quantitative markers of physical activity would be associated with 24-hour patterns of BP.

We therefore conducted a study to determine whether objective quantitative markers of physical activity, measured with a validated device, were associated with daytime or nighttime BP or with BP dipping in an unselected sample of patients referred for ABPM.

METHODS

Participants

Participants for the study were recruited prospectively among patients more than 16 years old who were referred for ABPM by primary-care physicians or by specialists in an outpatient setting to the outpatient hypertension clinic of the nephrology service at the Lausanne University Hospital from April 2008 to February 2010. The reasons for referral for ABPM were a confirmation of hypertension, the exclusion of white-coat hypertension, or the control of BP during treatment for hypertension. All patients were asked to wear an ABPM device and an actigraph simultaneously for 24 hours. Nightshift workers and patients with an arteriovenous fistula in their upper arm were excluded from the study. The study was approved by the local institutional review committee. Participants gave their informed consent and were assessed in accordance with institutional guidelines.

Demographic measures

Age, height, weight, the presence or absence of smoking or diabetes, and the patient's medication history were recorded before the devices were installed.

Monitoring of ambulatory blood pressure

Ambulatory BP was measured with Diasys Integra devices (Novacor, Rueil-Malmaison, France),¹⁴ with measurements made every 20 minutes during the day and every 30 minutes at night. Arm circumference was measured and a BP cuff was chosen accordingly. Quality control was governed by an experienced observer on the basis of the first two readings of the ABPM device after patients had been seated for 5 minutes, with a Y-tube connected to a mercury sphygmomanometer. The BP monitoring time and the actigraph time were synchronized with a dedicated computer.

Monitoring of physical activity

The SenseWear Pro Armband (Body Media, Pittsburgh, PA) is an actigraph developed to assess energy expenditure through multiple sensors measuring skin temperature, galvanic skin response, and heat flux. It also includes a two-axis accelerometer that permits the detection of body position as either horizontal or erect. Data were recorded every minute

for 24 hours. Algorithms have been developed for different activities and allow the estimation of AEE, total energy expenditure (TEE), METS, SC, and sleep. The accuracy of the SenseWear Pro ArmbandTM for estimating daily energy expenditure and AEE during exercise has been compared with that of doubly-labeled water (DLW), the gold-standard method for measuring energy expenditure, and that of indirect calorimetry, respectively.^{15,16} These studies showed good correlation with the use of DLW and accurate estimates of AEE when specific algorithms were used. The SenseWear Pro Armband device has also been validated for BP monitoring during the period of sleep.¹⁷ The study subjects wore the device on the arm opposite that with the cuff of the ABPM device.

Blood pressure and categories of physical activity

Daytime and nighttime periods of ABPM were defined from recordings of the actigraph, because fixed or invariable periods of nighttime and daytime BP monitoring can influence mean daytime and nighttime BP.^{18–20} A BP reading was considered to be a nighttime BP reading if the actigraph indicated that the subject was asleep in the 5 minutes preceding ABPM measurement and the measurement was made in the period from 5 PM to 9 AM. Patients were considered hypertensive if they were taking one or more antihypertensive medication or if their daytime BP > 135/85 mm Hg or their nighttime BP > 120/70 mm Hg. These values are considered abnormal according to the European Society of Hypertension guidelines.²¹

Reverse dippers were defined as patients with a dipping of mean BP (DBP + 1/3 of pulse pressure) of less than 0%, nondippers as those with a dipping of mean BP of 0–10%, dippers as those with a dipping of mean BP of 10–20%, and extreme dippers as those with a dipping of mean BP of more than 20%.

Patients were defined as sedentary, moderately active, or active if their SC numbers during the 24-hour monitoring period were < 5,000, 5,000-9,999, or > 10,000, respectively, according to the system used by Tudor-Locke et al.²²

Statistical analysis

Sample size was determined from a pilot study of 30 patients, with power analysis used for linear regression models. A power of 0.8 and a level of significance of P = 0.05 were used for the calculation of sample size. With night-time BP used as the dependent variable, number of steps as the independent variable of interest, and mean 24-hour BP, age, sex, diabetes, and the use of antihypertensive medication as predictors, it was estimated that a sample size of 105 patients would be needed for statistical reliability. In order to account for possible missing data, an additional 5 patients were included, to make a total sample size of 110 patients.

Data are presented as mean $(\pm SD)$ or as median and interquartile range, for variables of interest that were not normally distributed. The Spearman rank correlation of parameters of activity and of BP was calculated. In multivariate linear regression analyses, SC and AEE were square-root-transformed and METS were log-transformed to better achieve a normal distribution of the residuals. For the relationship between nighttime systolic BP (SBP) or BP dipping as the dependent variables, and each of the categories of physical activity, taken one at a time, as the independent variable of interest, we used, as predictors in fully adjusted models, age, sex, diabetes, the use of antihypertensive medication, and mean 24-hour arterial BP. We used the statistics of the Wald test to assess the physical activity parameter most significantly associated with the dependent variable of interest. In unadjusted analyses we used the nptrend function in Stata, developed by Cuzick, which is a nonparametetric test for trend across categories of physical activity, and is an extension of the Wilcoxon rank-sum test.

Statistical analyses were done with Stata 11.0 (Stata. College Station, TX), and the nominal level of statistical significance was set at P < 0.05.

RESULTS

A total of 110 patients participated in the study. Seven patients removed their ABPM device at night because of discomfort, making 24 hour ABPM and actigraph data available for 103 patients. Of these 103 patients, 34% were women. Half of the patients were taking antihypertensive drugs. The mean number of drugs taken by treated hypertensive patients was 2.3 ± 1.1 . The overall prevalences of lean (BMI < 25 kg/m^2), overweight (BMI = $25-29.9 \text{ kg/m}^2$), and obese patients (BMI $\ge 30 \text{ kg/m}^2$) were 37%, 40%, and 23%, respectively. More than 90% of the patients were of Caucasian origin. No differences were seen in the demographic characteristics of the men and women in the study (Table 1). Ambulatory BP monitoring revealed that most of the patients had hypertension. Nighttime diastolic BP (DBP) was lower in the women than in the men in the study. The SC was highly variable across participants and did not differ in the men and women. Women had a lower TEE than men, but the AEE of the two sexes was similar (Table 1).

In the univariate analysis (Supplementary Table 1), the number of daytime steps, AEE, and METS were inversely associated with nighttime SBP but not with daytime SBP. Step count was also associated with nighttime dipping of both SBP and DBP. Age was negatively associated with SC, TTE, and METS, and BMI was positively associated with TEE and negatively associated with METS.

In the multivariate analysis, the daytime SC and AEE were associated with nighttime SBP independently of 24-hour mean BP, age, diabetes, sex, or the use of antihypertensive drugs (Table 2). Substituting the use of hypertensive drugs for BMI, duration of sleep, time spent lying down, or number of antihypertensive drugs in the model did not change the results (Supplementary Table 2). The association between SC and dipping of both SBP and DBP persisted in the multivariate analysis.

Nighttime SBP decreased progressively across the categories of sedentary, moderately active, and active participants (125 mm Hg, 116 mm Hg, and 112 mm Hg, respectively, P = 0.002), whereas daytime SBP was similar among the three categories (Figure 1). On the other hand, the degree of dipping of BP increased progressively across the three

categories of activity (8.9%, 14.6%, and 18.6%, respectively, P = 0.002 for systolic BP, and 12.8%, 18.1% and 22.2%, respectively, P = 0.006 for diastolic BP) (Figure 2).

The number of steps increased progressively across the categories of reverse dippers, nondippers, dippers, and extreme dippers (4,831, 6,775, 8,841 and 8,396 steps, respectively, P = 0.003 (Figure 3).

DISCUSSION

The main finding of this cross-sectional study is that physical activity expressed as daytime SC is independently associated with lower nighttime systolic BP. Daytime SC is also associated with the dipping of both SBP and DBP at night, independently of 24-hour mean BP. To the best of our knowledge, this is the first time that the continuous nature of the association of SC with nighttime BP and dipping has been reported. Active energy expenditure was also associated with lower nighttime SBP but not with increased nocturnal BP dipping.

Determinants of variability of BP, whether circadian or from one reading to the next, have been explored since ABPM first became available. However, nighttime BP has been shown to be the best prognostic indicator of cardiovascular events, with little added contribution from the nightto-day ratio of BP, dipping status, or reading-to-reading variability over and beyond 24-hour BP levels.^{23,24} Therefore, the association of such indicators of physical activity as SC and AEE with nighttime BP may have an important effect on the nonpharmacological management of hypertensive or prehypertensive patients.

The first evidence of the influence of physical activity on the circadian variation of BP was reported in a crossover study that included 10 normotensive and hypertensive subjects randomized to a period of 24 hours of complete bed rest followed by a 24-hour period that included normal daytime activity.²⁵ During the period of complete bed rest, the circadian variation of BP, as assessed with ambulatory intra-arterial BP monitoring, was reduced. Actigraphs were not used in the study. The authors the finding of a reduced circadian variation in BP to a higher nighttime BP.

The combined monitoring of physical activity and BP became easier when actigraphs became available. In a seminal study that included 160 participants without cardiovascular or renal disease and not using antihypertensive drugs, Kario et al. reported that only activity during sleep, and not daytime activity, was associated with nighttime DBP.⁸ However, the sleep/wake ratio of SBP to DBP, which is also used to define dipping, was inversely correlated with awake activity in their study, which is in accord with our findings. The lack of association between daytime activity and nocturnal BP in their study may have been the result of their assessment of physical activity with different actigraphs than those used in our study and of differences in their study population. Later, Hayashi et al. found an association between physical activity and 24-hour BP in a cohort of 67 patients composed of healthy volunteers, hypertensive patients, and diabetic patients¹³; unfortunately no distinction was made between daytime and nighttime BP.

	Women <i>n</i> = 35	Men <i>n</i> = 68	P-value	All subjects <i>n</i> = 103
n (%)	35 (34.0)	68 (66.0)		103
Age (Years)	53.3±17.6	56.1±13.9	0.37	55.1±15.2
BMI (kg/m ²)	25.9±4.9	27.3±4.3	0.15	26.8±4.5
Origin			0.83	
Caucasian, n (%)	32 (91.4)	63 (92.7)		95 (92.2)
African, n (%)	3 (8.6)	5 (7.3)		8 (7.8)
Diabetes, n (%)	4 (11.4)	10 (14.7)	0.65	14 (13.6)
Current smoker, n (%)	7 (20.0)	12 (17.6)	0.77	19 (18.4)
BP treatment, n (%)	17 (48.6)	37 (54.4)	0.58	54 (52.4)
Office SBP, mm Hg	136±18	141±22	0.23	139±21
Office DBP, mm Hg	84±11	85±14	0.71	85±13
SBP daytime, mm Hg	137±16	138±17	0.96	138±17
DBP daytime, mm Hg	88±12	88±13	0.98	88±12
HR daytime, bpm	83±10	79±11	0.07	80±11
SBP nighttime, mm Hg	116±14	118±14	0.67	117±14
DBP nighttime, mm Hg	69±9	73±8	0.045	72±9
HR nighttime, bpm	67±9	64±10	0.25	66±10
24-hour SBP, mm Hg	132±14	132±15	0.97	132±15
24-hour DBP, mm Hg	83±10	84±11	0.74	84±10
24-hour HR, bpm	78±9	75±10	0.07	76±10
Hypertension, n (%)	32 (91.4)	64 (94.1)	0.61	96 (93.2)
Dipper state			0.13	
Reverse dipper, n (%)	4/35 (11.4)	5/68 (7.4)		9/103 (8.7)
Nondipper, n (%)	4/35 (11.4)	16/68 (23.5)		20/103 (19.4)
Dipper, n (%)	8/35 (22.9)	24/68 (35.3)		32/103 (31.1)
Extreme dipper, n (%)	19/35 (54.3)	23/68 (33.8)		42/103 (40.8)
Number of steps	8,026±3120	7,659±3813	0.63	7,784±3,581
AEE, kcal	446±325	534 ± 486	0.34	504 ± 439
TEE, kcal	2,043±313	2,421±573	< 0.001	$2,293\pm530$
METS	1.34 ± 0.25	1.33 ± 0.31	0.91	1.34 ± 0.29
Sleeping time, minutes	402±79	403±117	0.95	403±105
Lving time, minutes	493±99	527±128	0.17	515±119

Table 1. Demographic characteristics of study participants with data from 24-hour ambulatory blood pressure monitoring and actigraphy

Data are mean \pm SD for continuous variables, or n (%) for categorical variables.

A P-value < 0.05 indicates a difference between men and women.

Abbreviations: ABPM, ambulatory blood pressure monitoring; AEE, active energy expenditure; BMI, body mass index; BP, blood pressure; BPM, beats per minute; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; TEE, total energy expenditure Lying time, time spent in the supine position.

Although studies correlating physical activity with daytime or nighttime BP per se are scarce, more data are available about the association between diurnal physical activity and circadian BP variability.^{8,9,12} In a study including 434 normotensive and hypertensive patients, Leary et al. showed that actigraph-measured mean daytime physical activity, expressed as dimensionless units, was associated with the magnitude of dipping of both SBP and DBP,⁹ which is concordant with our results. Furthermore, it has also been shown that dipping on a day in which an individual has a high level of physical activity is greater than dipping on a day with a low level of physical activity.¹² On the other hand, it has been shown in a number of studies that increased nighttime physical activity is associated with a lower magnitude of dipping.^{8–10,26–28} In our study, nighttime measures of physical activity, such as SC, METS, and AEE at night, were very low because nighttime was defined according to the periods of sleep shown by the actigraph. These markers may therefore

Dependent variable	Predictor variables ^a	Coefficient	(95% CI)	P-value
Nighttime SBP, mm Hg	Steps ^b	-5.37	(-8.52, -2.23)	< 0.001
	MBP24	0.78	(0.60, 0.95)	< 0.001
	Age	0.02	(0.13, 0.16)	0.83
	Sex	-0.13	(-4.25, 4.00)	0.95
	Antihypertensive drugs	3.16	(-1.06, 7.37)	0.14
	Diabetes	4.08	(-1.59, 9.76)	0.16
Adjusted R ² = 0.48				
Nighttime SBP, mm Hg	AEE°	-0.24	(-0.47, -0.03)	< 0.01
	MBP24	0.77	(0.58, 0.94)	< 0.001
	age	0.04	(-0.10, 0.18)	0.18
	sex	0.55	(-3.71, 4.81)	0.80
	Antihypertensive drugs	3.66	(-0.67, 7.99)	0.097
	Diabetes	4.20	(-1.5, 10.06)	0.16
Adjusted R ² = 0.44				
Nighttime SBP, mm Hg	METS ^d	-10.2	(-20.4, 0.2)	0.055
	MBP24	0.77	(0.58, 0.95)	< 0.001
	Age	0.04	(-0.11, 0.18)	0.63
	Sex	0.25	(-4.02, 4.53)	0.91
	Antihypertensive drugs	3.11	(-1.35,7.56)	0.17
	Diabetes	4.14	(-1.76, 10.04)	0.17
Adjusted R ² = 0.44				
Dipping SBP, %	Steps	0.04	(0.02, 0.07)	< 0.01
	MBP24	0.003	(0.001, 0.004)	< 0.01
	Age	0.0009	(-0.0003, 0.0021)	0.15
	Sex	-0.005	(-0.042, 0.032)	0.81
	Antihypertensive drugs	-0.016	(-0.054, 0.022)	0.40
	Diabetes	-0.026	(-0.077, 0.025)	0.31
Adjusted R ² = 0.26				
Dipping DBP, %	Steps	0.03	(0.003, 0.064)	0.033
	MBP24	0.005	(0.003, 0.006)	< 0.001
	Age	-0.00004	(-0.001, 0.001)	0.96
	Sex	-0.04	(-0.080, 0.001)	0.058
	Antihypertensive drugs	-0.004	(-0.045, 0.037)	0.85
	Diabetes	0.01	(-0.045, 0.066)	0.72

Table 2. Multivariate linear regression analysis of physical activity with nighttime systolic blood pressure and dipping

Adjusted $R^2 = 0.25$

^aMean 24-hour blood pressure, age, sex, diabetes, snd use of antihypertensive drugs were used as predictors.

^bSteps are expressed as square root of 1,000 steps.

°AEE is expressed as the square root of active energy expenditure.

^dMETS is expressed as the logarithm of METS.

Abbreviations: AEE, active energy expenditure; CI, confidence interval; DBP, diastolic blood pressure; MBP24, mean 24 hour blood pressure; METS, metabolic equivalents; SBP, systolic blood pressure.

be insufficiently sensitive to nighttime activity, as compared with movement recordings, to be associated with dipping.

Although there was no difference in the duration of sleep among the dipper categories in our study, which accords with an observation by Mansoor et al.,²⁸ there was

a significant trend toward spending more time in the supine position across the four dipper categories from reverse dipper to extreme dipper, indicating that for the same duration of sleep, reverse dippers spent more time in the supine position. This finding highlights the importance of precisely and



Figure 1. Daytime and nighttime systolic blood pressure across physical activity categories. White boxes: sedentary participants. Light grey boxes: moderately active participants. Dark grey boxes: active participants.



Figure 2. Systolic and diastolic blood pressure dipping across physical activity categories. White boxes: sedentary participants. Light grey boxes: moderately active participants. Dark grey boxes: active participants. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

differentially defining daytime and nighttime periods, such as lying time, sleeping time, patient-reported nighttime, and even fixed nighttime, since this may affect the distribution of categories of dippers.^{18–20} It may also explain why reproducibility may be limited when nighttime is not based on the subjects' true sleep–wake pattern.²⁹

There was a clear association between the awake energy spent per kilogram of body weight and BMI (Spearman rank test, -0.34, P = 0.0004), with less active energy spent by overweight and obese patients, whereas there was no association between the SC and BMI (Spearman rank test, -0.08, P = 0.44). The latter results suggest that BMI could differentially affect awake energy spent per kilogram of body weight and SC as indicators of physical activity.

A mechanism that could explain the effect of physical activity on nighttime BP and dipping could be related to autonomic function, with a decreased sympathetic drive or an increased vagal tone at night, or both. First, it has been shown that a decreased nighttime dipping of urinary catecholamine excretion is associated a blunted dipping of both systolic and diastolic BP, suggesting a possible influence of the sympathetic nervous system on BP dipping.¹¹ However, the study in which this was found did not assess daytime physical activity. Using power spectral analysis of SBP and heart-rate (HR) variability as markers of autonomic nervous activity, Iwane et al. demonstrated that in a cohort of 30 hypertensive male patients, walking over 10,000 steps per day for 12 weeks decreased office BP and sympathetic nervous activity but had no effect on parasympathetic nervous activity.³⁰ A sympathetic-inhibitory effect of exercise was also shown in a study that used the norepinephrine (NE) spillover technique.³¹ In that study, 1 month of regular exercise, as compared with 1 month of sedentary activity, decreased total NE spillover. Interestingly, resting renal NE spillover, but not cardiac spillover, was reduced by exercise. These findings may also partily explain the increased systemic vascular resistance found in non-dippers as compared with dippers.²⁶ Lastly, in a meta-analysis of the influence of aerobic endurance training on BP and BP-regulatory mechanisms, Cornelissen et al. reported that aerobic endurance



Figure 3. Step count across categories of dippers.

training decreased BP, peripheral vascular resistance, plasma NE, and plasma renin activity, suggesting a possible link between physical activity, sympathetic nervous activity, and BP.³² However, in the absence of a prospective study in which physical activity, daytime BP, and nighttime BP are measured simultaneously with tests of autonomic function, the effect of physical activity on autonomic function, and therefore on BP dipping, may only be hypothesized, and other mechanisms for BP dipping are likely to be implicated.

The use of devices such as pedometers or modern actigraphs simultaneously with ABPM may not only indentify patients at high cardiovascular risk, through ABPM, but also identify, through actigraphy, sedentary patients for whom recommended targets of physical activity could be set. So far, influencing the physical activity of patients has been a challenge for physicians. The combined use of both ambulatory BP monitors and actigraphs could therefore be of help in this effort. Indeed, it has been shown in a meta-analysis that setting a goal of 10,000 steps per day is a good objective for increasing physical activity. This may in turn have positive effects on BP,^{33,34} particularly on nighttime BP and dipping.

Our study has several limitations. First, the cross-sectional nature of the study did not allow us to establish a causal relationship of SC nocturnal BP and dipping. Second, we did not measure potential confounders known to influence the dipping of BP, such as sodium excretion and renal function. Third, most of the participants in our study were hypertensive, and more than half were being treated with antihypertensive medication. We believe, however, that this is exactly the population to target for intervention with physical activity because it is at risk by definition. The findings in our study may therefore not be extended to other settings. Nevertheless, the associations that we found between daytime SC and decreased nocturnal BP and dipping are independent of other potential confounders, such as age, sex, drug treatment, and particularly 24-hour mean BP.

This study shows that measures of physical activity, such as AEE or SC, recorded during ABPM, are associated with a lower nighttime SBP. In order to conclude that a causal relationship exists between activity and nighttime BP, there is a need for interventional studies targeting specific step counts and examining their effects on nighttime BP or dipping.

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DISCLOSURE

The authors declared no conflict of interest.

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