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Circadian rhythm and variability of large and small airway spirometric variables in healthy individuals

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Abstract

Objective: To assess the diurnal rhythm and variability of lung function in healthy individuals, encompassing both large and small airways.

Methods: A prospective study enrolled 35 healthy adults without a history of smoking. Initial spirometry and a bronchodilation test were performed using the Jaeger spirometer, followed by a seven-day continuous home monitoring using the GOSPT2000. We evaluated repeatability using the intraclass correlation coefficient and agreement through linear regression and Bland–Altman analyses. Circadian rhythm and variability in spirometric measurements were analyzed using the coefficient of variation (CV) and daily variation rate.

Results: The GOSPT2000 demonstrated strong repeatability and high agreement with the Jaeger spirometer. Notable findings included a decrease in nocturnal forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and FEV_3 by 44, 59, and 53 mL, respectively. In contrast, peak expiratory flow at noon showed an increase of 0.143L/min. Small-airway variables, including forced expiratory flow at 50% and 75% of the FVC and maximum midexpiratory flow, showed no significant diurnal variation. The nocturnal CV for large-airway variables was $\leq 4\%$, while for small-airway variables, it was $\leq 11.89\%$.

Conclusion: This study has established a spectrum of variability for both large and small airways in healthy populations. The variability of small-airway variables is higher than that of large-airway variables. The investigation into the diurnal rhythms and variability characteristics of both large and small airway variables in the healthy population can serve as a foundation for diagnosing asthma or assessing the efficacy of asthma treatments.

Keywords

Pulmonary function, circadian rhythm, variation, home monitoring, portable spirometer

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Introduction

Asthma affects more than 330 million people globally and the disease burden is increasing in many countries,[1,2] with high rates of misdiagnosis, uncontrolled symptoms,[3] acute attacks, and death. Airflow obstruction follows a circadian pattern,[3–9] contributing to the nocturnal worsening of asthma.[9] The diurnal variation of lung functions is more prominent in patients with asthma, which is an important criterion for diagnosing asthma.[1] Consecutive spirometry monitoring of large-airway functions (such as forced vital

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capacity [FVC], forced expiratory volume in 1 s [FEV_1], FEV_1/FVC, FEV_3) and small-airway functions (such as forced expiratory flow at 50% of the FVC [MEF50], MEF25 and maximum mid-expiratory flow [MMEF]) is helpful in diagnosing asthma,[10–12] predicting acute attacks and evaluating therapeutic response.[13–15]

The circadian rhythm and variability of lung function in healthy individuals are crucial for interpreting the results of telehome monitoring. Assessed with conventional spirometers, FEV_1 and FEV_1/FVC increased from 9 a.m. until noon and decreased thereafter in healthy individuals.[16] Peak expiratory flow (PEF) has been shown to peak around 4 p.m.[16–18] However, those results from conventional spirometer cannot be directly applied to telehome monitoring because: (1) difference between professional on-site guided and home-based self-supervised operation of spirometers may cause the accuracy bias; (2) trials using conventional spirometry are typically shorter in duration[16–18] compared with telehome monitoring; (3) the influence of environmental factors, such as acclimatization to the hospital environment, disrupted sleep due to spirometry, exposure to outdoor pollutants, and brief cessation of social activities and work, in studies of conventional spirometry remains unclear; and (4) recording of the time of day (such as 4 a.m. and 4 p.m.) in conventional spirometer trials offers limited practicality for real-world, home-based monitoring strategies.[17,18]

The purpose of our prospective cohort study was to estimate the circadian rhythm and variability of spirometric variables using a portable spirometer in healthy individuals during a seven-day diurnal and nocturnal home monitoring period with GOSPT2000. The GOSPT2000 spirometer (Shanghai Zhuomiao Electronic Technology Co., Ltd, Shanghai, China) is a product of GoSprio (Monitored Therapeutics Inc., Dublin, OH, USA) approved by the Food and Drug Administration in the United States (K163249). The repeatability, agreement and stability of the results from the portable spirometer and the subjects' adherence were also evaluated.

Methods

The study has been exempted from the Ethics Committee of Shanghai General Hospital, Shanghai Jiao Tong University.

Chinese Clinical Trial Registry; Website: www.chictr.org.cn; No.: ChiCTR2100050355.

Participant characteristics

The prospective study was approved by the Ethics Committee of Shanghai General Hospital, Shanghai Jiao Tong University (No.2021KY073).

Thirty-five healthy volunteers who consented to participate in the trial and met the following inclusion criteria were enrolled, and homogenized in terms of gender, age, and education degree. The inclusion criteria were as follows: aged 18–65 years; no clinical symptoms within the past eight weeks; normal medical reports (complete blood counts, biochemistry tests, carcinoembryonic antigen, alpha-fetoprotein, B-ultrasonic, electrocardiography and chest high-resolution computed tomography scan) within the past month; no history of smoking; no allergic diseases; and no chronic respiratory diseases.

Subjects were excluded if they had any systemic diseases or symptoms, including unstable cardiovascular status, diabetes, gastroesophageal reflux, nausea, vomiting, abdominal pain, stress urinary incontinence, or if they had undergone surgery of the chest, abdomen, or eye within the previous two weeks. Additionally, those unsuitable for spirometry or with mental diseases and cognitive disorders were also excluded.

Study design and setting

A schematic diagram of the study is presented in Figure 1. We assessed demographics, height, weight and medical history. After confirming the absence of respiratory symptoms (cough, chest tightness, fever, sputum production, breathlessness), subjects underwent spirometry and a bronchodilation test using the hospital spirometer, guided by a trained medical technician in the morning. Subsequently, they were provided with the GOSPT2000 device to take home for pulmonary function monitoring over the next seven consecutive days. The built-in software program prompted users to report any respiratory symptoms before each test. Testing times were set between 8 a.m.–9 a.m. and 8 p.m.–9 p.m.

Spirometry and bronchodilation test

Spirometry was performed using a Jaeger spirometer (Jaeger Co., Hoechberg, Germany), following the performance criteria recommended by the American Thoracic Society/European Respiratory Society standardization of spirometry.[18] Spirometric variables including PEF, FVC, FEV_1, FEV_3, MEF50, MEF25, and MMEF were expressed as absolute values and as percentages of the predicted value. Ratios such as FEV_1/FVC and FEV_3/FVC were expressed as absolute values.

The bronchodilation test was conducted before and 20 min after the administration of a bronchodilator (Salbutamol 400 ug). An improvement in FEV_1 of less than 12% from predose with an absolute increase of less than 200 mL was defined as negative.

Portable spirometer and home monitoring

The introduction of GOSPT2000 is included in supplemental data.

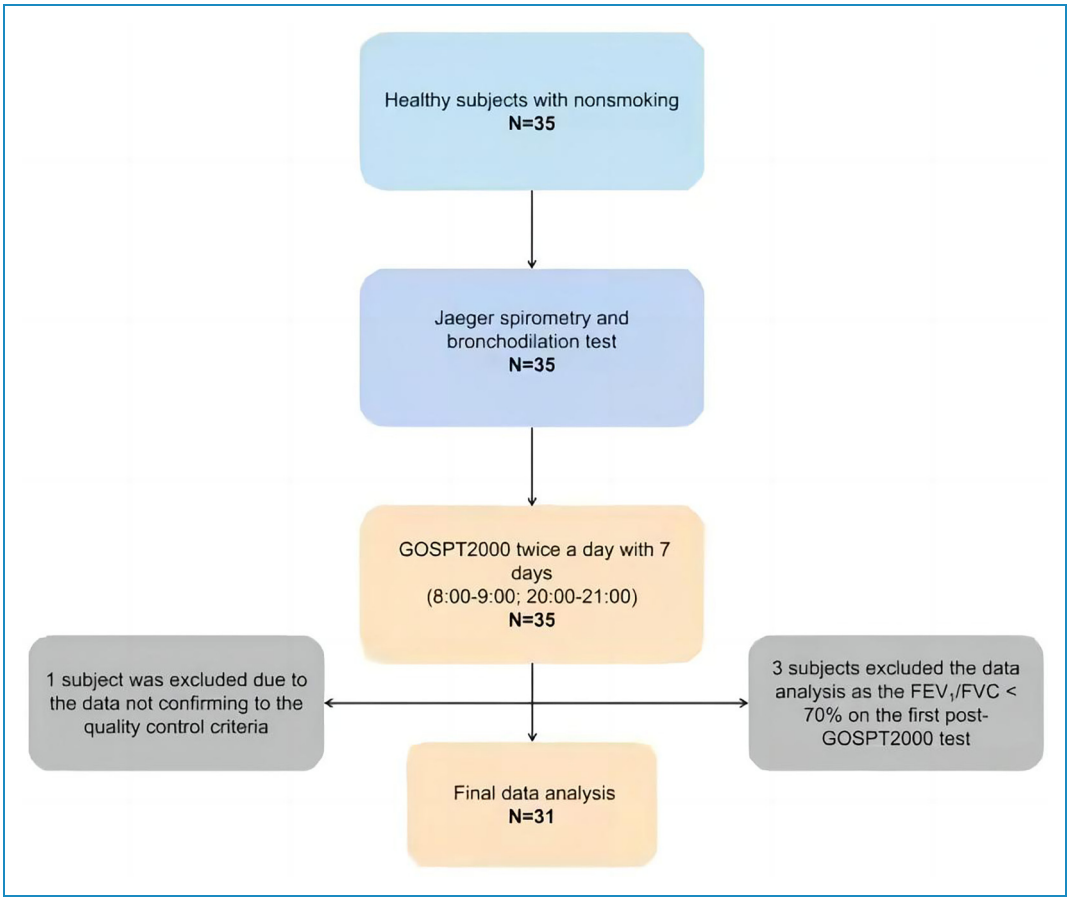

Figure 1. Schematic presentation of study design.
Thirty-five participants completed spirometry and bronchodilation test using Jaeger spirometer and the seven days portable spirometer monitoring, among whom three were excluded since the $FEV_1/FVC < 70\%$ on the first GOSPT2000 test and 1 was excluded for not meeting the quality-control criteria, leaving 31 participants included for final analysis. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

After seven consecutive days of measurements, we collected data for PEF, FVC, FEV_1, FEV_3, MEF50, MEF25, and MMEF. The back-extrapolated volume (BEV) had to be less than 5% of the FVC or 0.100 L to confirm that FEV_1 resulted from a maximal effort.[18]

Diurnal variability was calculated from twice-daily spirometric measurements as the day's highest value minus the day's lowest value, divided by the mean of the day's highest and lowest values, averaged over one week.

Sample size calculation

In this study, we mainly focus on the circadian rhythm of small-airway variables, and we expect a 20% change in day-night differences of small-airway variables to be clinically significant, so 0.20 was used as our effect size (dz). The desired level of significance (alpha) is set at 0.05. The power of the study (1—beta) is 0.80 as commonly used. The noncentrality parameter (δ) was computed as 2.82. The critical *t*-value was found to be 1.97. The degrees of freedom (df) were calculated as 198. In this case, a sample size of 199 was necessary to achieve a power of 0.80 at a significance level of 0.05, given the effect size of 0.20. Each subject underwent repeated tests for seven consecutive days, resulting in $199/7 = 28.42$. Obtaining data for 199 daytime and nighttime measurements necessitates 29 individuals. Anticipating a dropout rate of 20%, we plan to enroll 35 subjects according to the inclusion criteria, and they were homogenized in terms of gender, age, and education degree to ensure the stability of results.

Statistical analysis

Data were analyzed using GraphPad Prism Version 5.01 (GraphPad Software, San Diego, CA, USA) and SPSS Version 21.0.

The normality of distribution was tested with the Shapiro–Wilk test. Normally distributed data were expressed as mean ± standard deviation (SD) or 95% confidence interval (CI). Nonnormally distributed data were

expressed as median and interquartile ranges (IQRs). Nonparametric tests were used for comparison between groups. A paired *t*-test was used to compare the differences between diurnal and nocturnal variables.

Repeatability was assessed using the intraclass correlation coefficient (ICC). The agreement was evaluated through linear regression analysis and Bland–Altman analysis, calculating the mean difference and 95% limits of agreement (LoA).

The coefficient of variation (CV), defined by the standard deviation, relative to the mean was calculated for each continuous variable to demonstrate variability.

$$\textit{The diurnal CV} = \frac{\text{SD of seven-day diurnal values}}{\text{mean of seven-day diurnal values}} \times 100\%$$

$$\textit{The nocturnal CV} = \frac{\text{SD of seven-day nocturnal values}}{\text{mean of seven-day nocturnal values}} \times 100\%$$

$$\textit{The intracohort CV} = \frac{\text{SD of values from all participants}}{\text{mean of values from all participants}} \times 100\%$$

$$\textit{The seven} - \textit{day CV} = \frac{\text{SD of seven-day diurnal and nocturnal values}}{\text{mean of seven-day diurnal and nocturnal values}} \times 100\%$$

$$\textit{Daily variation rate} = \frac{2\,(\text{Highest value-lowest value of the day})}{(\text{Highest value} + \text{lowest value of the day})} \times 100\%$$

The threshold for statistical significance for all analysis was set at $p < .05$.

Table 1. Demographic data and laboratory spirometric variables of subjects.

Variables	*M*	*SD*	*p*-value	Intracohort CV of all the subjects
Age, years	36.68	11.64	> .10	31.74%
Height, cm	168.9	8.791	> .10	5.21%
Weight, kg	65.55	10.38	.0791	15.84%
FVC, L	3.95	0.9438	> .10	23.89%
FEV_1, L	3.259	0.7941	> .10	24.37%
FEV_3, L	3.798	0.9291	> .10	24.46%
PEF†, L/min	8.135	1.987	> .10	24.43%
MEF50, L	3.856	0.9106	> .10	23.62%
MEF25, L	1.495	0.6424	> .10	42.98%
MMEF, L	3.251	0.8975	> .10	27.61%
FEV_1/FVC, %	82.48	4.898	.0859	5.94%
FEV_3/FVC, %	96.04	2.755	> .10	2.87%
FVC%	99.16	9.201	> .10	9.28%
FEV_1%	96.3	8.937	> .10	9.28%
PEF%†	103.6	15.7	> .10	15.16%
MEF50%	83.19	17.18	> .10	20.65%
MEF25%	70.82	21.43	> .10	30.26%
MMEF%	79.8	15.59	> .10	19.53%

CV: coefficient of variance; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; FEV_3: FEV in 3 s; MEF50: forced expiratory flow at 50% of forced vital capacity; MEF25: forced expiratory flow at 75% of forced vital capacity; MMEF: forced expiratory flow between 25% and 75%; PEF: peak expiratory flow; SD: standard deviation; MMEF: maximum mid-expiratory flow.
†$n = 31$.

Results

Demographic and baseline characteristics

All 35 subjects completed Jaeger's spirometry and the seven-day portable spirometer measurement. Three participants were excluded from the data analysis because their FEV_1/FVC were less than 70% on the first GOSPT2000 lung function test. Additionally, one participant was excluded because the BEV was greater than 5% of the FVC and greater than 0.100L, as indicated by the built-in quality control of GOSPT2000 device. This left 31 participants for the final data analysis. The mean age was 36.68 (*SD* 11.64) years and 41.94% (13 out of 31) were male (Table 1). White blood cells ($3.5–9.5 \times 10^9$/L), lymphocytes ($1.1–3.2 \times 10^9$/L), and eosinophils ($0.02–0.3 \times 10^9$/L) are all within normal ranges for the 31 subjects.

No subject discontinued home monitoring with GOSPT2000 during the seven days. Of the 448 sets of spirometry data, only 16 sets (10 sets from one individual) did not confirm to the acceptability and repeatability criteria.

For large-airway variables, the intracohort CV was 9.28% for both FEV_1 and FVC, 5.94% for the FEV_1/FVC ratio and 15.16% for PEF. Among the MEFs, the highest intracohort CV was 30.26% for MEF25, followed by 20.65% for MEF50 and 19.53% for MMEF. FEV_3/FVC

ratio exhibited the lowest intracohort CV with 2.87%. All the participants had negative bronchodilation tests.

Repeatability and agreement of GOSPT2000 compared with Jaeger spirometer

FVC and FEV_1 showed excellent repeatability, with ICC values of 0.982 (95% CI [0.963 to 0.991]) for FVC and 0.990 (95% CI [0.980 to 0.995]) for FEV_1. The GOSPT2000-measured values for FVC and FEV_1 were consistent with those obtained from the Jaeger spirometer (ICC > 0.98 for both) (Figure 2A and B). The Bland–Altman plot revealed that the mean FVC measured by GOSPT2000 was 0.058L lower than that measured by Jaeger, with a 95% LoA ranging from −0.006L to 0.121L (Figure 2C). Similarly, the mean FEV_1 measured by GOSPT2000 was 0.043L lower, with a 95% LoA of 0.002L to 0.084L (Figure 2D). Only two FVC values fell outside the LoA, and no FEV_1 measurement was beyond the LoA.

Circadian rhythm of large and small airway spirometric variables

As shown in eTable 1, mobile spirometry monitoring confirmed significant diurnal variations in large airway variables. Diurnal results were significantly higher than nocturnal values (Figure 3, $p < .001$ for FEV_1, FVC, and FEV_3). Compared with daytime data, nocturnal FEV_1, FVC, and FEV_3 decreased by 44, 59, and 53 mL, respectively. Conversely, nocturnal PEF increased by 0.143 L/min ($p < .001$). No significant day–night differences were observed for the FEV_1/FVC ratio or the small airway variables ($p > .05$ for all).

Variability of large and small airway variables

In healthy individuals undergoing seven-day diurnal and nocturnal home monitoring with GOSPT2000, lower diurnal CVs were observed in large airway variables (2.72% for FVC, 2.57% for FEV_1, 2.18% for FEV_3, 3.52% for PEF) compared to small-airway variables (8.59% for MEF50, 10.91% for MEF25 and 7.19% for MMEF; Figure 4, eTable 2). Notably, two outliers of PEF were identified on the same day in one subject; their exclusion in a sensitivity analysis did not significantly alter the concordance or correlation measures. Additionally, four outliers of PEF across four different days were identified in another subject and were excluded from the final analysis. Nocturnal CVs for large airway variables (2.87% for FVC, 2.76% for FEV_1, 2.59% for FEV_3, and 4.0% for PEF) were also lower than small-airway variables (8.31% for MEF50, 11.89% for MEF25, and 7.22% for MMEF).

The daily variation rates of small-airway variables were higher than those of large-airway variables. with 3.39 (IQR:2.02–5.13)% for FVC, 2.50 (IQR:2.25–4.72)% for FEV_1, 2.98 (IQR:2.37–4.73)% for FEV_3, 7.20(IQR:5.63–10.15)% for MEF50, 14.04 (IQR:10.55–18.34)% for MEF25, 7.89 (IQR:5.23–10.81)% for MMEF and 4.43 (IQR:3.21–6.00)% for PEF. (Figure 5, eTable 3).

Discussion

This study contributes significantly to the understanding of lung function variability, especially in terms of circadian rhythms and the repeatability of measurements in both large and small airways. The demographic and baseline characteristics of our study provide a solid foundation for interpreting these results. Participants were homogenized by gender, age, and education degree. No bronchial hyperresponsiveness was present, as confirmed by bronchodilation tests. By focusing on a healthy, nonsmoking adult population with an average age of 36.68 years, we ensured a relevant sample that minimizes confounding factors like smoking or preexisting lung diseases.

The study highlights significant diurnal variations in large airway variables, with lower nocturnal values for FEV_1, FVC, and FEV_3, but an increase in nocturnal PEF. There were no significant day–night differences in small-airway variables. Day–night differences in large-airway function are well documented.[3–6] However, most spirometry assessments occur in hospitals with professional oversight and are typically limited to 1–3 days, continuous or otherwise. Our study provides new information on long-term home-based spirometry, enhancing precision with detailed variability data. This aligns with existing literature[19] indicating circadian influences on lung function and suggests that time of day is an important consideration in both clinical and research spirometry. These findings have potential clinical implications, such as timing medication for optimal control, understanding the diurnal pattern of symptoms in respiratory diseases, evaluating asthma control and predicting acute attacks. Besides that, finding additional markers that correlate with symptoms and prognosis is of great clinical significance. For example, a study found airway nanoparticles to correlate with symptoms and lung functions better than spirometry in healthy smokers.[20] We believe that circadian rhythm and variability in pulmonary function tests might also prove to be of such value based on further research.

Circadian variation in large-airway function has been recorded in both healthy individuals[6,16] and patients with asthma.[3–5] To minimize circadian variation errors in spirometry,[16] we calculated diurnal and nocturnal CVs for all spirometric variables separately. The diurnal and nocturnal CVs for FVC, FEV_1 and FEV_3 reflect minimal individual differences. The inquiry arises as to whether the criterion for diagnosing asthma in bronchodilator testing, which

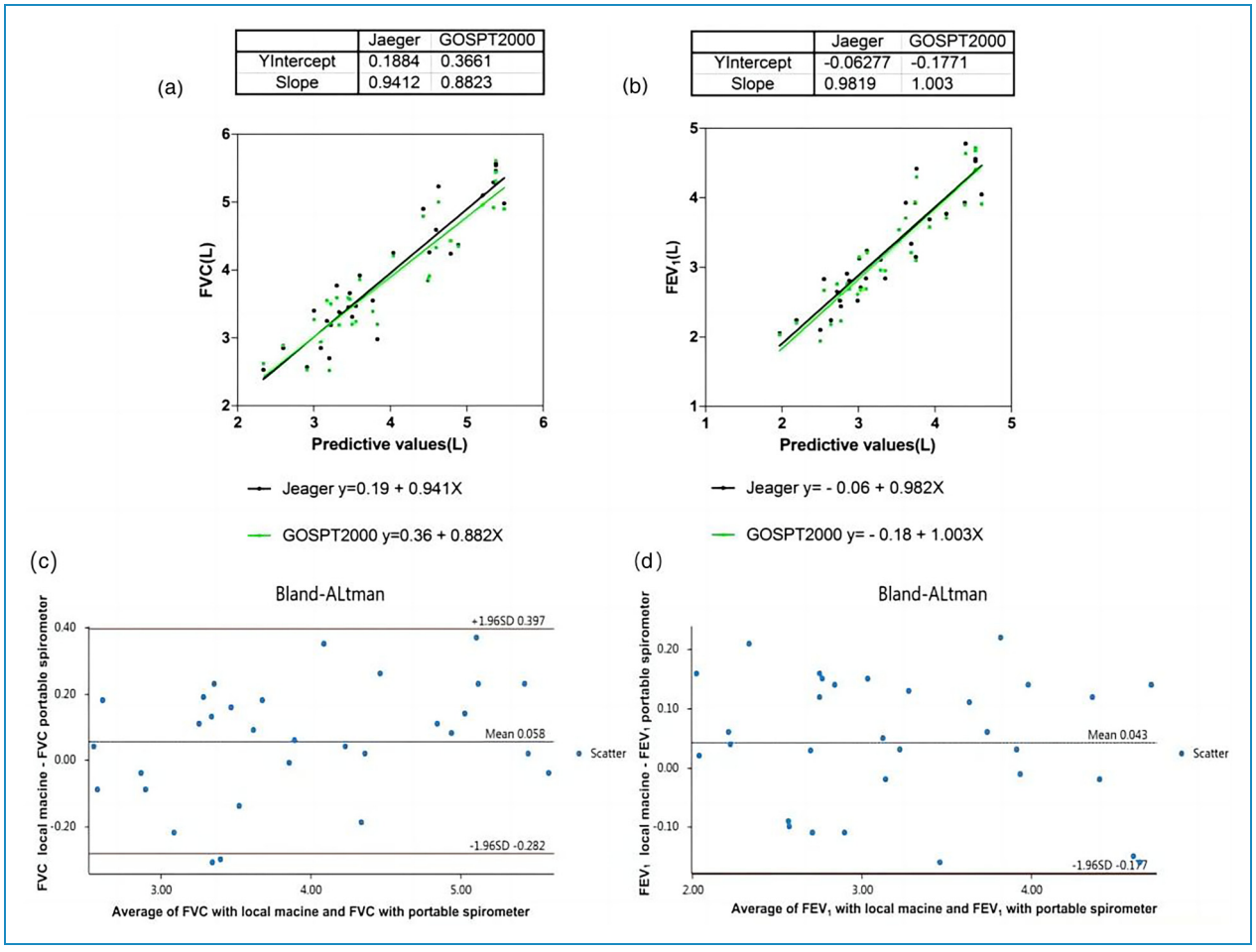

Figure 2. ICC and Bland–Altman analysis.
For FVC (Panel A) and FEV_1 (Panel B), GOSPT2000-measured values in this cohort were consistent with the values from Jaeger (ICC > 0.98 for both). The FVC (Panel C) and FEV_1 (Panel D) measured by GOSPT2000 presented a mean bias of 0.058 and 0.043 L (95% LoA was −0.006 to 0.121 for FVC and 0.002 to 0.084 for FEV_1) compared to that measured by Jaeger spirometer. ICC: intraclass correlation coefficient; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s.

necessitates an increase in FEV_1 of 12% or more, is reasonable, particularly in light of the study's finding of a nocturnal CV for FEV_1 less than 4%. The slightly higher nocturnal CVs suggest their greater clinical significance in predicting treatment response and acute exacerbation when monitoring variations in airway function simultaneously. Conducting spirometry at relatively fixed time points can minimize circadian rhythm influences, enabling prompt detection of improvements postdiagnostic treatment and providing evidence-based advice for follow-up timings and retesting of pulmonary functions, thereby avoiding hormone overuse and asthma overdiagnosis.

The greater variability in small-airway variables compared to large-airway variables observed in this study is a novel finding. This could be attributed to the inherent differences in the structure and function of large and small airways, as indicated in our previous trial,[21] age was the main influencing factor of both large and small airway function variability, especially for the small airway function in the evening. When diagnosing asthma, if small-airway variables are included, a relatively higher variability threshold should be adopted. Our previous studies indicate that a 15.26% increase in MMEF or a 26.04% increase in MEF25 during bronchodilation tests can predict a response to antiasthma therapy, as compared to a 3.50% improvement in FEV_1.[12] The elevated daily variation rates could contribute to the higher cutoff values for small-airway variables in treatment response prediction.[12] This monitoring could be particularly helpful for the early clinical detection of those at high risk for asthma. Further detailed studies or specific data on these variables might provide more insights, but the existing evidence points to a notable circadian variation in small-airway functions, which is an important consideration for both clinical diagnosis and management of respiratory conditions like asthma.

Despite international guidelines advocating the use of peak flow meters (PFMs) in patients with poorly controlled

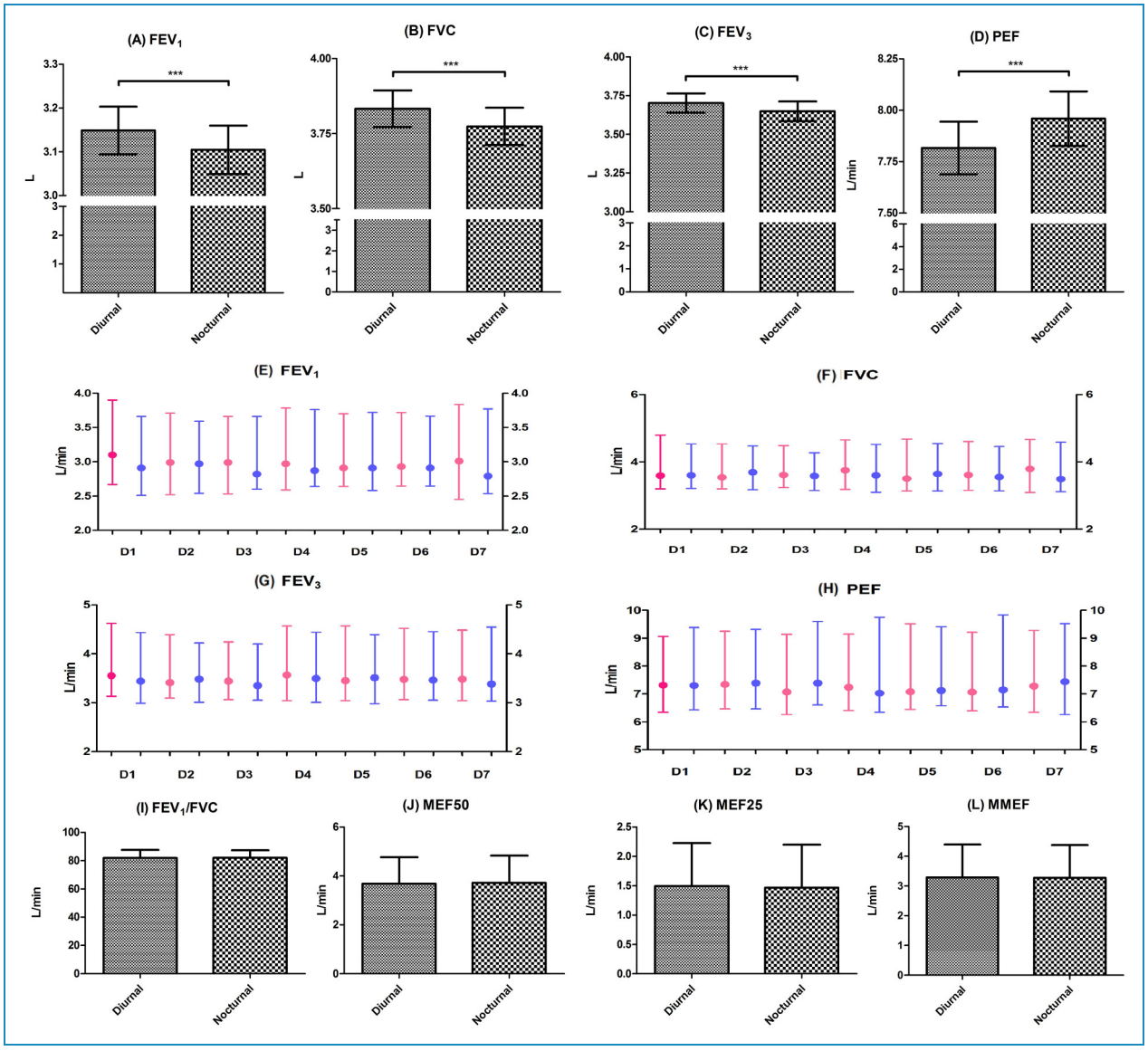

Figure 3. Circadian rhythm of large- and small-airway function variables in GOSPT2000 spirometer.
Compared with daytime data, the nocturnal results of FEV_1 (Panels A, E), FVC (B, F), and FEV_3 (C, G) decreased. Nocturnal PEF (D, H) increased. No significant day–night differences were proved for FEV_1/FVC (I) and the small-airway indicators (J–L). For panels A–D and I–L, data were expressed as mean with SD. For panels E–H, red indicated diurnal data and blue indicated nocturnal data, expressed as median with interquartile range. ICC: intraclass correlation coefficient; FVC: forced vital capacity; FEV_3: forced expiratory volume in 3 s; PEF: peak expiratory flow.

asthma symptoms, few physicians educate their patients about them, due to the high intraindividual variability of PEFs and low patient adherence.[22–25] Our study found that the GOSPT2000 offered significantly lower diurnal and nocturnal CVs in PEF measurements compared to those offered by traditional PFMs in healthy subjects,[26] indicating its higher stability and reliability.

The study's findings have several implications for clinical practice and future research. The results obtained from telehome monitoring exhibited strong repeatability and high agreement with in-hospital spirometry measurements, which enhances the persuasiveness of our findings. Then comes the implications, first, the observed variability in lung function, especially in the small airways, might aid in the early detection of respiratory diseases. Regular monitoring of lung function using portable spirometers could become an essential part of preventive health check-ups, especially for individuals at risk. Second, understanding individual variability in lung function, particularly in relation to circadian rhythms, could lead to more personalized approaches in treating respiratory diseases. The concept of on-demand asthma treatment,

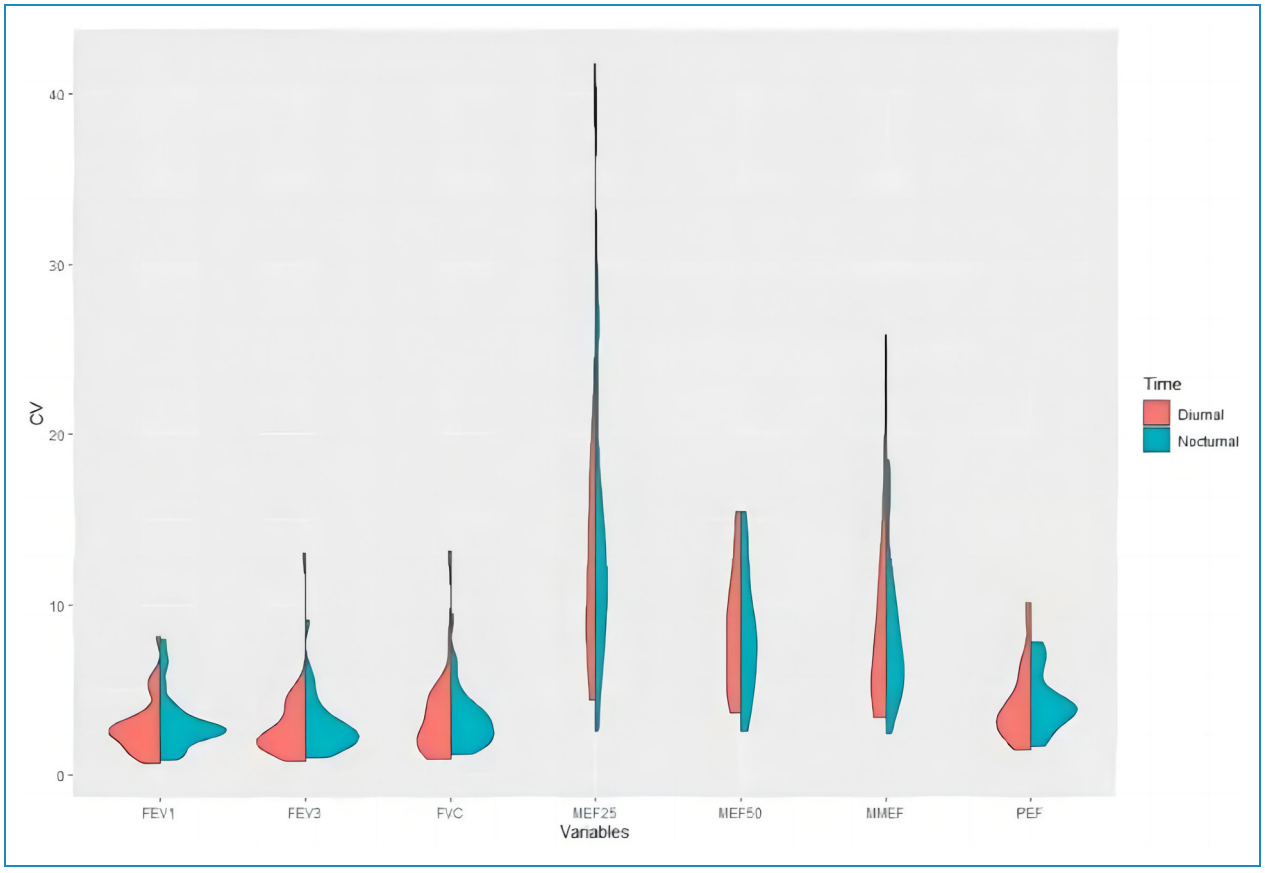

Figure 4. The diurnal CVs and nocturnal CVs of GOSPT2000 spirometry indicators for seven days.
The CV was 2.72% (diurnal) and 2.87% (nocturnal) for FVC, 2.57% (diurnal) and 2.76% (nocturnal) for FEV_1, 2.18% (diurnal) and 2.59% (nocturnal) for FEV_3. For MEFs, the CV was 8.59% (diurnal) and 8.31% (nocturnal) for MEF50, 10.91% (diurnal) and 11.89% (nocturnal) for MEF25 and 7.19% (diurnal) and 7.22% (nocturnal) for MMEF. The CV of PEF was 3.52% (diurnal) and 4.0% (nocturnal), respectively.
MMEF: maximum mid-expiratory flow; CV: coefficient of variance; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; PEF: peak expiratory flow.

particularly for mild asthma, is garnering increased attention. However, patients often misjudge the timing for starting or stopping on-demand treatment due to a deficient understanding of their symptoms, leading to overtreatment or undertreatment. For instance, adjusting medication timing based on individual diurnal patterns could enhance treatment efficacy. Third, the study's results could inform public health initiatives aimed at lung health, especially in educating the public about the importance of lung function monitoring and the potential benefits of early detection of changes in lung function. By delineating the range of circadian rhythm variations and day–night spirometric variable fluctuations in healthy individuals, we provide a reliable reference for the pathological fluctuation thresholds in asthma patients. What's more, the study opens avenues for further research, especially in exploring the mechanisms underlying the greater variability in small airways and the clinical significance of these findings in the context of early disease detection and management.

While the study provides valuable insights, there are limitations to consider. The sample size, though adequate for this study, could be expanded in future research to include a more diverse population, including the pediatric population. Additionally, extending the monitoring period beyond seven days might provide more comprehensive data on lung function variability.

Conclusions

This study significantly advances our understanding of lung function variability, particularly highlighting the circadian rhythm influences on large and small airway measurements. The inquiry arises as to whether the criterion for diagnosing asthma in bronchodilator testing, which necessitates an increase in FEV_1 of 12% or more, is reasonable, particularly in light of the study's finding of a nocturnal CV for FEV_1 less than 4%. What's more, our findings emphasize greater variability in small-airway variables, suggesting a higher variability threshold for them in asthma diagnosis. These insights offer important clinical implications for early disease detection and personalized treatment strategies, emphasizing the need for regular lung function

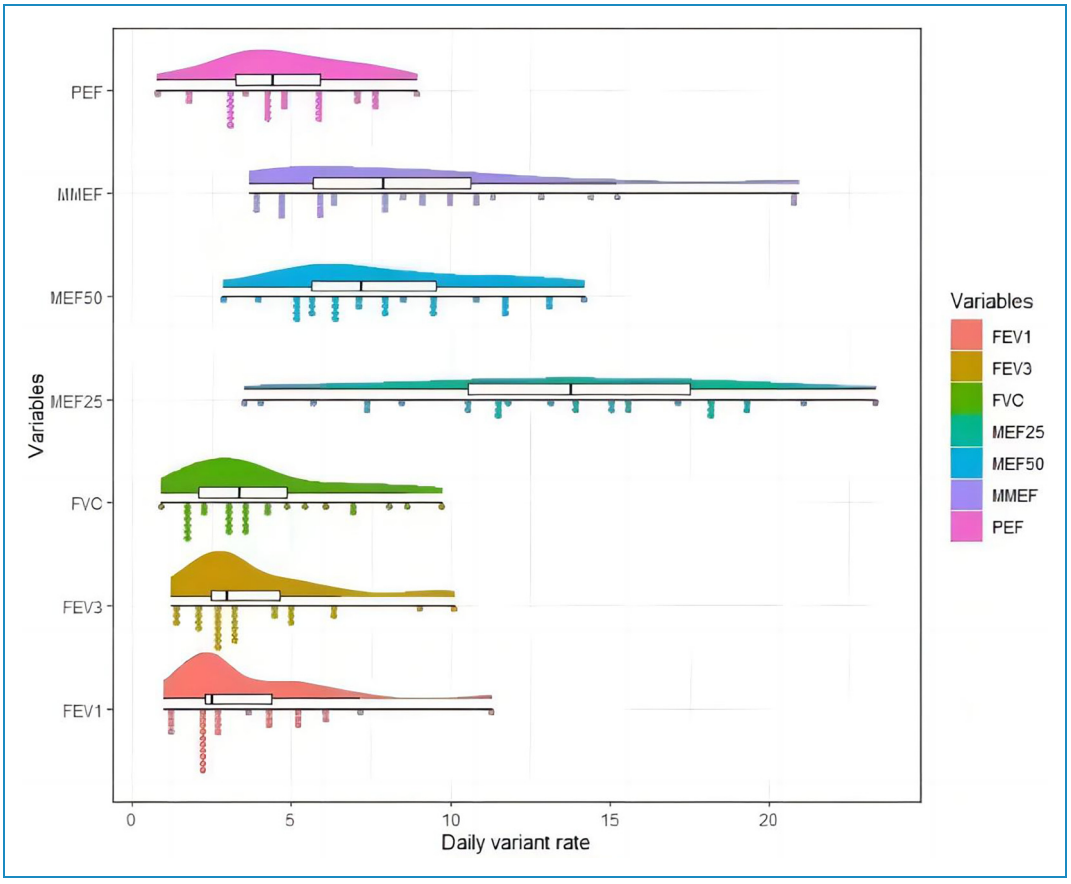

Figure 5. The daily variation rate of variables by GOSPT2000.
The daily variation rate was 3.393% for FVC (IQR 2.016%–5.133%), 2.5% for FEV_1 (IQR 2.248%–4.722%), 2.983% for FEV_3 (IQR 2.365%–4.732%), 7.196% for MEF50 (IQR 5.628%–10.15%), 14.04% for MEF25 (IQR 10.55%–18.34%), 7.886% for MMEF (IQR 5.233%–10.81%) and 4.434% for PEF (IQR 3.211%–5.999%). MMEF: maximum mid-expiratory flow; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; PEF: peak expiratory flow; IQR: interquartile range.

monitoring. Furthermore, our results reinforce the potential utility of home-based spirometry in providing precise, long-term variability data, crucial for effective asthma management and treatment optimization.

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Guarantor: WPB.

Contributorship: MZ, WPB, XZ, and YYZ conceptualized and designed the study. WPB and XZ searched the literature. CJL, JWL, and YYZ acquired the data. WPB, XZ, LZ, YTW, YML, and MZ verified the data. WPB independently did the statistical analyses. MZ verified the statistical analyses. An external mathematical statistician verified all data and statistical analyses. YYZ, YTW, XZ, WPB, and MZ drafted the manuscript. All authors approved the final version of the manuscript.

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References

1. Available at: https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf.
2. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet* 2018; 392: 1789–1858.
3. Clark TJ. Diurnal rhythm of asthma. *Chest* 1987; 91: 137S–141S.
4. Hetzel MR and Clark TJ. Comparison of normal and asthmatic circadian rhythms in peak expiratory flow rate. *Thorax* 1980; 35: 732–738.
5. Kelly EA, Houtman JJ and Jarjour NN. Inflammatory changes associated with circadian variation in pulmonary function in subjects with mild asthma. *Clin Exp Allergy* 2004; 34: 227–233.
6. Wang R, Murray CS, Fowler SJ, et al. Asthma diagnosis: into the fourth dimension. *Thorax* 2021; 76: 624–631.
7. Sutherland ER. Nocturnal asthma. *J Allergy Clin Immunol* 2005; 116: 1179–1187.
8. Kraft M, Pak J, Martin RJ, et al. Distal lung dysfunction at night in nocturnal asthma. *Am J Respir Crit Care Med* 2001; 163: 1551–1556.
9. Calhoun WJ. Nocturnal asthma. *Chest* 2003; 123: 399S–405S.
10. Bao W, Zhang X, Lv C, et al. The value of fractional exhaled nitric oxide and forced mid-expiratory flow as predictive markers of bronchial hyperresponsiveness in adults with chronic cough. *J Allergy Clin Immunol Pract* 2018; 6: 1313–1320.
11. Bao W, Zhang X, Yin J, et al. Small-airway function variables in spirometry, fractional exhaled nitric oxide, and circulating eosinophils predicted airway hyperresponsiveness in patients with mild asthma. *J Asthma Allergy* 2021; 14: 415–426. Published 2021 Apr 21.
12. Hao H, Bao W, Xue Y, et al. Spirometric changes in bronchodilation tests as predictors of asthma diagnosis and treatment response in patients with FEV1 $\geq$ 80% predicted. *J Allergy Clin Immunol Pract* 2021; 9: 3098–3108.e4.
13. Jain VV, Allison R, Beck SJ, et al. Impact of an integrated disease management program in reducing exacerbations in patients with severe asthma and COPD. *Respir Med* 2014; 108: 1794–1800.
14. van den Berge M, ten Hacken NH, van der Wiel E, et al. Treatment of the bronchial tree from beginning to end: targeting small airway inflammation in asthma. *Allergy* 2013; 68: 16–26.
15. van der Wiel E, Postma DS, van der Molen T, et al. Effects of small airway dysfunction on the clinical expression of asthma: a focus on asthma symptoms and bronchial hyperresponsiveness. *Allergy* 2014; 69: 1681–1688.
16. Borsboom GJ, van Pelt W, van Houwelingen HC, et al. Diurnal variation in lung function in subgroups from two Dutch populations: consequences for longitudinal analysis. *Am J Respir Crit Care Med* 1999; 159: 1163–1171.
17. Spengler CM and Shea SA. Endogenous circadian rhythm of pulmonary function in healthy humans. *Am J Respir Crit Care Med* 2000; 162: 1038–1046.
18. Goyal M, Goel A, Bhattacharya S, et al. Circadian variability in airways characteristics: a spirometric study. *Chronobiol Int* 2019; 36: 1550–1557.
19. Goyal M, Goel A, Kumar P, et al. Circadian rhythm of peak expiratory flow rate in healthy north Indian men. *Indian J Physiol Pharmacol* 2008; 52: 64–68.
20. Freund O, Rotem-Green M, Rahat M, et al. Nanoparticles in induced sputum - a window to airway inflammation among active smokers. *Nanomedicine (Lond)* 2023; 18: 303–315.
21. Zhang X, Zhang Y, Zhou Y, et al. Age-related circadian rhythm and variability of large- and small-airway function in healthy non-smoking adults: data from 7-day diurnal and nocturnal home monitoring using an electronic portable spirometer. *Front Public Health* 2022; 10: 946988.
22. Akinbami LJ, Salo PM, Cloutier MM, et al. Primary care clinician adherence with asthma guidelines: the national asthma survey of physicians. *J Asthma* 2020; 57: 543–555.
23. Cabana MD, Rand CS, Becher OJ, et al. Reasons for pediatrician nonadherence to asthma guidelines. *Arch Pediatr Adolesc Med* 2001; 155: 1057–1062.
24. Cloutier MM, Salo PM, Akinbami LJ, et al. Clinician agreement, self-efficacy, and adherence with the guidelines for the diagnosis and management of asthma. *J Allergy Clin Immunol Pract* 2018; 6: 886–894.e4.
25. Hegewald MJ, Crapo RO and Jensen RL. Intraindividual peak flow variability. *Chest* 1995; 107: 156–161.
26. Lebowitz MD, Knudson RJ, Robertson G, et al. Significance of intraindividual changes in maximum expiratory flow volume and peak expiratory flow measurements. *Chest* 1982; 81: 566–570.