# Cough frequency has a high daily variation in patients with chronic cough



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*To the Editor:*

Chronic cough (coughing lasting 8 weeks or longer) is a burdensome disease, causing low quality of life due to the disruption that frequent coughing causes to daily life [1–3]. Its prevalence is estimated to be 10% of the global population [4]. Chronic cough can be due to underlying conditions such as asthma and COPD, or can persist despite treatment (refractory chronic cough) or have unidentified origins (unexplained chronic cough) [5, 6]. Due to its prevalence and lack of effective treatments, there is high interest in developing drugs for refractory and unexplained chronic cough. Cough frequency, represented as coughs per hour measured over 24 h or awake time, has been used as a key endpoint in multiple clinical drug trials [7, 8].

The most commonly used equipment for such cough frequency assessment involves a device worn on the patient's hip with wires connecting to a lapel microphone and a microphone placed near the patient's neck [9]. After a standard 24-h measurement period, the recording is compressed by removing silent parts and trained human listeners aurally count the coughs. Due to the size of the equipment and the manual counting procedure, this cough frequency measurement is often limited to a few days during treatment. Such a snapshot approach may lack the statistical power to detect clinically meaningful differences if a high variability of daily cough frequency is present.

Due to a lack of alternative methods, there is limited data on the variability of cough frequency in chronic cough patients. Here, we report an analysis of the variability of cough frequency over 2 weeks from an ongoing clinical study using an automatic continuous cough monitoring system.

36 patients with chronic cough (those with cough that has lasted for at least 12 months and been persistent for the previous 8 weeks, and are considered to have refractory chronic cough), mean age 66 years, two-thirds female, took part in an observational clinical study (NCT05689307) for the SIVA Cough Monitoring System. As part of this system, patients wore a small wearable device around their neck during the day and placed it on a wireless charger near their bed for nighttime, where the device continued monitoring their cough. The SIVA Cough Monitoring System detects the exact time stamps of the cough explosions from audio data using a neural network-based cough detection algorithm. The cough algorithm used in this study relies on an improved version of the clinically validated version [10].

To ensure that we only analyse sufficiently representative days, a minimal wearing time of 8 h (device worn around the neck of the patient during daily activities) was defined, and days with fewer hours were excluded from the analysis. The data collected by the device's internal accelerometer is used to exclude measurement periods where the device was not on the charger and not worn by the patient. A minimum of three measured days were required for a patient to be included in the analysis. The daily cough frequency was calculated as the total number of coughs per day divided by hours of measured data. The daily cough frequency data was normally distributed so parametric analysis is reported.

We analysed 436 days of cough frequency measurements with a median of 13.5 days per patient (range 3–15 days) and a median wearing time of 12.79 h (range 9.65–14.48 h). Total median active time of 22.82 h (range 18.66–24.00 h). The mean±SD cough frequency was 11.62±9.74 coughs·h$^{-1}$, with a median of 6.98 coughs·h$^{-1}$ (range 1.30–33.56 coughs·h$^{-1}$).

Shareable abstract (@ERSpublications)
**Continuous cough monitoring using a wearable device analysed by machine learning for automated cough detection has revealed considerable day-to-day variability in cough counts. Single-day recording is thus subject to error.** https://bit.ly/3yYCRbX

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To analyse the variability of cough frequency, we calculated the standard deviation of the cough frequency over all the days for each patient. The mean standard deviation over all patients was 3.69±3.15 coughs·h$^{-1}$ with a median standard deviation of 2.78 (range 0.49–14.03 coughs·h$^{-1}$), as shown in figure 1. The mean relative standard deviation was 37.27±15.08% with a median value of 38.10% (range 10.45–89.43%).

To provide a more intuitive insight into the day-to-day variability of cough frequency, we calculated the average absolute deviation (AAD) of the daily cough frequency for each patient. The mean AAD over all patients is 2.90±2.54 coughs·h$^{-1}$ with a median ADD of 2.22 coughs·h$^{-1}$ (range 0.37–11.48 coughs·h$^{-1}$). The average relative AAD (AAD/mean) over all the patients is 28.19±9.51%, with a median of 28.89% (range 8.68–48.84%). Assuming that the average cough frequency best estimates the patient's cough load during the measurement period, the AAD shows that any single-day measurement would on average, be off by 2.90 coughs·h$^{-1}$ or 28.19% with regards to the best estimate.

This analysis shows a high daily variability of cough frequency among patients suffering from chronic cough. Thanks to the development of compact wearable devices and machine-learning approaches for automatic cough detection, cough frequency monitoring has become feasible over extended periods. This is the first dataset involving up to 2 weeks of continuous cough count measurements in chronic cough patients captured with a wearable device with a fixed wearing position. Prior studies have estimated the variability in daily cough frequency among mainly young, healthy individuals [11]; patients suffering from choring cough [12]; or patients suffering from tuberculosis [13], using an application running on a smartphone. Data collected with a smartphone can be intermittent due to difficulties in fixing the smartphone's location and lack of patient compliance for carrying the smartphone in a visible position where the phone's microphone can reliably capture cough sounds. Despite the limitation, these studies have observed high daily variability in cough frequency and support the need for continuous cough measurements to assess the patient's cough count with sufficient accuracy.

These observations have limitations. They are derived from single clinic in the USA and clearly some patients were in a quiescent phase of their illness. Such low cough counts would, however, tend to decrease the observed variability rather than exaggerate it. A larger dataset consisting of patients with different diseases, healthy individuals, and varying demographics should be included for a comprehensive understanding of cough variability. Additionally, the data gathered with automatic cough detection approaches rely on the cough

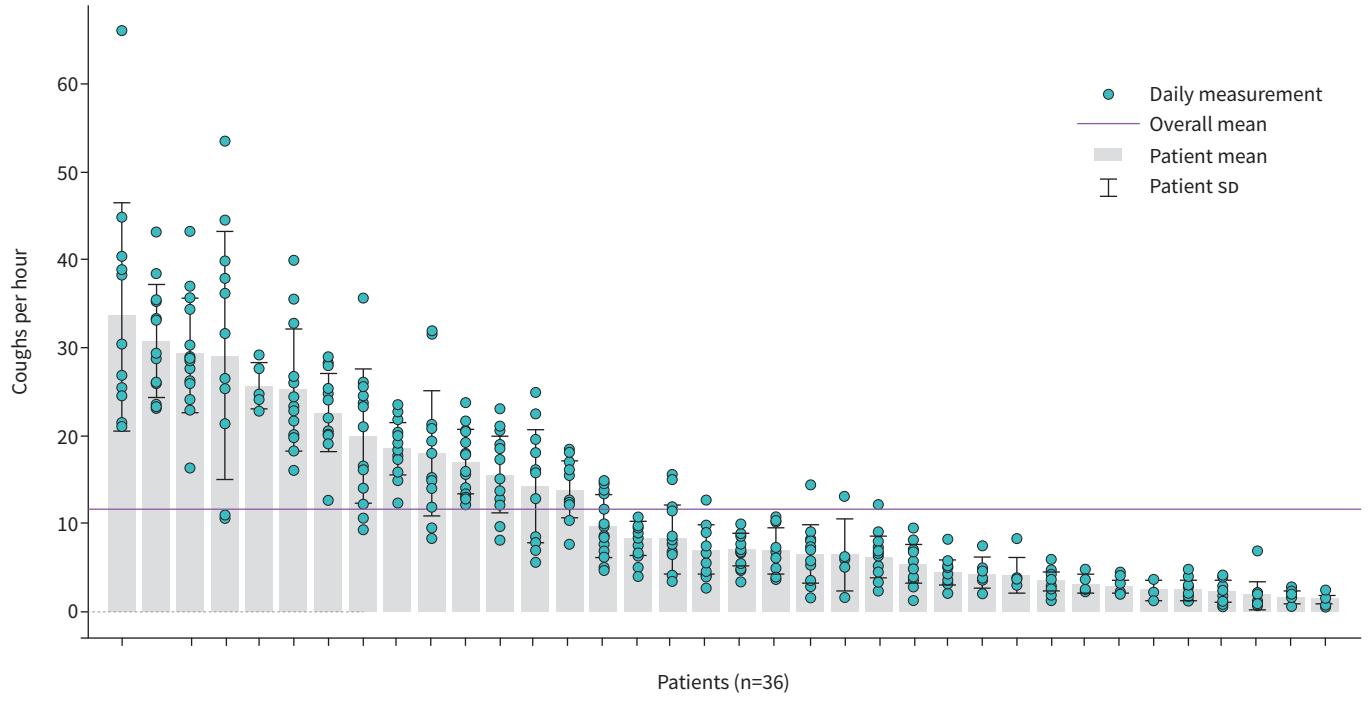


FIGURE 1 Daily cough frequency. The daily measured cough frequency (24 h) for all patients (n=36) ordered by mean cough frequency. Each blue dot represents a measurement of a single day. The grey bars and the error lines show the mean and SD of the cough frequency of a patient.

algorithm's performance. The system used in this study relies on an improved version of a clinically validated cough algorithm [10], and it has been recently approved as a class IIa medical device in the EU (according to the Medical Device Regulation (EU) 2017/745).

This analysis exemplifies the need for considering daily cough frequency variability in clinical trial endpoints. Additionally, given that previous drug trials aimed to demonstrate a 30–40% improvement from baseline [7, 14], using multi-day continuous measurements may enable detection of efficacy despite inherently high variability in daily measurements. Similarly, this analysis highlights the potential for assessing cough over multiple days in clinical settings for in a wide variety of respiratory disease.

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Conflict of interest: A. Morice has received consulting fees from Bellus, Merck, NeRRi, Trevi; lecture fees from Merck; and grant support from Bellus, Merck, Nocion, Philips, NeRRi and Trevi. He is founder and CEO of Tussogenics Ltd and holds a share option with SIVA Health. He is an associate editor of this journal. M. Alge and L. Kuett are employees of SIVA Health. S. Hart and A. Rigby are associate editors of this journal. D. Elkayam has received grant support from SIVA Health.

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