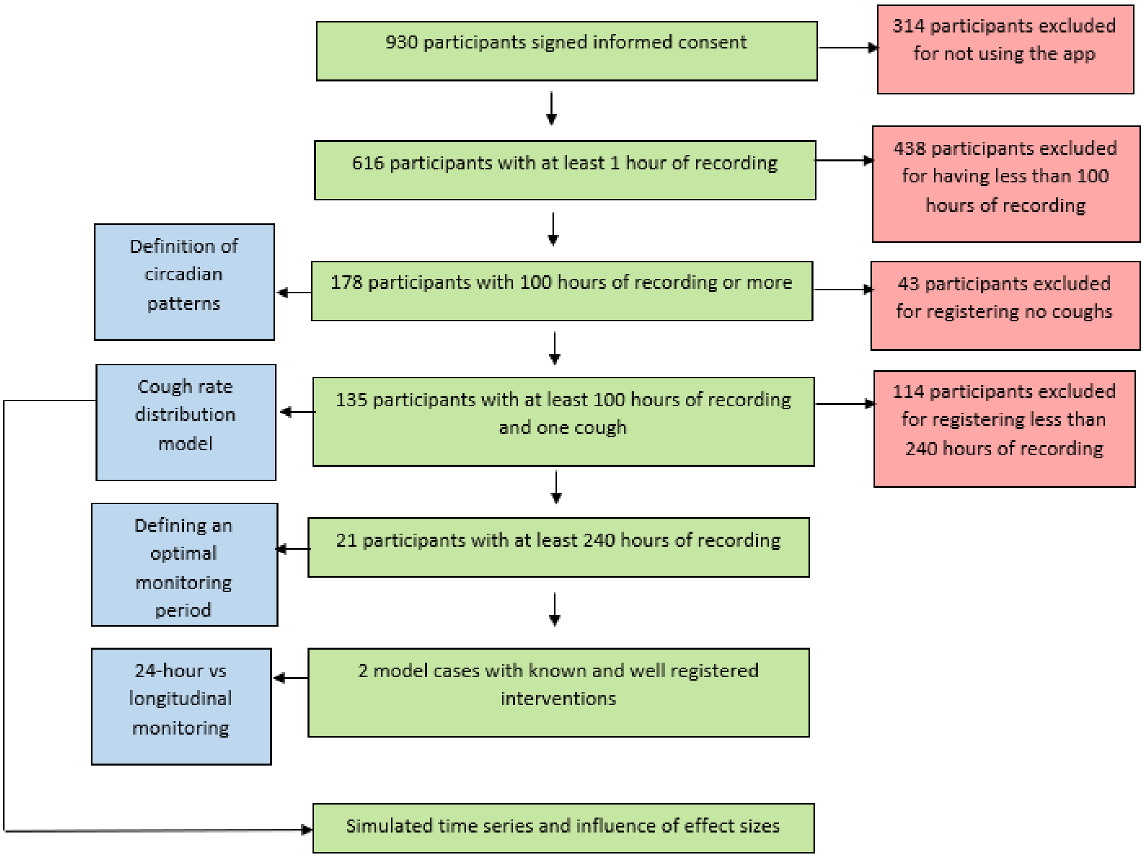
Supplementary material

Contents

E-Figure 1: Participant flow chart and demographic characteristics



Participant flowchart: After excluding participants based on their limited adoption of the cough recording protocol (red boxes) different subgroups of participants (green boxes) were used for specific analyses (blue boxes), based on the number of hours they used Hyfe Cough tracker to monitor their cough frequency.

Changes in cough frequency based on self-reported history of respiratory disease

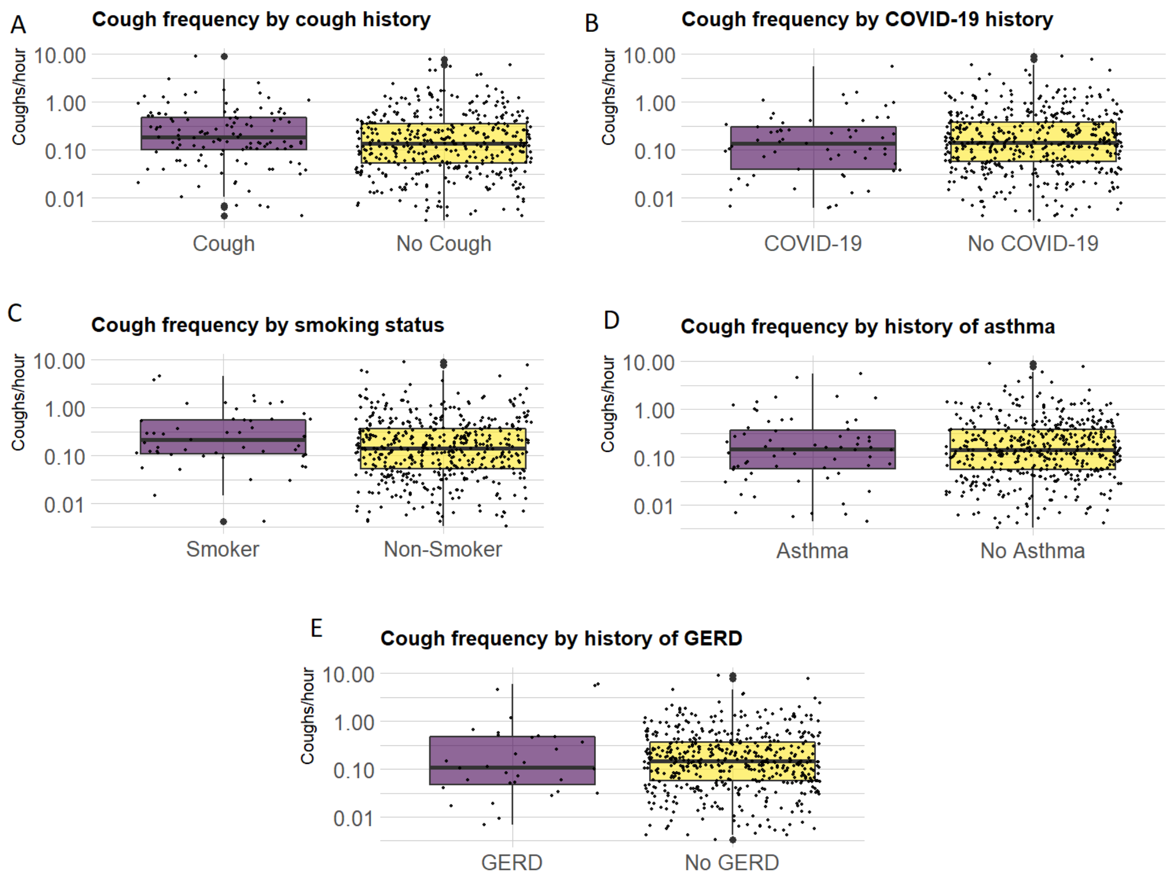
The hourly cough frequency of participants who self-reported having a history of any of the respiratory diseases or symptoms listed in E-Table 1 was compared. Since each participant could have reported having more than one respiratory disease, individual comparisons were performed between those participants who reported having each individual condition and those who did not. While participants who reported having a history of acute or chronic cough, asthma, GERD, and smokers had higher cough frequencies, these differences were not statistically significant (E-table 1, E-figure 2).

E-Table 1: Cough frequency of participants with self-reported medical history

Self-reported condition	**n**	**Mean coughs/hour**	***P* value**
Cough (acute or chronic)			
Yes	138	0.38	
No	478	0.31	0.39
COVID-19			
Yes	73	0.28	
No	543	0.32	0.61
Smoker			
Yes	67	0.40	
No	549	0.32	0.40
Asthma			
Yes	70	0.41	
No	546	0.31	0.40
GERD			
Yes	35	0.63	
No	581	0.31	0.20

GERD: Gastroesophageal Reflux Disease.

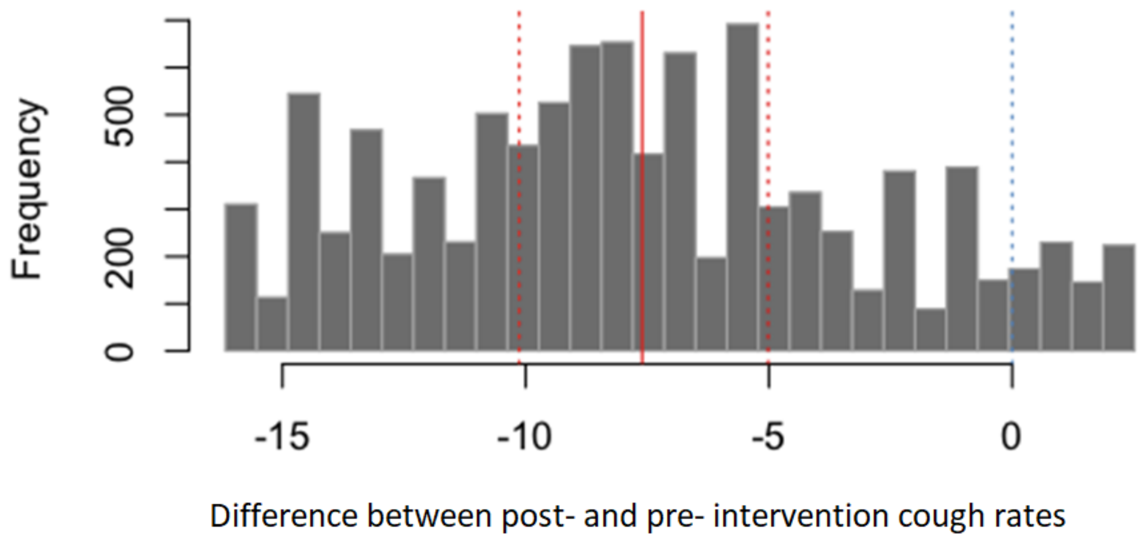
E-Figure 2:



Cough frequency of participants with different self-reported baseline conditions. A: Acute or chronic cough, B: COVID-19, C: Smoking habit, D: asthma, E: Gastroesophageal reflux (GERD).

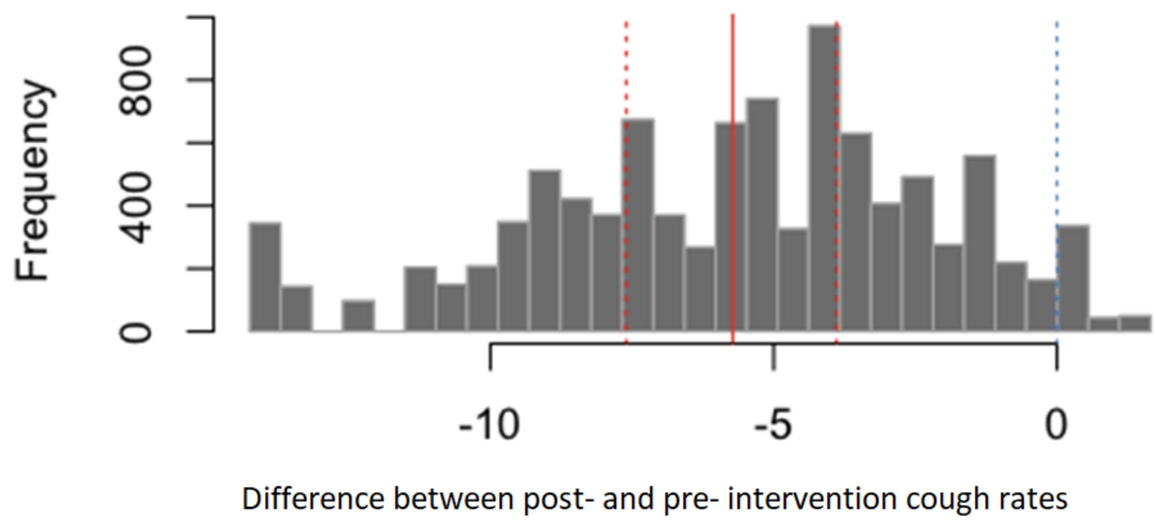
Randomization routine for illustrative case 1

E-Figure 3



Randomization routine for illustrative case 1 following the beginning of treatment with Gabapentin: The red, continuous line represents the true effect size as determined by longitudinal monitoring. Dotted red lines signal the 95% CI of true effect size as determined by iterative bootstrapping of the longitudinal record. The fraction of observations in the distribution outside of dotted red lines are the failure rate for estimating the effect size, while the fraction of observations above zero (dotted blue line) represent the failure rate for estimating that there is an effect (a reduction in cough rates following treatment with Gabapentin).

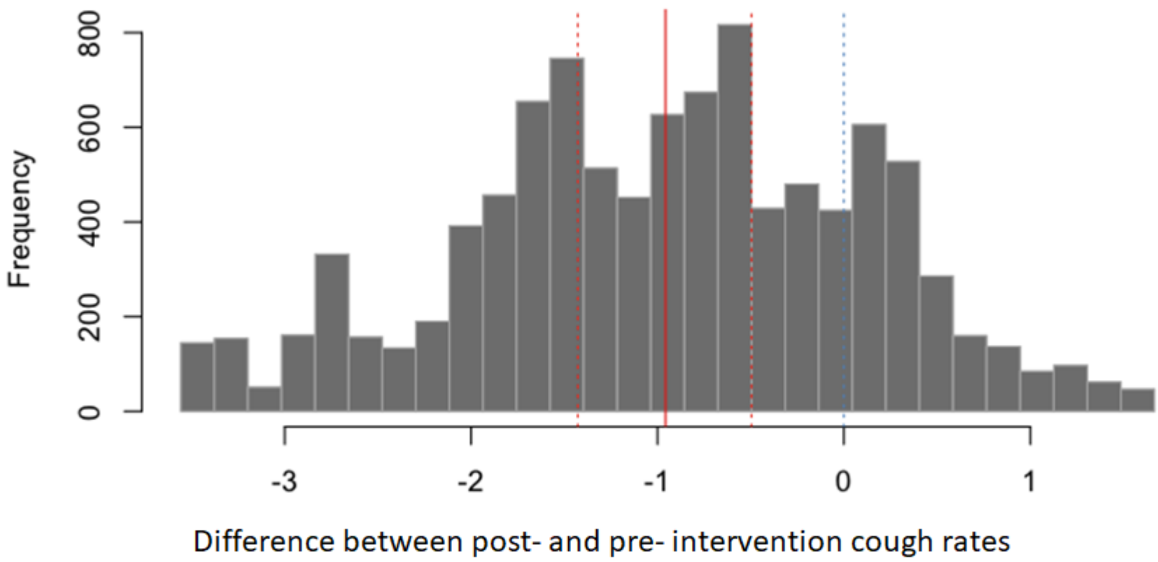
E-Figure 4



Randomization routine for illustrative case 1 following the beginning of treatment with Omeprazole: The red, continuous line represents the true effect size as determined by longitudinal monitoring. Dotted red lines signal the bootstrap 95% CI of true effect size. The fraction of observations in the distribution outside of dotted red lines are the failure rate for estimating the effect size, while the fraction of observations above zero (dotted blue line) represent the failure rate for estimating that there is an effect (a reduction in cough rates following treatment with Omeprazole).

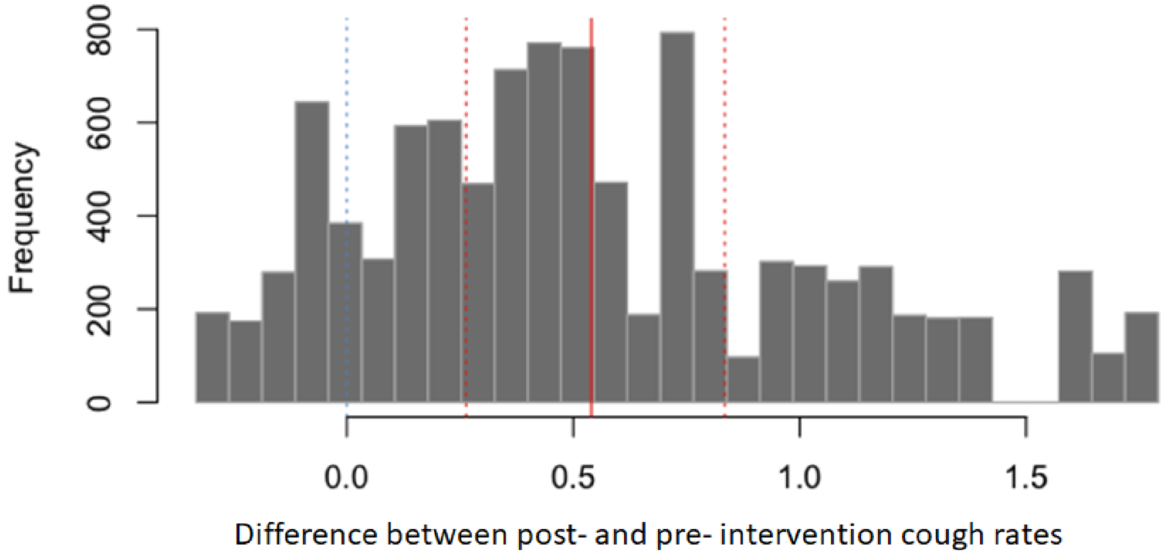
Randomization routine for illustrative case 2

E-Figure 5



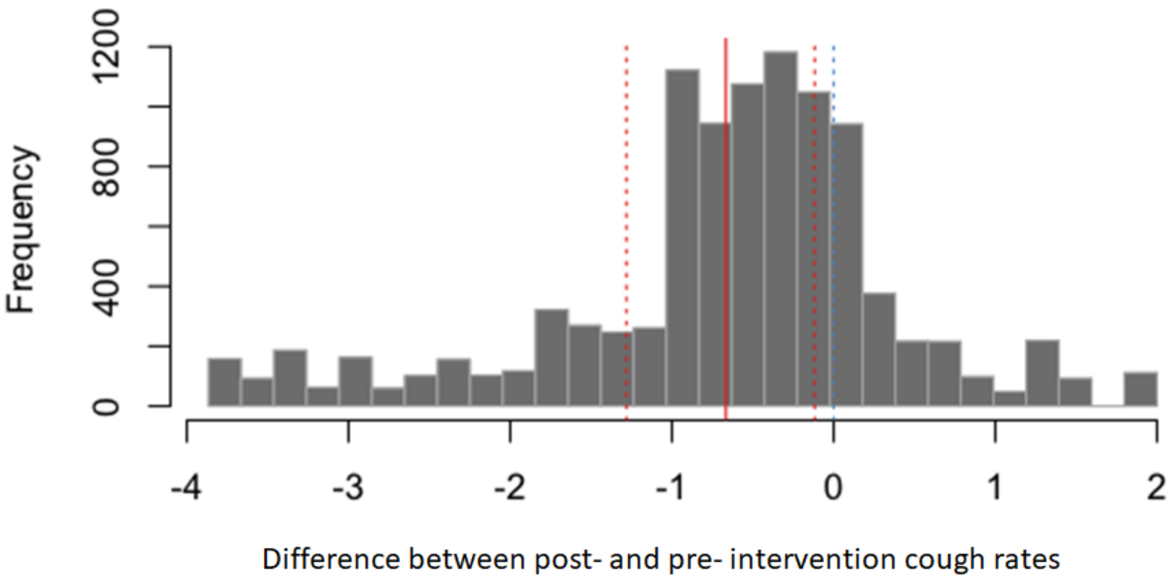
Randomization routine for illustrative case 2's first smoking cessation event: The red, continuous line represents the true effect size as determined by longitudinal monitoring. Dotted red lines signal the bootstrap 95% CI of true effect size. The fraction of observations in the distribution outside of dotted red lines are the failure rate for estimating the effect size, while the fraction of observations above zero (dotted blue line) represent the failure rate for estimating that there is an effect (a reduction in cough rates following smoke cessation).

E-Figure 6



Randomization routine for case 2's smoking relapse: The red, continuous line represents the true effect size as determined by longitudinal monitoring. Dotted red lines signal the bootstrap 95% CI of true effect size. The fraction of observations in the distribution outside of dotted red lines are the failure rate for estimating the effect size, while the fraction of observations below zero (dotted blue line) represent the failure rate for estimating that there is an effect (an increase in cough rates following the relapse).

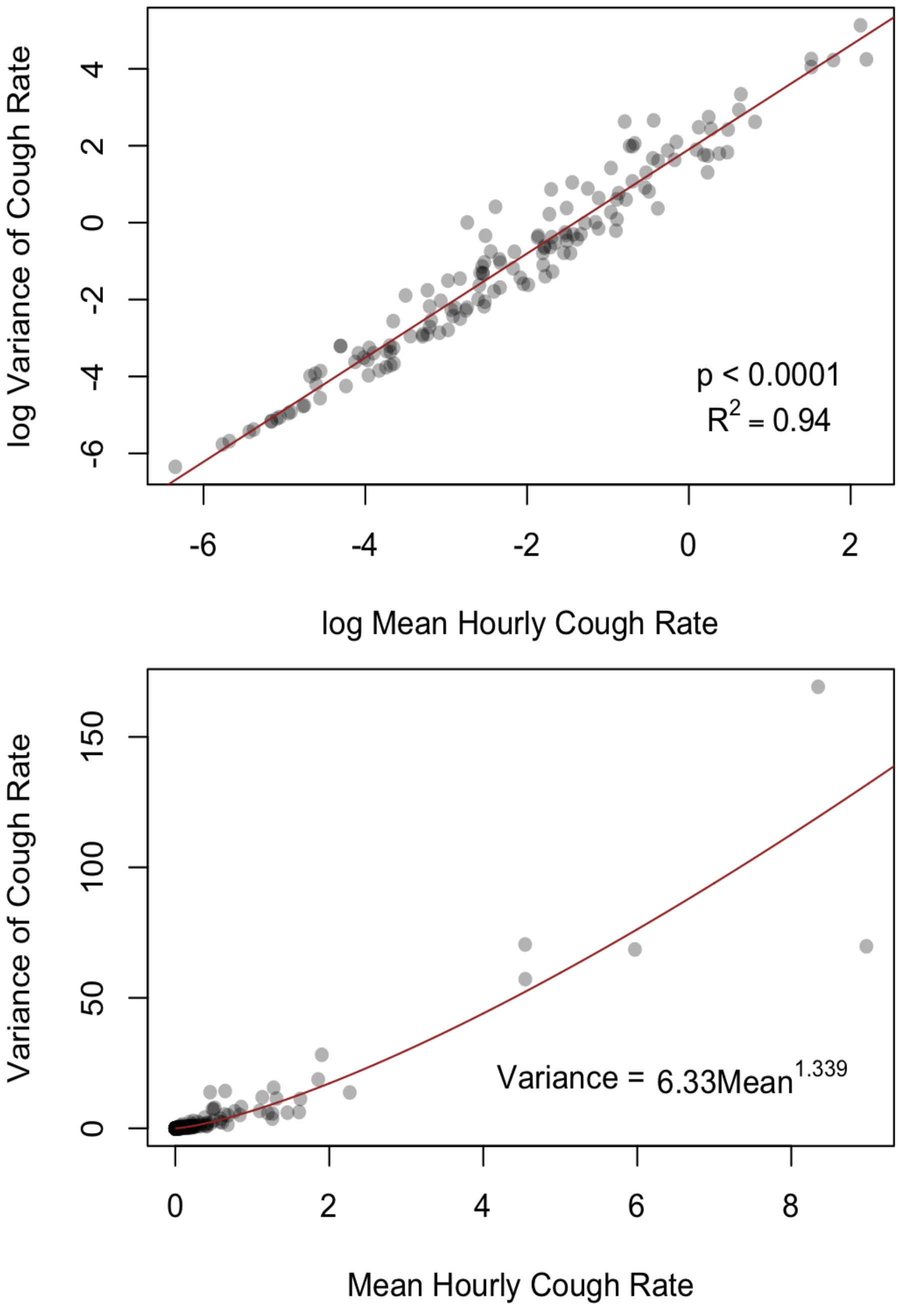
E-Figure 7



Randomization routine for illustrative case 2's second smoking cessation event: The red, continuous line represents the true effect size as determined by longitudinal monitoring. Dotted red lines signal the bootstrap 95% CI of true effect size. The fraction of observations in the distribution outside of dotted red lines are the failure rate for estimating the effect size, while the fraction of observations above zero (dotted blue line) represent the failure rate for estimating that there is an effect (a reduction in cough rates following smoke cessation).

Linear relationship between mean cough rate and variance

E-Figure 8



Linear relationship between mean cough rate and variance in participants with at least 100 hours of records and at least one cough

Full medical history of illustrative cases

Illustrative Case 1: Unexplained chronic cough

A 56-year-old female with no history of tobacco use or occupational exposures, was enrolled in the cohort on January 29, 2021 and started using the cough tracking app systematically throughout the day. Her only previous diagnosis was iron deficit anemia due to heavy menstrual bleeding treated with a levonorgestrel-releasing intrauterine device. She used no other medication beyond multivitamins, omega-3 supplements and eye drops.

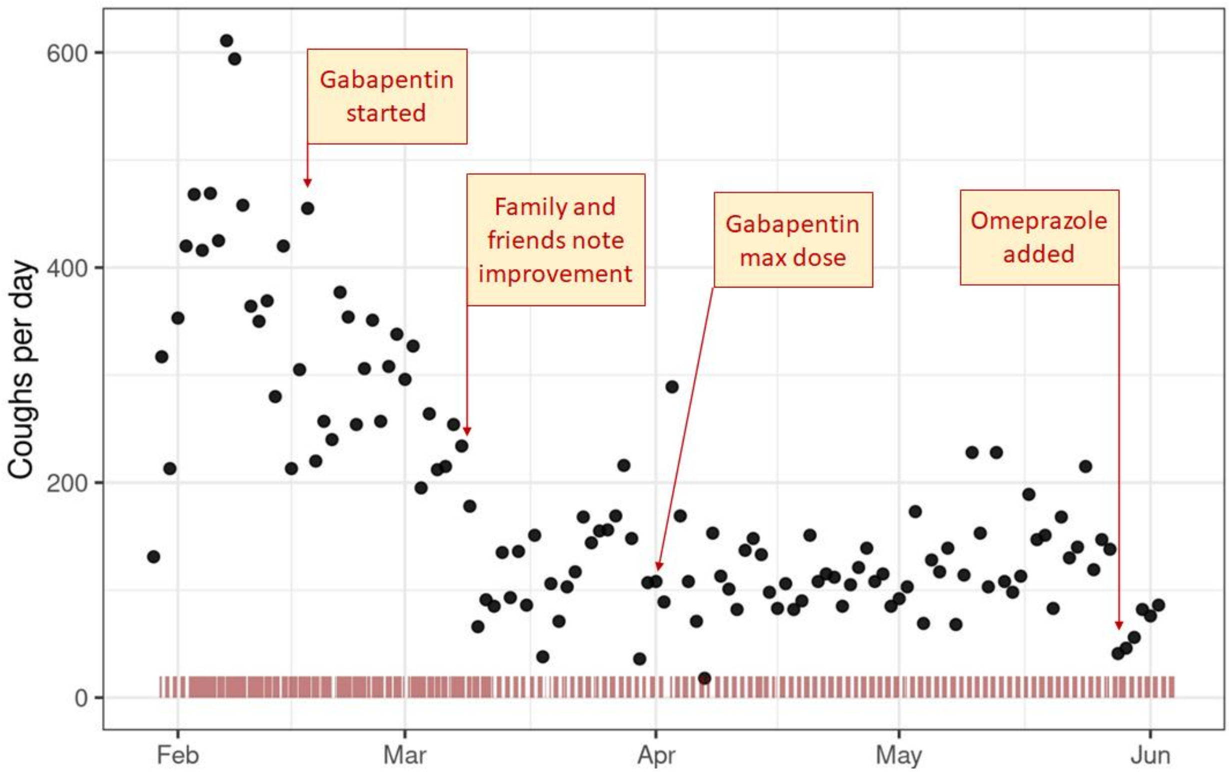
She started coughing during the winter of 2016. The cough was initially dry and associated with pharyngeal itching. These episodes lasted for a few days and were intercalated with periods of 1-2 weeks free of cough. By 2019, these episodes had increased in frequency and intensity. She reported never coughing at night, not even when waking up to urinate. She was evaluated by her primary care physician who conducted the following tests:

- Full spirometry and bronchodilator test: normal results
- Methacholine challenge: normal results
- Allergy skin tests: negative
- 24-h esophageal pH monitoring: normal
- Gastroscopy: normal
- Head and neck CT scan: normal
- Laboratory tests including full blood count, erythrocyte sedimentation rate, C-reactive protein, renal function, liver enzymes: within normal range

In January 2020, her primary care physician conducted a therapeutic test with Omeprazole 40 mg OD for a month, which resulted in discreet and transient improvement. She reported that her usual cough pattern returned after two weeks. In November 2020, she contracted uncomplicated COVID-19 with mild symptoms lasting for about five days, resulting in no perceived change in her baseline cough afterwards. At this stage, her cough frequency was limiting her capacity to use public transport given apprehension from other riders during the pandemic.

In February 2021, having heard about the study, she approached the research team hoping to get some insight about her cough. The app detected up to 600 coughs a day (around 25 coughs per hour of recording) (E-Figure 8). The pattern was indeed diurnal with almost no coughs occurring in the time window 1-7 am (her usual bedtime is at midnight) (Supplementary material). She was referred to the University of Navarra Clinic where the treatment guidelines for unexplained chronic cough were followed. Her work-up was completed with a thoracic CT scan, which revealed no significant findings, and a therapeutic trial of gabapentin was started on February 17. The starting dose of 300 mg was increased gradually to improve her tolerance as she presented some dizziness. By March 30, she reached full dosing of 900 mg twice a day. Her coughs were reduced to 150 per day (around 10 per hour of recording), and family, friends and co-workers commented on her noticeable improvement. On May 27, her cough remained unaltered (an average of eight per hour of recording throughout April and May), at this point, in spite of the absence of cough during the night, given the history of transient improvement with Omeprazole in 2020, a course of Omeprazole 40 mg OD was started on May 28 with considerable additional improvement recording about 50 coughs a day suggesting a potential multi-factorial origin for her problem. She reports a greatly improved quality of live as her cough was no longer a distinctive feature in her daily interactions with other people. She completed a three-month course of gabapentin and at full dose and Omeprazole before tapering it. After tapering the gabapentin her cough increased again (see August 2021 in Figure 5 of the main manuscript) and she restarted a second course of gabapentin with positive results.

E-Figure 9



E-Figure 8. Black lines show total coughs recorded every day. Red bars mark the App session times.

Illustrative Case 2: Smoking cessation and relapse

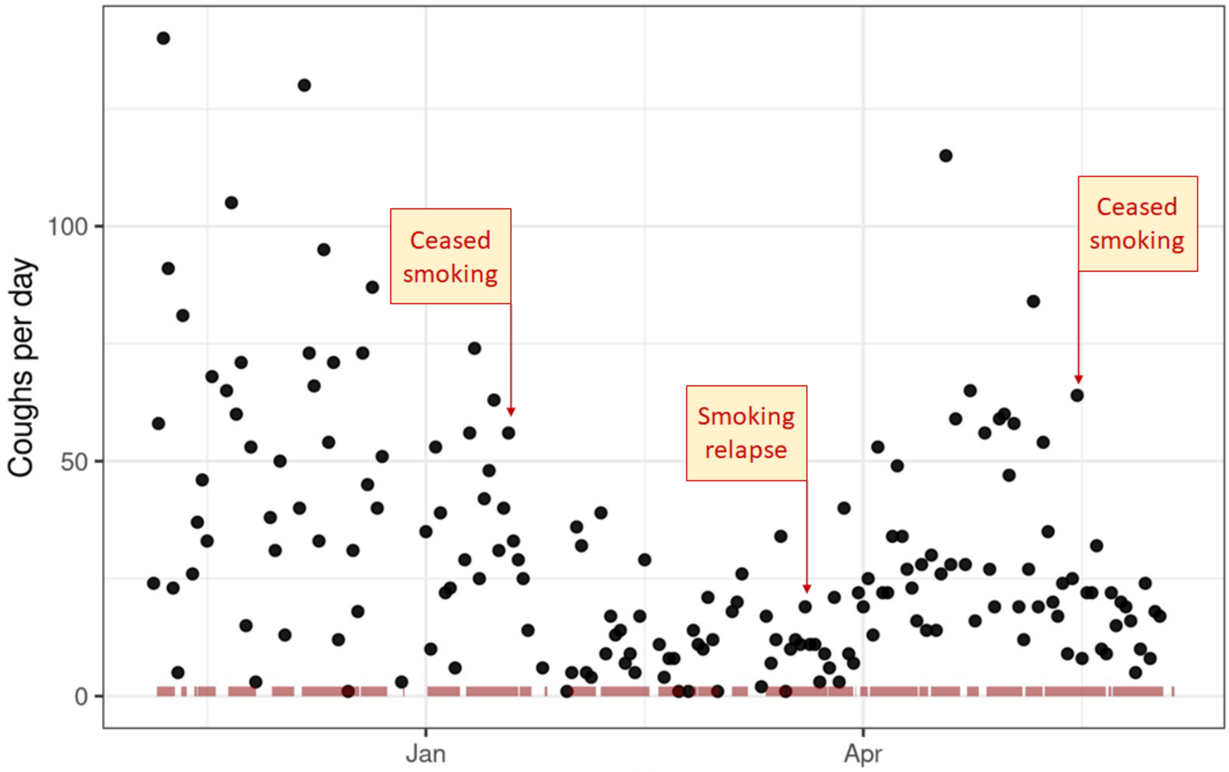
A 70-year-old female retired nurse, was enrolled in the cohort on November 6, 2020 and started using the cough tracking app systematically throughout the day. Her past medical history revealed two to three episodes of upper respiratory tract infections per year. These episodes usually led to 15-20 days of non-productive cough associated with pharyngeal itching. Between episodes, she reported a dry cough that was not remarkable in frequency or intensity to her or those around her.

She had previously smoked 20-40 cigarettes per day from age 18 to 36. She did not smoke again until she was 67 years old, when she progressively reached 20 cigarettes per day over the course of a few months. In December 2019, she had another episode of an upper respiratory tract infection after which she did not return to her baseline dry cough but to one of noticeably higher frequency and intensity.

Upon enrolment, the app detected an average of 52 coughs per day in November and 44 in December (range 0-147 per day or 0-6.1 mean coughs per hour of monitoring). On January 18, 2021, she and her husband decided to quit smoking together. She was prescribed nicotine patches (starting with 21 mg/daily for 14 days and tapering to 14 mg/daily for 28 days) and she successfully quit smoking. She subjectively noticed improvement in her cough. This was quantified by the cough tracking app, which showed that her average number of coughs per day went down to 12 in February and March (Range 0-39 per day or 0-1.3 mean coughs per hour of monitoring) (E-Figure 9).

By March 20, she had tapered her nicotine dose to 7 mg/day and relapsed her smoking habit with an average of five cigarettes per day, sporadically reaching a full pack during recreative activities. This was paralleled by an increase in self-perceived coughing also quantified by the app. Her average coughs per day tripled in April to reach 34 (ranging 12-86 or 0.5-3.6 mean coughs per hour of monitoring) (Figure 3). At this stage, although she expressed dislike of consulting her cough charts on the screen, she kept using the app.

During the first week of May, the research team noticed the objective increase in cough frequency in the dashboard and contacted her. She mentioned having noticed the temporal correlation between the smoking relapse, self-perceived increase in coughs and quantification by the app. She then had renewed motivation for smoking cessation partly influenced by the objective changes in her cough shown by the app. She resumed using the 21-mg nicotine patches and stopped smoking once again. A subsequent reduction in her coughs per day was again detected by the app.



E-Figure 10

E-Figure 9. Cough evolution and relevant relation with smoking. Black dots show total coughs recorded every day. Red bars mark the App session times. Note almost continuous recording throughout the observed period.