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Juan C. Gabaldón-Figueira, Eric Keen, Matthew Rudd, Virginia Orrilo, Isabel Blavia, Juliane Chaccour, Mindaugas Galvosas, Peter Small, Simon Grandjean Lapierre, Carlos Chaccour

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Longitudinal Passive Cough Monitoring and Its Implications for Detecting Changes in Clinical Status

Juan C. Gabaldón-Figueira M.D.[1]*	juancarlos.gabaldon@isglobal.org
Eric Keen Ph.D.[2]	eric.k@hyfe.ai
Matthew Rudd Ph.D.[2, 3]	matthew.r@hyfe.ai
Virginia Orrilo B.Sc.[4]	vorrillo@alumni.unav.es
Isabel Blavia B.Sc.[4]	iblavia@alumni.unav.es
Juliane Chaccour M.Sc.[1]	jchaccourd@unav.es
Mindaugas Galvosas M.D.[2]	mindaugas.g@hyfe.ai
Peter Small M.D. Ph.D.[2,5]	Peter.Small@stonybrookmedicine.edu
Simon Grandjean Lapierre M.D. Ph.D.[6,7†]	simon.grandjean-lapierre.chum@ssss.gouv.qc.ca
Carlos Chaccour, M.D. Ph.D.[1,8,9†]	cchaccour@unav.es

† These authors contributed equally.

*Corresponding author:

Instituto de Salud Global de Barcelona (Centre Esther Koplowitz), Rosello 153, 08036, Barcelona, Spain

[1] Department of Microbiology and Infectious Diseases, Clinica Universidad de Navarra, Pamplona, Spain

[2] Research and Development Department, Hyfe Inc, Wilmington, Delaware, USA

[3] Department of Mathematics and Computer Science, The University of the South, Sewanee, Tennessee, USA

[4] School of Pharmacy and Nutrition, University of Navarra, Pamplona, Spain.

[5]Department of Global Health, University of Washington, Seattle, WA, USA

[6] Immunopathology Axis, Research Center of the University of Montreal Hospital Center, Montréal, Québec, Canada

[7] Department of Microbiology, Infectious Diseases and Immunology, Research Center of the University of Montreal Hospital Center, Montreal, Quebec, Canada

[8] Centro de Investigación Biomédica en Red de Enfermedades Infecciosas, Madrid, Spain

[9] ISGlobal, Hospital Clinic, University of Barcelona, Barcelona, Spain.

Take home message

When compared to continuous monitoring, limiting observation to 24 hours can lead to inaccurate estimates of change in cough frequency, influenced by its mean frequency and variance. This is important when evaluating small changes in cough frequency.

Abstract

Research Question: What is the impact of the duration of cough monitoring on its accuracy in detecting changes in the cough frequency?

Materials and Methods: This is a statistical analysis of a prospective cohort study. Participants were recruited in the city of Pamplona (Northern Spain) and their cough frequency was passively monitored using smartphone-based acoustic artificial intelligence software. Differences in cough frequency were compared using a one-tailed Mann-Whitney U test and a randomization routine to simulate 24-hour monitoring.

Results: 616 participants were monitored for an aggregated duration of over 9 person-years and registered 62,325 coughs. This empiric analysis found that an individual's cough patterns are stochastic, following a binomial distribution. When compared to continuous monitoring, limiting observation to 24 hours can lead to inaccurate estimates of change in cough frequency, particularly in persons with low or small changes in rate.

Interpretation: Detecting changes in an individual's rate of coughing is complicated by significant stochastic variability within and between days. Assessing change based solely on intermittent sampling, including 24-hours, can be misleading. This is particularly problematic in detecting small changes in individuals who have a low rate and/or high variance in cough pattern.

Introduction

Cough is common in patients with respiratory diseases, and relatively rare in healthy individuals. (1) Detecting changes in its frequency is important in managing patients with cough and for evaluating novel drugs. (2, 3) An optimal objective cough monitoring period has not yet been defined (4-7), but in most clinical research settings, it remains limited to 24-hour periods. (8, 9).

While 24-hour monitoring is the most commonly used approach in clinical research, (9, 10) this strategy's ability to capture longer trends, or discontinuous changes remains unclear. Estimates of shorter cough frequency can be confounded by circadian changes (11, 12).

Recent progress in the field of artificial intelligence (AI) has enabled the development of tools to unobtrusively monitor cough over protracted periods of time. This includes smartphone-based applications that employ acoustic artificial intelligence to detect and track cough. We recently reported the use of one such tools to monitor cough among the inhabitants of Pamplona, Spain. (13) We now present a statistical analysis of the data collected in that cohort and explore its implications for patient care and drug development.

In this study we aim to determine the impact that the duration of cough monitoring has in the capacity to detect changes in its frequency, and hypothesise that, given the stochastic nature of cough, protracted longitudinal monitoring could provide more representative estimates of its frequency.

Methods

Study subjects

The data used for this analysis is from participants in a cohort study conducted in the city of Pamplona (northern Spain), as well as the University of Navarra's students and staff between fall 2020 and fall 2021. The aim of the study was to assess the potential correlation between the local

incidence of respiratory diseases and the coughs in the cohort captured using a smartphone-based system. We targeted participants with and without respiratory diseases. Recruitment strategies included a broad information campaign carried out via social networks and through face-to-face meetings, with support from university and municipal authorities. A full protocol describing inclusion criteria has been published. (14) All participants signed informed consent, and this project was reviewed and approved by the Ethics Committee for Medical Research of the Chartered Community of Navarra (PI2020/107) and the Comité d'éthique à la recherche du Centre Hospitalier de l'Université de Montréal (2021-9247). The main study was registered in www.clinicaltrials.gov, under the number: NCT04762693 and its results have been submitted separately for publication.

Study design

The overarching objective of this analysis was to assess the impact of the duration of cough monitoring on the capacity to detect changes in its frequency. Specific objectives include: (i) describing the distribution and circadian pattern of cough frequency in the studied cohort, (ii) evaluating the role of effect size on the capacity to detect such changes, and (iii) determining an optimal monitoring period, and (iv) comparing the capacity of estimates based on 24-hour monitoring to longitudinal records to detect changes in cough frequency

This is an empiric statistical analysis of a larger cohort acoustic surveillance study. Sample size calculations and the study's main results have been described elsewhere. (13, 14).

Monitoring

Cough frequency was monitored using Hyfe Cough Tracker (Wilmington, Delaware, United States, https://www.hyfeapp.com/, henceforth referred to as Hyfe). Hyfe uses on device and cloud based neural networks (CNN) to identify cough while preserving privacy. The CNN assigns a cough prediction score to each sound, if such score lies above a predetermined value (in this study, 0.70

out of 1.0), the sound is labelled as a cough. The analytical performance of the algorithm was evaluated in a pilot sub-study that reported a sensitivity of 96.34%, and a specificity of 96.54% among detected sounds,(14) and better characterized in a nested study with solicited sounds from 49 participants submitted jointly with this manuscript. Additional clinical validation in specific diseases is underway (NCT05042063). All participants were instructed to install Hyfe in their personal mobile phones and use it for at least 6 hours a day, during the night-time. Those willing to use it continuously, or for longer periods were encouraged to do so.

Analysis

Participants with less than 1 hour of recording data were excluded from all further analysis. To compare the capacity of 24-hour monitoring with longitudinal records to detect changes in cough frequency, a randomization routine was used to simulate the data that would have been obtained by monitoring two participants for a 24-hour period. These two participants were selected for having used the monitoring system regularly throughout the study, and because they received interventions that clearly modified their cough frequency. In each randomization, a 24-hour period of monitoring in before and after such intervention was selected at random temporal points and the difference between both periods (after-before intervention) was calculated. This process was repeated 100,000 times to construct a distribution of after-before differences. To determine the accuracy of 24-hour sampling, we calculated the proportion of randomizations that fall outside of the 95% confidence interval of the difference between the arithmetic means, and the percentage of randomizations in which the 24-hour method detects a false direction for the change in cough. Similarly, the cough rates before and after the interventions were compared using a one-tailed Mann-Whitney U test, and the effect size of the reduction, measured in coughs/hour, determined using non-parametric bootstrapping (10,000 iterations). A significance level of 0.05 was used in these tests.

To characterise circadian patterns in cough, records of participants with at least 100 hours of monitoring were analysed, considering only hours with at least 30 minutes of recording. Cohort-wide cough rates in each circadian hour (1h – 24h) were summarised. The mean cough rate in each hour and for each user was calculated, keeping only users with at least 10 hours of monitoring within that hour. The mean and standard error of cough rate across users for each hour was then obtained.

We then modelled an individual's cough pattern using a negative binomial distribution. Cough records from users with at least 100 hours of monitoring and at least one cough were analysed, keeping only the hours with 30 continuous minutes of recording. The mean and variance of each user's cough distribution was calculated and used to determine the empirical correlation between these two parameters with a linear model. This regression was subsequently used to simulate a realistic cough rate distribution for any given mean cough rate.

To determine the influence of effect size in the capacity to detect changes, a simulation based upon the hourly cough rate distribution described above was used to model trends following certain interventions. In these simulations, the "before intervention" and "after intervention" periods were each simulated using 336 hours (two weeks) of coughs and a "before intervention" cough rate of 4 coughs/hour. The same randomization routine described above was used to calculate the fraction of differences that failed to detect the direction of the effect. This was repeated 100 times to produce distributions for the rates of failure, and implementing 19 different effect sizes, ranging from 1% to a 95% reduction in cough.

Finally, records of participants who used Hyfe regularly were used to determine how much monitoring is required to achieve accurate estimates of cough rates. Data from users with at least 240 hours of recording (10 days; need not be continuous) and a mean cough rate of at least 0.5 cough/hour or 12 coughs/day were used for this analysis.

For each user, a cough rate based on the full monitoring period (referred to as the "actual" cough rate) was compared to estimates based upon subsamples from 12 hours to 240 hours. For this, the

user's time series was binned using a rolling 1-hour window (step = 1 second), keeping all windows with at least 30 minutes of monitoring. These windows were sampled pseudo-randomly, ensuring that no two windows overlapped in time, and used to evaluate how the participant's "actual" cough rate differs from estimates based on shorter periods. This was repeated 100 times for each user to get an average error rate at each subsample duration. Error was defined as the absolute proportional difference between estimated cough rates based on subsamples, compared to the participant's "actual" rate.

All data analysis was carried out using R Studio version 1.3 (RStudio Team, 2020. RStudio: Integrated Development for R. RStudio, PBC, Boston, MA).

Results

As reported elsewhere, (13) we collected over 9 person-years of cough data and 62,325 coughs between November 2020 and August 2021 from 616 participants who recorded at least one hour of data, and 22.4% of which reported a history of acute, or chronic cough. In total, 178 participants registered more than 100 hours of monitoring, and 21 registered at least 240 hours (Figure 1). A flowchart describing participant subgroups used in individual analyses can be found in the supplementary material (E-figure 1). There were no significant differences in the cough frequency of participants regardless of their self-reported history of respiratory disease, as can be observed in the supplementary data (E-table 1, and E-figure 2). Similarly, the daily cough frequency of participants diagnosed with COVID-19 during the study showed a similar pattern to that of the rest of study subjects. (supplementary material).

Longitudinal Monitoring vs 24-hours

Comparison between two participants with self-perceived changes and who monitored their coughs continuously during the study period revealed differences between estimates obtained longitudinally, and those derived from 24-hour monitoring.

Cough follows a diurnal pattern

To understand why short-term monitoring was inaccurate, we explored the pattern of cough among users with over 100 hours of recording (n=178). Their cough followed a circadian pattern, being higher during daytime and the evening, but reducing later in the night, most notably after midnight (Figure 2).

Even accounting for diurnal changes, we observed considerable day to day and hour to hour variability in cough rates. Data from 135 participants with over 100 hours of monitoring and at least one cough were used to model the distribution of cough rates. Coughing for an individual user is a stochastic process, leading to zero-inflated and over-dispersed cough rates, adequately modelled by the negative binomial distribution. The variance of cough estimates increases with higher mean cough rates. Fitting these distributions to cough patterns, however, requires knowing the mean and variance of cough rates. These statistics show a strong linear relationship after log transformation ($p < 0.0001$, $R^2 = 0.94$; e-Figure 7). These parameters were used to create a functional cough rate model.

Small changes are missed often

Seeing an apparent inverse correlation between effect size and the chance of detecting a false change in cough frequency, simulations of cough time series before and after different effect sizes were analysed. While 24-hour monitoring is expected to detect large effect sizes most of the time (a 65% reduction in cough frequency would be detected over 95% of the time), this is not the case when changes in cough rates are small. If the effect is a 10% reduction in cough, any reduction will be missed in 42% of trials (95%CI = 21% - 60%). Even when the reduction is as high as 40%, a false increase might be detected 17% of the time (95%CI= 6%-33%, Figure 3).

Longitudinal monitoring reduces variability

To explore the differences between cough rate estimates based on monitoring periods of different lengths and the overall estimate ("actual" rate), we analysed data from 21 participants with over 240 hours of recording (monitoring range = 270 - 5,246 hours; cough rate range = 0.55 - 9.84 coughs/hour).

The error in estimates decreased as the monitoring period increased. With 24 hours of monitoring, observed cough estimates were, on average, 47% different than its "actual" rate (range: 25%-80%), reducing to an average of 14% error (range: 5% to 27%) after 240 hours, equivalent to 10 days of monitoring (Figure 4). These results remained consistent after excluding participants with known interventions described in previous sections.

An optimal monitoring period depends on the cough frequency of individual participants

Participants of this subgroup (n=21) with lower cough rates require longer periods of monitoring to achieve lower proportional errors. In our cohort, the proportional error of cough estimates did not drop below 10% for any participant until at least 4 days of monitoring. Users with fewer than 2.5 coughs/hour required 6 - 22 days of monitoring, while users with the most coughs in our dataset (>7.5 coughs/hour) required 4 - 6 days, although the latter result is based on only two participants with a cough frequency of such magnitude.

Illustrative case 1: refractory chronic cough

A 56-year-old woman with chronic cough began using Hyfe on January 29th, 2021 (see supplementary material for a full medical history and test results). To help reduce her cough, her primary care physician began administering Gabapentin on February 17th, reaching its max dose (900 mg twice a day) on March 30th. Comparing thirteen days prior to starting Gabapentin (mean 21.31 coughs/hour, 95% CI: 19.18 - 23.48) to the 14 days following a 5-day buffer centred on

February 17 (mean 13.72 coughs/hour; 95% CI: 12.19 - 15.19), longitudinal monitoring with Hyfe detected a decrease in cough of 7.58 coughs/hour (95% CI = 4.96 - 10.10), representing a 35% reduction (*p*=0.00002, Figure 5A, table 1). In contrast, random resampling 24 hours periods before and after the change demonstrates that the decrease would have fallen outside the 95% CI 57% of the times and 8% of the time the cough would appear to have increased (supplementary material).

On 28 May, Omeprazole (40 mg) was added. Comparing the two weeks prior (mean 9.70 coughs/hour, 95% CI: 8.21 - 11.16, n=13 days) to the two after (mean 3.98 coughs/hour; 95% CI: 2.92 - 5.03, n=14 days, with a 5-day buffer around May 28th), Hyfe detected a 59% reduction in cough (p=0.000002, table 1). An increase in cough frequency would have been noticed in 4% of 24-hr trials, and the effect size would have fallen outside 95% CI 62% of the times (supplementary material).

Illustrative case 2: smoke cessation, relapse and cessation

On November 6th, 2020, a 71-year-old woman began monitoring her cough (see supplementary material for a full medical history and test results). On January 18th, 2021, she decided to quit smoking. Based on her monitoring record during the 21 days which had more than 12 hours of recording between December 8 and January 8, her mean cough rate prior to quitting was 1.53 coughs/hour (95% CI: 1.14 - 1.95). After quitting her cough rate decreased between January 28 and February 28 to 0.58 coughs/hour (95% CI: 0.39 - 0.78). This 62% reduction of 0.95 coughs/hour (95% CI = 0.507 - 1.417) was highly significant (p = 0.0009, Figure 5B, table 1). Using only the 24-hour monitoring simulations, 68% of the estimates fell outside of the confidence interval of the longitudinal mean and would have falsely indicated an increase in cough rates in 21% of the 24-hour trials. (Supplementary material)

By March 20th, 2021, this participant had recommenced smoking. Comparing the 8 days prior to relapse (0.70 coughs/hour, 95% CI: 0.55 - 0.86) to the thirteen days after (1.2 coughs/hour, 95% CI: 1.00 - 1.49), with a 10-day buffer on each side of 20th March, Hyfe detected a 71% increase in cough

of 0.54 coughs/hour (95%CI= 0.270 - 0.836) that was statistically significant (p = 0.003, Figure 5B, table 1). The effect size would have fallen outside the 95% CI 43% of the time, while a false reduction in cough frequency would have been detected in 14% of 24-hour trials. (Supplementary material)

This patient quit smoking again during the first week of May 2021. Comparing the thirteen days prior (1.61 coughs/hour, 95% CI: 1.09 - 2.12) with the fourteen days after (0.94 coughs/hour, 95% CI: 0.65 - 1.22) with a 10-day buffer on each side of May 1st, Hyfe measured a 42% decline of 0.68 coughs/hour (95%CI: 0.127 - 1.287) which was statistically significant (p = 0.008, table 1). The effect size would have fallen outside 95% CI 50% of the time. A false increase in cough would have been detected in 23% of 24-hour trials. (Supplementary material)

All changes detected by the monitoring system matched subjective improvements reported by participants to research staff.

Discussion

This study monitored cough continuously and unobtrusively in a large cohort, allowing to compare, for the first time, the accuracy of cough estimates derived from observation periods of different length. While the lack of significant differences in the cough frequency of participants with history of different baseline respiratory conditions is surprising, it can be explained by the fact that this information was self-reported by participants, and by the fact that no specific time limits for the presence of each condition were pre-specified by the research team. This translated into many participants reporting having a certain respiratory condition despite having remained asymptomatic for years.

Despite this limitation, two participants, a chronic cougher and the smoker had self-perceived changes in the severity of their cough during the study, and these were associated with statistically significant changes in continuously recorded measurements. We demonstrated that the magnitude

of these changes was often missed, and the trends even reversed when cough is only measured for 24-hour periods, as is typically done in most research settings (9). A major limitation of this study is that the combination of long-term, continuous app usage and precise clinical information was only available for these two subjects, making these observations not generalizable. However, simulations constructed with parameters derived from the observation of over 100 participants showed similar results. This suggests that the duration of monitoring can affect the accuracy of cough frequency estimates, as can be explained by the intrinsic variability of an individual's cough within and, particularly, between days.

This variability implies that three key parameters influence our ability to assess an individual's cough precisely: the average and variance of the individual's coughs per hour and the length of the observation period. Having observed empirically that higher cough rates correspond to larger variances in coughs per hour, estimating individual cough parameters accurately demands longer observation periods.

Intermittent monitoring might be particularly problematic in a context where detecting small effect sizes is important, as for instance, clinical trials comparing different antitussive therapies (9, 15, 16). Furthermore, this statistical analysis suggests that recognizing changes in individual cough patterns requires a deeper understanding of their dependence on both the average and variance of the individual's coughs per hour. It is interesting to speculate that recent trials demonstrating that the novel antitussives are most effective on patients with the highest cough rate may be largely a consequence of this statistical issue and not intrinsic to the drug's efficacy.

Another limitation of this study is that it was conducted with a cough monitoring tool that has not been fully validated. Although Hyfe's performance was analysed in a pilot stage of the study, (14), its sensitivity and specificity for detecting cough in different practical settings are only now being formally quantified. (NCT05042063) It is, however, reassuring that it did detect changes in those patients who reported changes, and found a diurnal pattern consistent with prior publications (17).

This is the first population-based description of cough epidemiology. However, while 22% of them reported a history of cough, most were young and presented either mild, acute respiratory symptoms, or no symptoms at all, at the moment of enrolment. Thus, the cohort may not be representative of those patients who would benefit the most from objective cough monitoring, nor the target population of clinical trials that would benefit from more accurate assessment of changes in cough. Thus, this study should be replicated in a better-defined cohort using a validated device.

Given our preliminary observations, we propose that significant changes in coughs need to be defined individually, and based on the basal cough rates of patients, and that longitudinal monitoring is likely to provide more accurate estimates of a patient's basal state. The ability to devise such individualised models in real time may help patients and providers to promptly detect clinical changes. Early detection of clinical deterioration has been shown to improve outcomes in respiratory diseases such as refractory chronic cough and COPD. (18-20)

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Authors' contributions

Conceptualization: JCGF, EK, SGL, and CCh

Methodology: JCGF, EK, SGL, and CCh

Software: EK, MR

Formal Analysis: EK, MR

Investigation: JCGF, VO, IB, JC

Data Curation: EK, JCGF, CCh

Writing original draft: JCGF, CCh, SGL, PS, MG

Writing: Review and editing: All authors. Visualisation: EK, MR Funding acquisition: SGL

Conflicts of interest

EK, PS, MG, and MR are employees of Hyfe, Inc. CC has received consultancy fees and owns equity in Hyfe Inc. All other authors declare no conflict of interest.

Data and code availability statement

Datasets including individual cough and monitoring data, and code used to analyse it are available in github (https://github.com/ericmkeen/navarra).

Figures and tables

Table 1: Changes in cough frequency on two participants with chronic cough

Intervention	Cough freq. before intervention[a] (Cough/hr)	Cough freq. after intervention[a] (Cough/hr)	Proportional change	*P* value	Proportion of times the effect size is inaccurate (24-hour)	Proportion of times the direction of the effect is reversed (24-hour)
Case 1: Participant with chronic cough						
Gabapentin	21.31	13.72	-35%	0.00002	57 %	8%
Omeprazole	9.70	3.98	-59%	0.000002	62 %	4%
Case 2: Chronic smoker						
Smoking stopped	1.53	0.58	-62%	0.0009	68 %	21%

Smoking restarted	0.70	1.2	+71%	0.003	43%	14%
Smoking stopped	1.61	0.94	-42%	0.008	50%	23%

[a] The interventions were different for both participants: Treatment with gabapentin and omeprazole in case 1, and smoking cessation/relapses in case 2.

Figure 1: Participants monitored in function of monitored time

Figure 1: The number of participants as a function of the cumulative hours of monitoring they recorded. The red lines indicate participants who recorded for at least 100 hours in which there was at least 30 minutes of recording (N=178), and those who recorded for 240 or more hours and had a mean cough rate of at least 0.5 coughs per hour (N=21).

Figure 2: Circadian pattern of cough frequency in the cohort

Figure 2: The circadian pattern of cough rate for the 178 participants showing a nadir in cough in the early morning and higher rates of coughing in the morning and evening. For each hour, the relative cough rate is calculated as the ratio of an individual's cough rate and the cohort-wide average cough rate for all hours of the day.

Figure 3: Influence of effect size in the capacity to detect changes in cough frequency with 24-hour monitoring

Figure 3: The likelihood of failing to detect a change in cough frequency decreases as the absolute magnitude of the change increases. One hundred simulations were run for each effect size using the same 'before' rate (4 coughs per hour). Dots represent the failure rate from a single simulation run. The orange line represents the mean failure rate for all 100 simulations**.**

Figure 4: Error cough rate estimates decrease with longer monitoring periods

Figure 4: Ability to measure cough is a function of the mean cough rate, its variance, and the duration of monitoring. Here the monitoring records of 21 users (blue lines) were subsampled, each with different cough patterns, to see how much error can be expected (y-axis) with various monitoring durations (x axis). Only users with 240 total hours of monitoring and a cough rate of at least 0.5 coughs per hour were included. The red line is the mean error for all those participants**.**

Figure 5: Changes in cough rates for two selected participants following specific interventions

Figure 5: A participant treated for a refractory chronic cough (Case 1, Panel A) and a chronic smoker attempting to quit (Case 2, Panel B). The dotted lines indicate the date of specific interventions. The shaded areas represent the periods used to calculate the pre- and post-intervention mean cough rates surrounding a buffer period.

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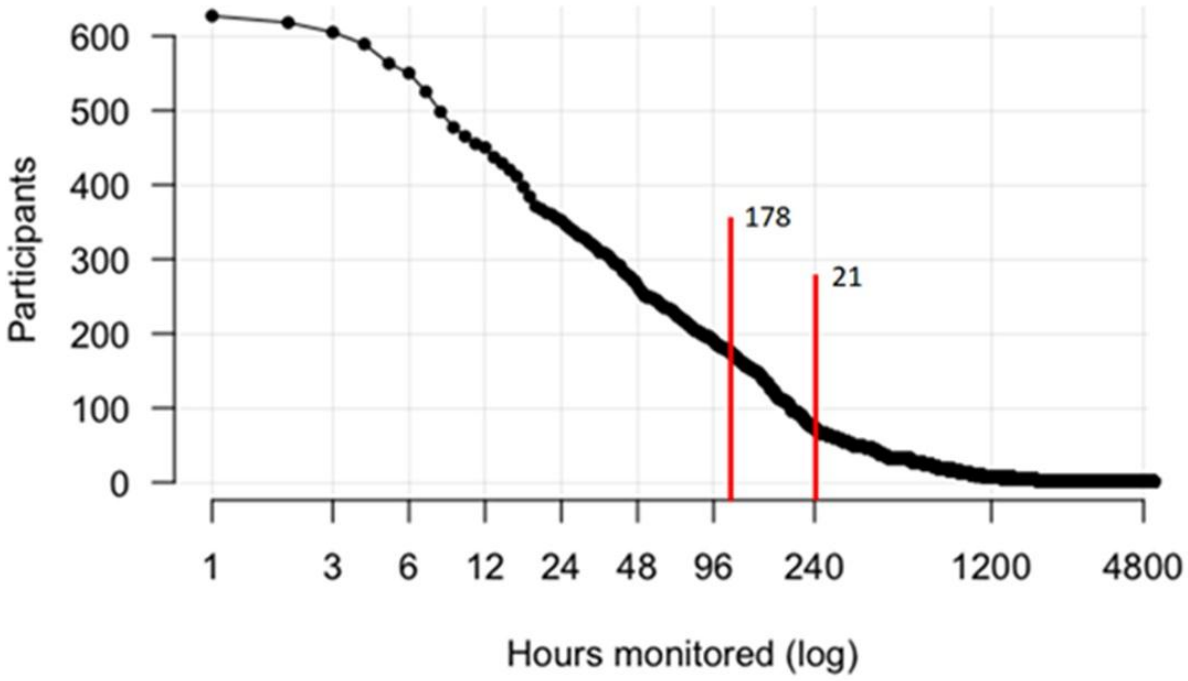
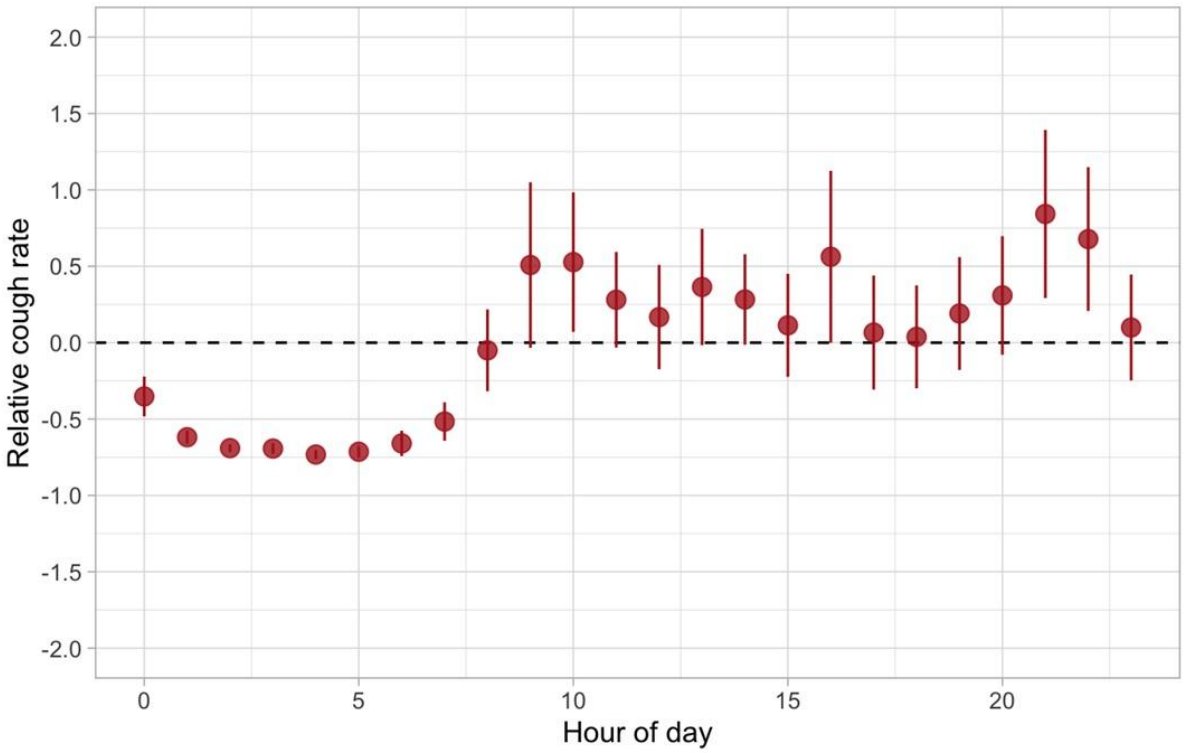
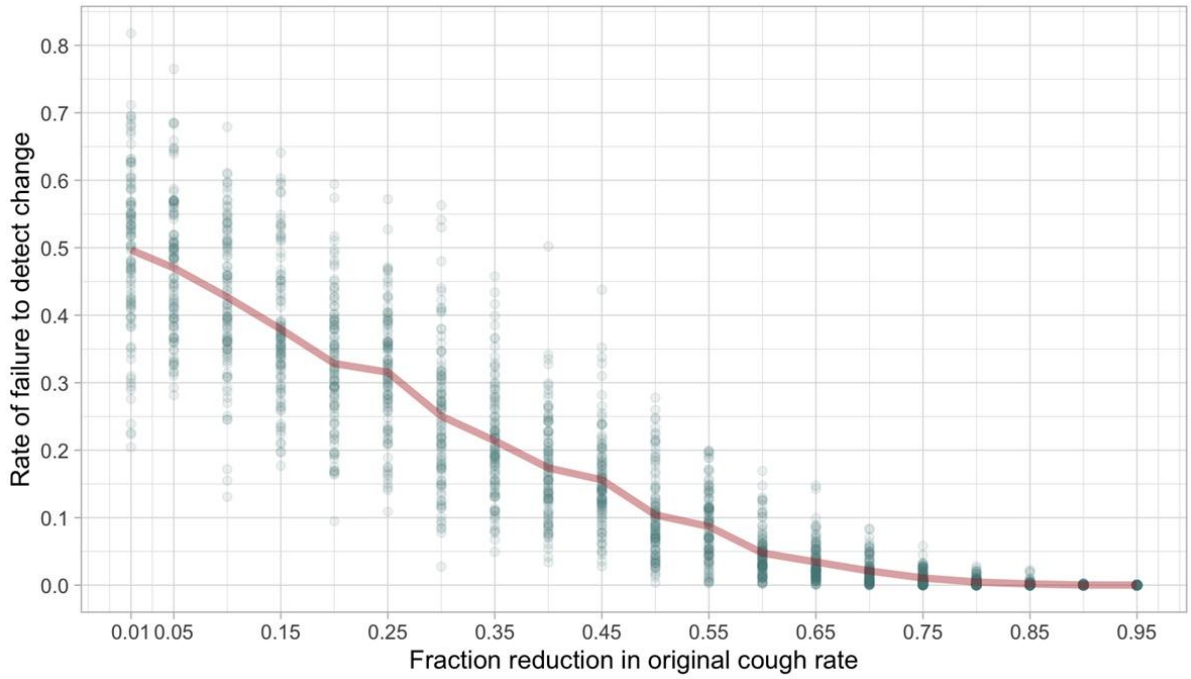
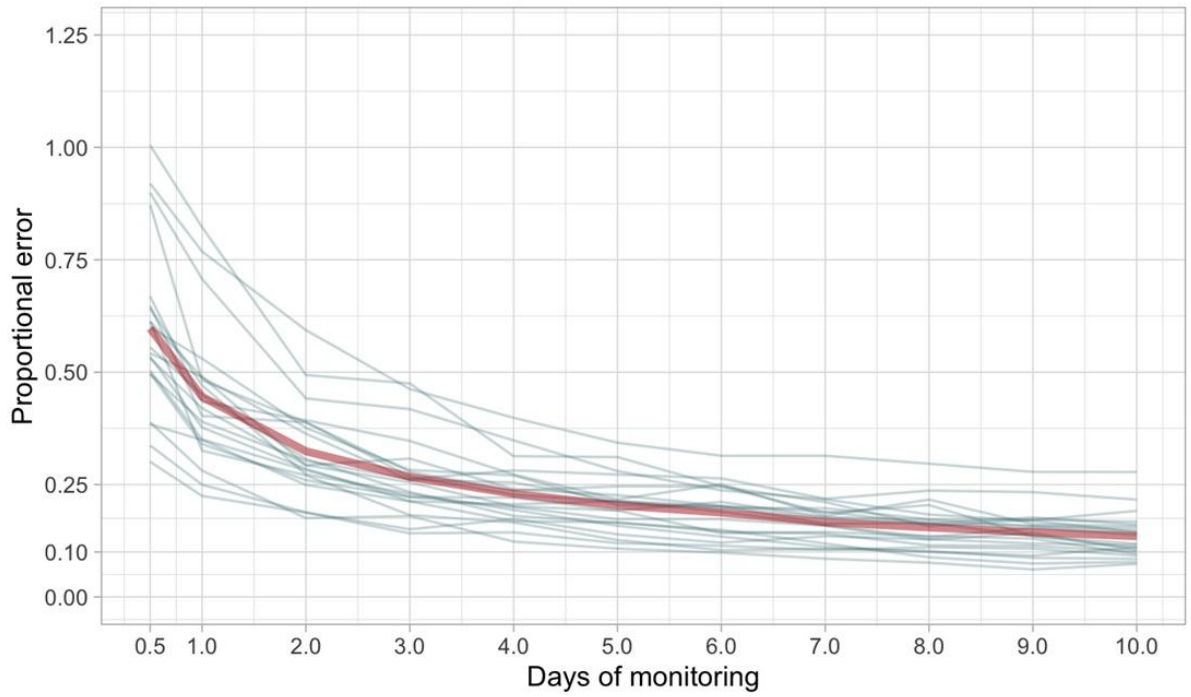
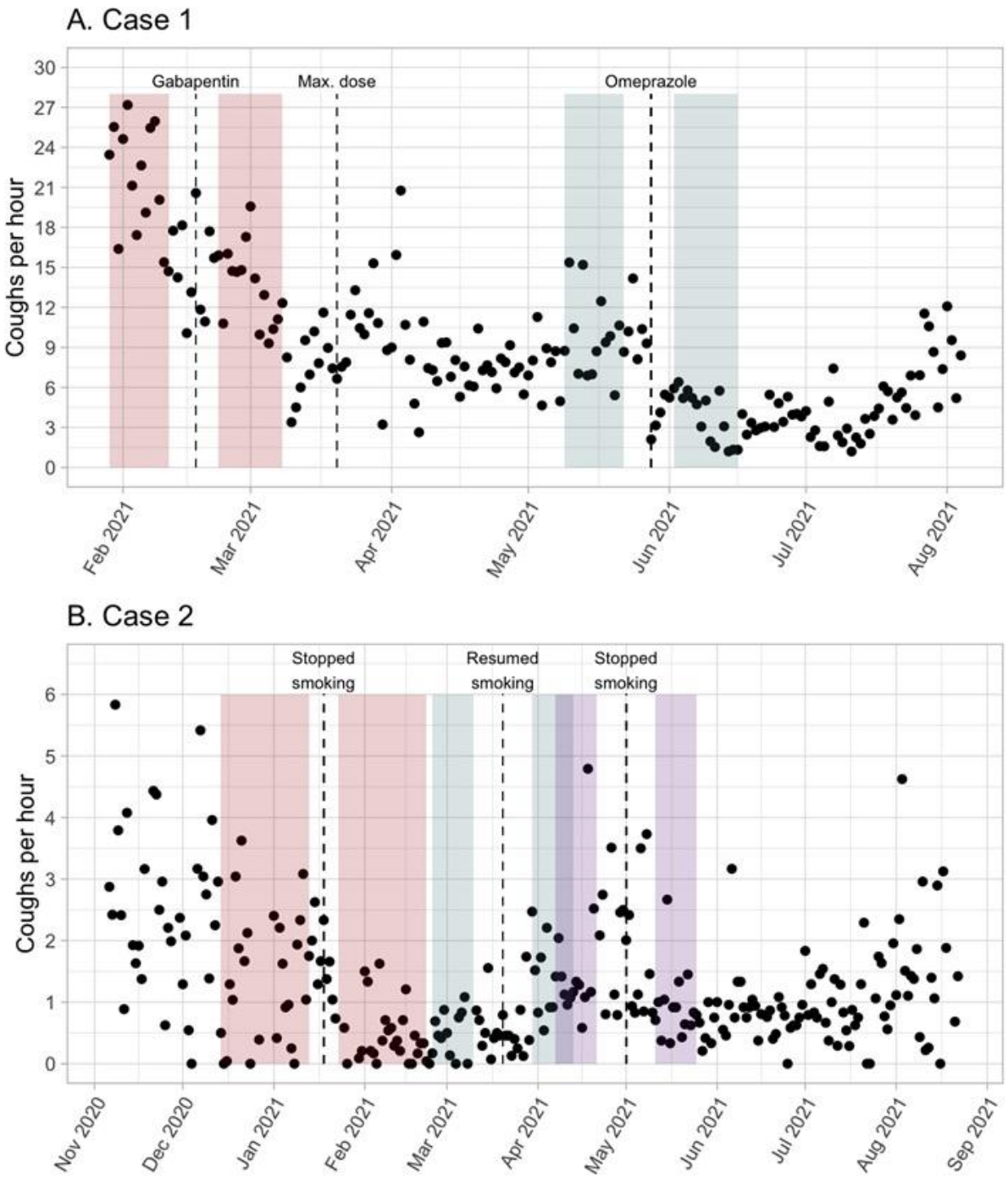

600
500
400
300
200
100
0
Participants
178
21
1
3
6
12
24
48
96
240
1200
4800
Hours monitored (log)


Relative cough rate
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
0
5
10
15
20
Hour of day


Rate of failure to detect change
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.01 0.05
0.15
0.25
0.35
0.45
0.55
0.65
0.75
0.85
0.95
Fraction reduction in original cough rate

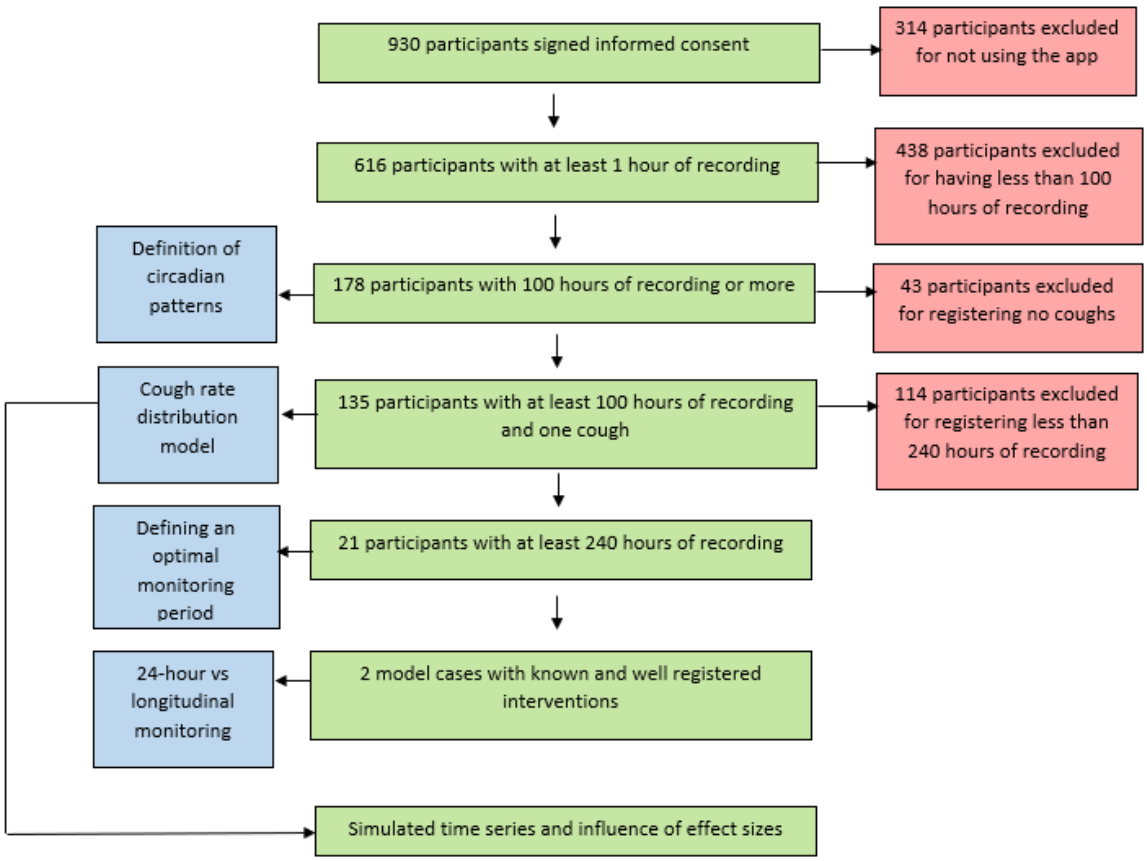

1.25
1.00
0.75
0.50
0.25
0.10
0.00
Proportional error
0.5
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
Days of monitoring


A. Case 1
Gabapentin
Max. dose
Omeprazole
Coughs per hour
0
3
6
9
12
15
18
21
24
27
30
Feb 2021
Mar 2021
Apr 2021
May 2021
Jun 2021
Jul 2021
Aug 2021
B. Case 2
Stopped smoking
Resumed smoking
Stopped smoking
Coughs per hour
0
1
2
3
4
5
6
Nov 2020
Dec 2020
Jan 2021
Feb 2021
Mar 2021
Apr 2021
May 2021
Jun 2021
Jul 2021
Aug 2021
Sep 2021

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

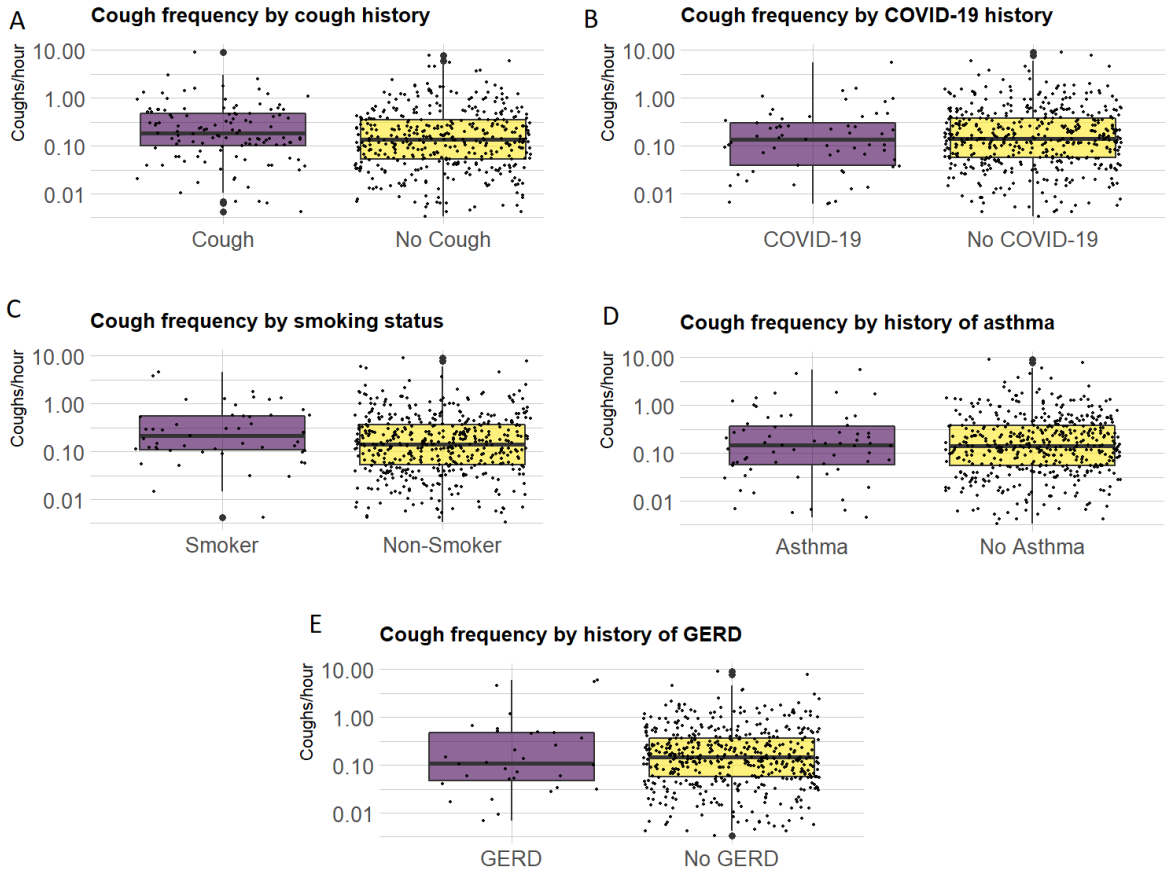
The hourly cough frequency of participants who self-reported having a history of any of the respiratory diseases or symptoms listed in E-Table 1 was compared. Since each participant could have reported having more than one respiratory disease, individual comparisons were performed between those participants 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.

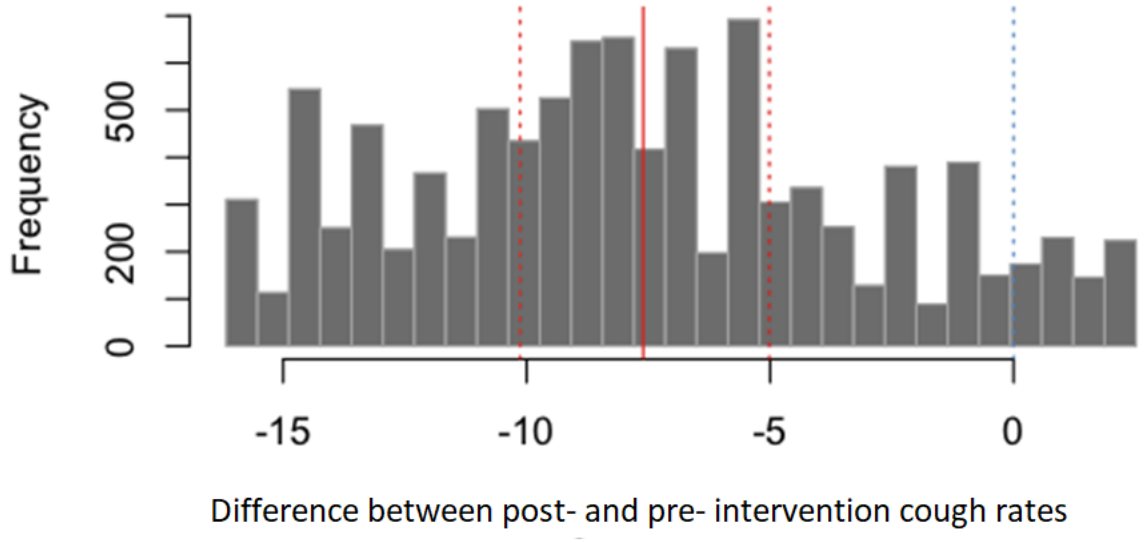
E-Figure 2:



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).

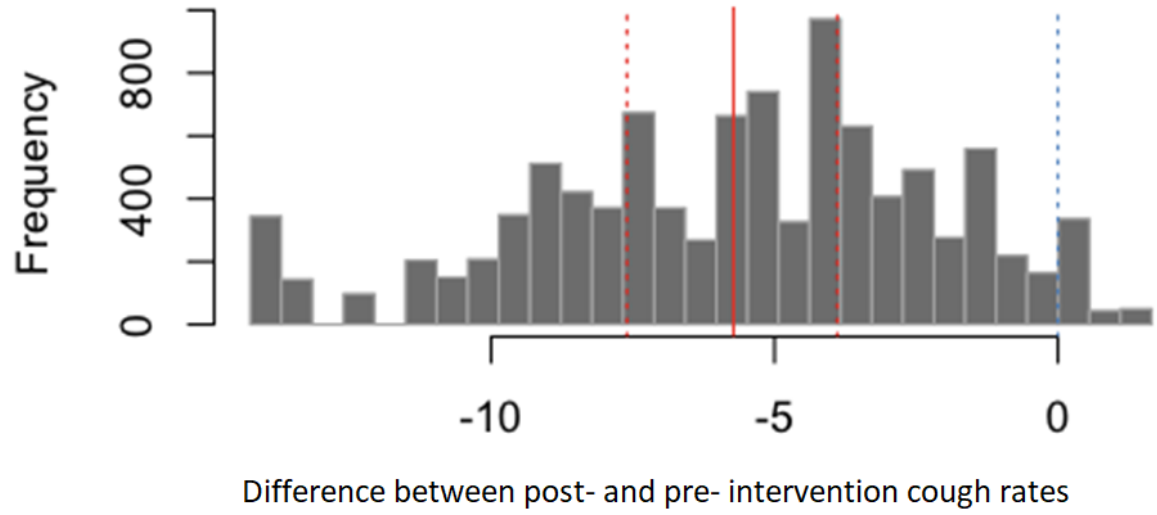
Randomization routine for illustrative case 1

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

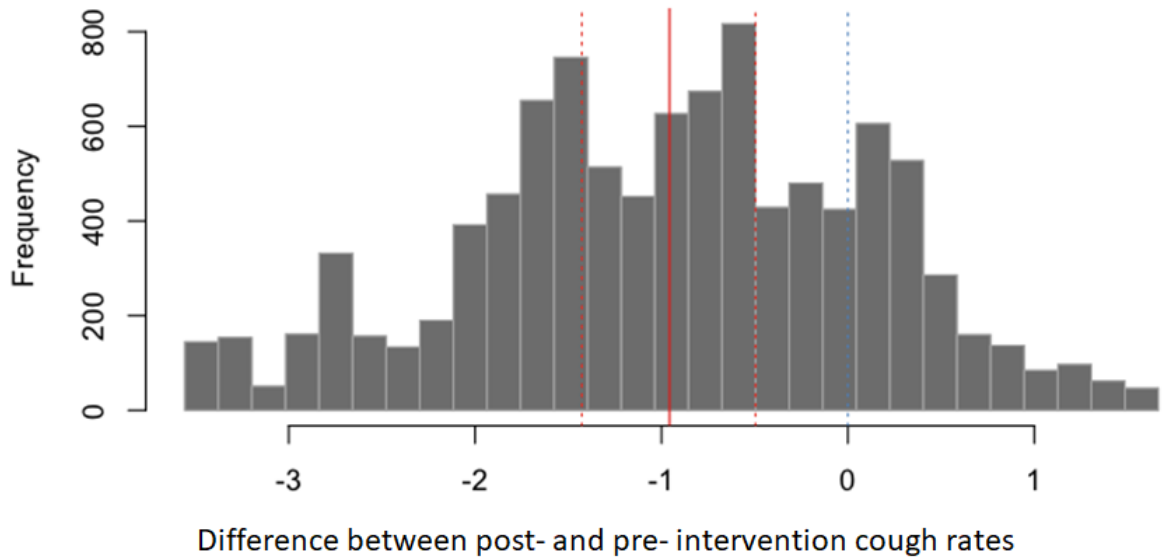


Randomization routine for illustrative case 1 following the beginning of treatment with Omeprazole: The red, continuous line represents the true effect size as determined by longitudinal monitoring. Dotted red lines signal the bootstrap 95% CI of true effect size. The fraction of observations in the 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).

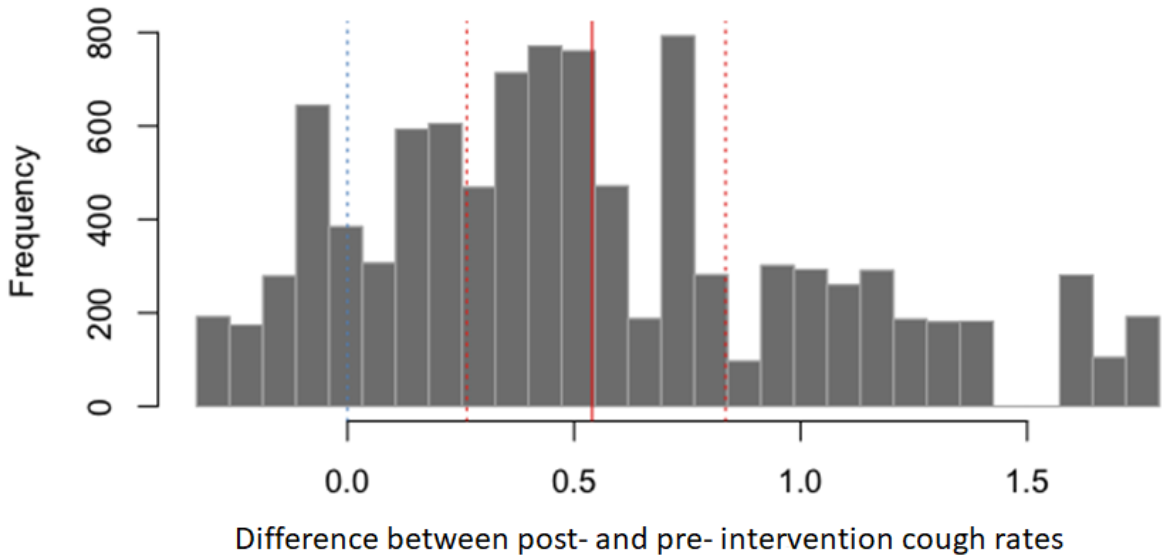
Randomization routine for illustrative case 2

E-Figure 5



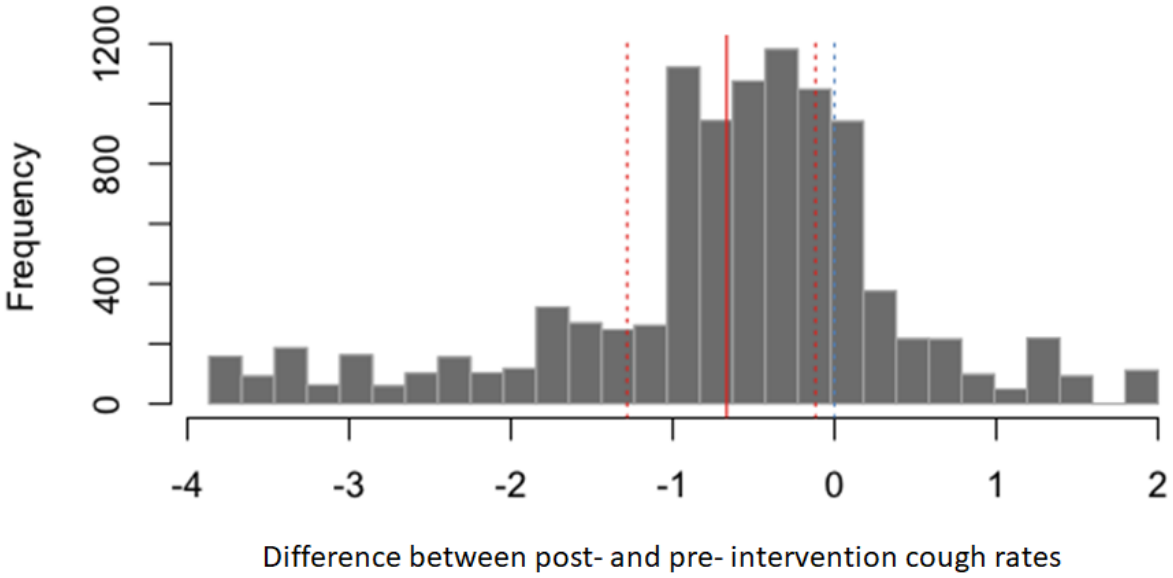
Randomization routine for illustrative case 2's first smoking cessation event: The red, continuous line represents the true effect size as determined by longitudinal monitoring. Dotted red lines signal the bootstrap 95% CI of true effect size. The fraction of observations in the distribution outside 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

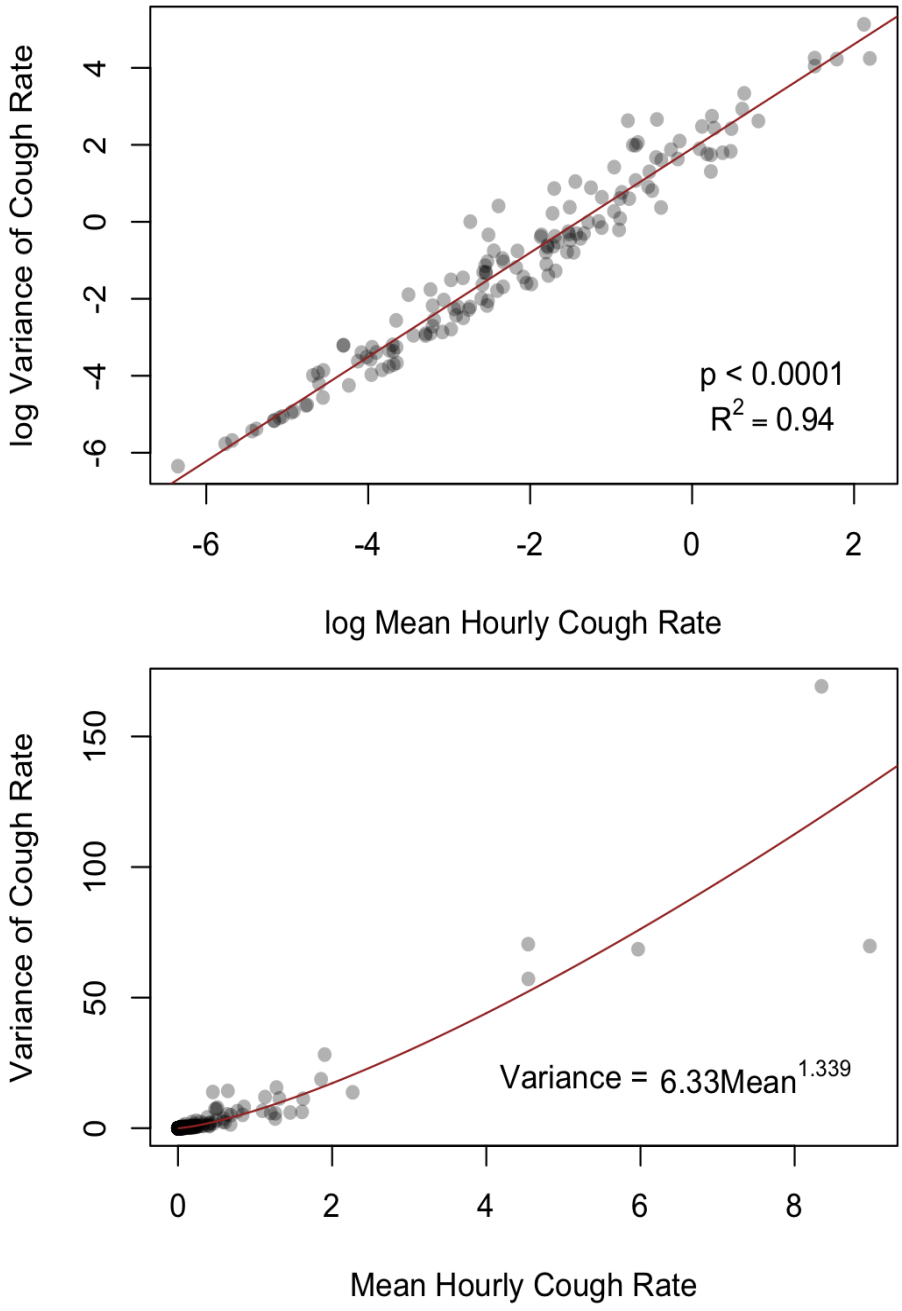


Randomization routine for illustrative case 2's second smoking cessation event: The red, continuous line represents the true effect size as determined by longitudinal monitoring. Dotted red lines signal the bootstrap 95% CI of true effect size. The fraction of observations in the distribution outside 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:

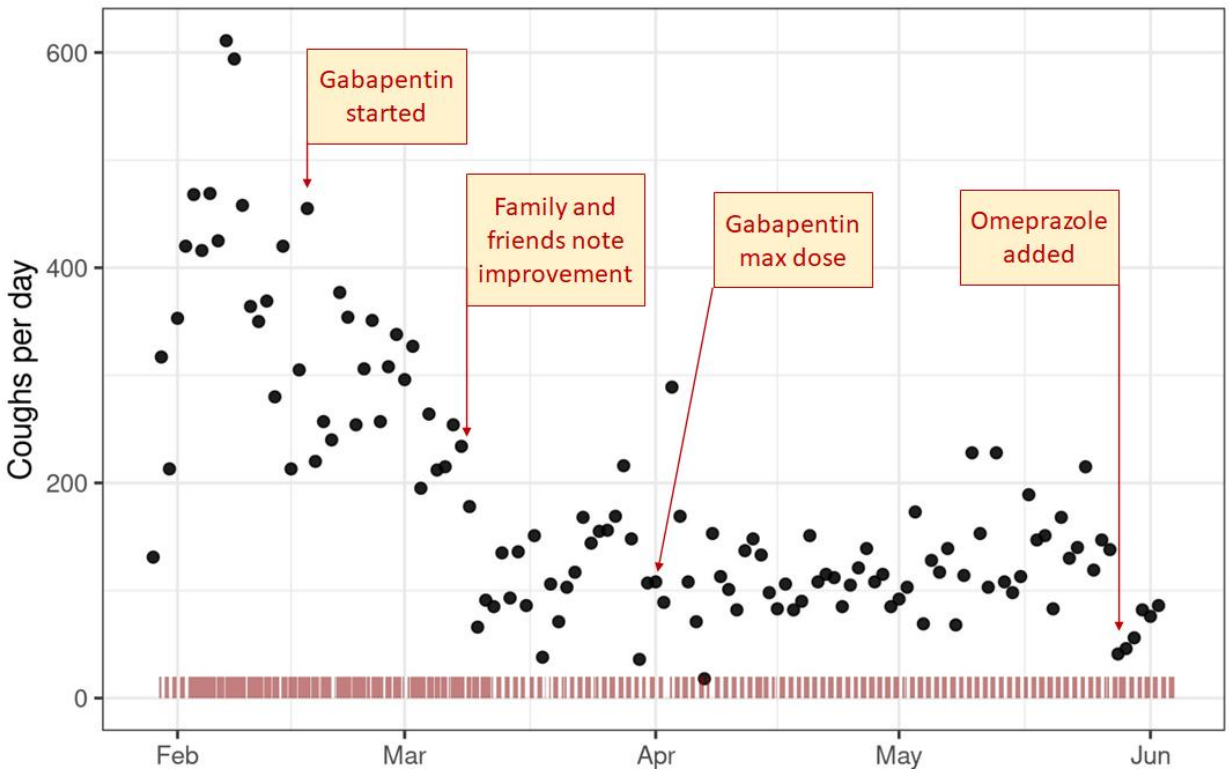
- Full spirometry and bronchodilator test: normal results
- Methacholine challenge: normal results
- Allergy skin tests: negative
- 24-h esophageal pH monitoring: normal
- Gastroscopy: normal
- Head and neck CT scan: normal
- Laboratory tests including full blood count, erythrocyte sedimentation rate, 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

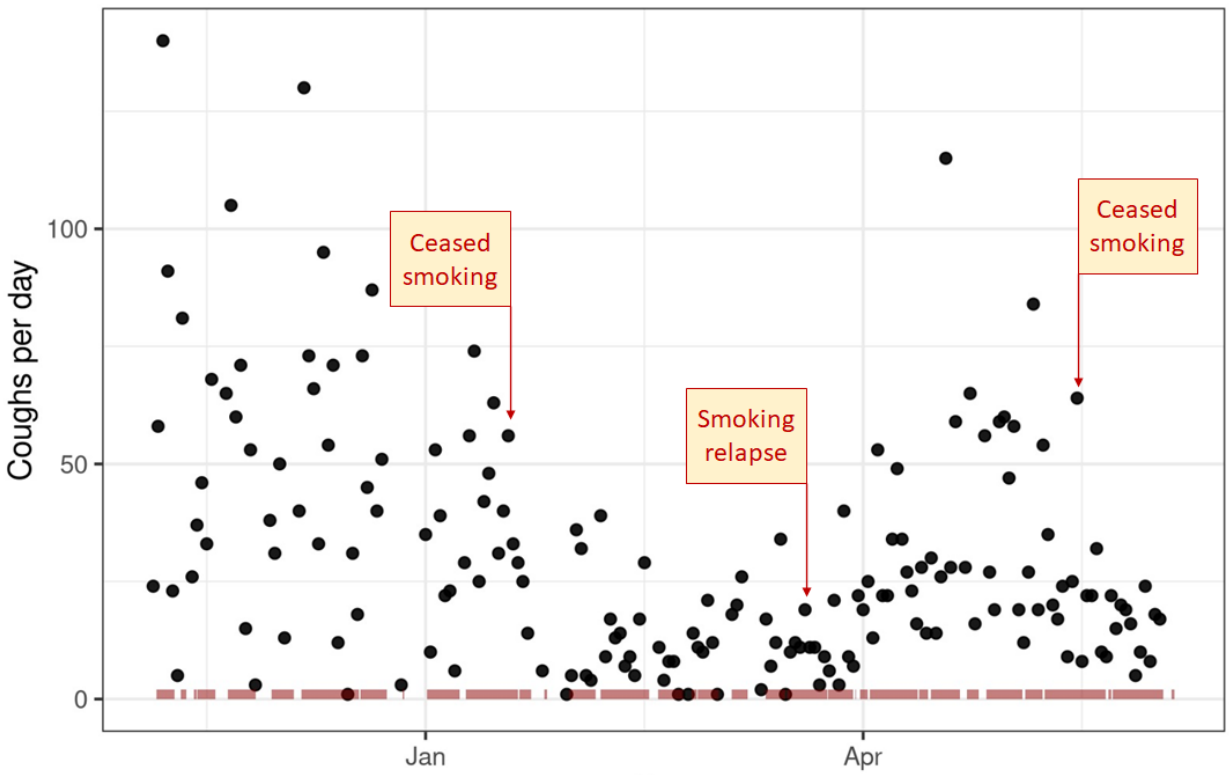
A 70-year-old female retired nurse, was enrolled in the cohort on November 6, 2020 and started using the cough tracking app systematically throughout the day. Her past medical history revealed two to three episodes of upper respiratory tract infections per year. These episodes usually led to 15-20 days 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.