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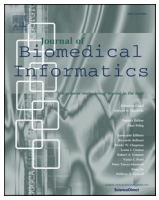

Original Research

Digital cough monitoring – A potential predictive acoustic biomarker of clinical outcomes in hospitalized COVID-19 patients

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ABSTRACT

Purpose: Recent developments in the field of artificial intelligence and acoustics have made it possible to objectively monitor cough in clinical and ambulatory settings. We hypothesized that time patterns of objectively measured cough in COVID-19 patients could predict clinical prognosis and help rapidly identify patients at high risk of intubation or death.

Methods: One hundred and twenty-three patients hospitalized with COVID-19 were enrolled at University of Florida Health Shands and the Centre Hospitalier de l'Université de Montréal. Patients' cough was continuously monitored digitally along with clinical severity of disease until hospital discharge, intubation, or death. The natural history of cough in hospitalized COVID-19 disease was described and logistic models fitted on cough time patterns were used to predict clinical outcomes.

Results: In both cohorts, higher early coughing rates were associated with more favorable clinical outcomes. The transitional cough rate, or maximum cough per hour rate predicting unfavorable outcomes, was 3·40 and the AUC for cough frequency as a predictor of unfavorable outcomes was 0·761. The initial 6 h (0·792) and 24 h (0·719) post-enrolment observation periods confirmed this association and showed similar predictive value.

Interpretation: Digital cough monitoring could be used as a prognosis biomarker to predict unfavorable clinical outcomes in COVID-19 disease. With early sampling periods showing good predictive value, this digital biomarker could be combined with clinical and paraclinical evaluation and is well adapted for triaging patients in overwhelmed or resources-limited health programs.

1. Introduction

Background - Cough is a hallmark symptom of COVID-19 and is routinely used for symptom-based screening and clinical monitoring of symptomatic cases. [1–2] The emerging field of *Acoustic Epidemiology* now enables objective monitoring of cough and development and evaluation of cough-based digital biomarkers for diagnostic, prognostic, and treatment monitoring of lung disease. [3] Most impactful studies published to date leveraged coughs' acoustic signature for classification of sounds associated with specific lung disease aetiology. [4–5] The temporal evolution pattern of objective cough recordings has not yet been used for clinical decision making. [3].

Problem - To date, the absence of reliable data on the natural evolution of cough in COVID-19 disease has precluded the development of such clinical tools.

Proposed method - We hypothesized that acoustic prognosis tools

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could be derived from objectively measured cough time patterns to complement clinical assessment of patients at high risk of severe disease and poor clinical outcomes after a short clinical observation period. Such tools could support clinical decision making when admitting or discharging patients or when initiating specific therapies which need to be administered within a short therapeutic window to maximize efficacy. [6] In a pandemic or endemic setting, this approach could support both limited and overwhelmed health systems in low, middle as well as high-income countries. We describe the natural evolution of cough among hospitalized COVID-19 patients in two independent populations of Gainesville, Florida and Montreal, Canada. Using the longitudinal cough evolution patterns of participants, we develop a cough-based prognosis score allowing the precise identification of patients at higher risk of disease progression towards intubation or death. We report on the accuracy of the cough detection AI algorithm, the operational aspects of deploying digital cough monitoring technology for routine clinical monitoring in hospital settings, the natural history of cough and its prognostic value in hospitalized COVID-19 disease.

2. Materials and methods

2.1. Study setting and population

Participants were consecutively recruited in the University of Florida Health Shands Hospital (UFHSH) in Gainesville, Florida and the Centre Hospitalier de l'Université de Montréal (CHUM) in Montreal, Canada. These are tertiary care centers with 1,162 beds and 770 beds, respectively. Adults requiring hospitalization for newly diagnosed COVID-19 infection were included. In both settings, administered therapies for COVID-19 included dexamethasone for all patients requiring oxygen support and remdesivir or tocilizumab, as appropriate, for severe and critical COVID-19. Diagnosis was confirmed by COVID-19 PCR testing (Xpert Xpress SARS-CoV-2, Cepheid and BioFire RP 2·1, Biomerieux at Gainseville and cobas 8800 SARS-CoV-2, Roche at Montreal). This strategy purposely included patients presenting with a wide range of symptom severity ranging from those not requiring any supplemental oxygen who had been admitted for observation to patients requiring intensive non-invasive ventilatory support. Patients requiring rapid intubation upon admission were not included. Study participation was terminated upon hospital discharge, intubation, or death.

2.2. Digital cough monitoring

Participants' coughs were recorded using previously validated Hyfe Research (https://www.hyfeapp.com/) smartphone application running on Motorola G6 android devices. Hyfe Research runs in smartphone background interface, monitoring ambient sound levels, and records short snippets of "explosive" sounds (<0.5 s). Those half-seconds containing at least one explosive sound are transferred and analyzed on a server-based convolutional neural network (CNN) AI model which distinguishes coughs from or non-cough sounds. This CNN model was previously shown to have above 96·0% analytical sensitivity and specificity and was re-validated using gold-standard human sound labelling within this study's specific setting. [7–9] Phones were positioned at the head of hospital beds with microphones oriented towards the patients within three feet of the patients' mouths. Phones were left charging with the Hyfe Research application activated until the completion of their enrolment period. All participants were hospitalized in single closed rooms with airborne precaution. Between patients, phones were handled and cleaned following recommended biosafety protocols in collaboration with local infection control services (Supp. 1).

2.3. Designing a cough detection-based COVID-19 prognosis model

Study population socio-demographic and clinical information were collected upon enrollment. Factors which could impact baseline cough patterns (e.g. smoking habits, lung comorbidities), and those influencing severity and clinical evolution of COVID-19 disease (e.g. age, comorbidities especially features of metabolic syndrome) were collected. [10] Oxygen and respiratory support was continuously monitored throughout the enrolment period to classify disease severity according to a standard severity scale used in WHO international COVID-19 studies. [11].

To describe the natural history of cough in COVID-19 disease, participants' cough per hour rates were aggregated at cohort level and tracked in time. Hospital admission date and study enrolment were used as the zero mark in separate analyses. Participants were monitored until hospital discharge, intubation, or death.

To develop a sensitive prediction model for unfavorable clinical outcomes, a logistic model was fitted on patients' coughs per hour as the explanatory variable. The dependent variable was a dichotomous response distinguished between unfavorable outcomes (mechanical ventilation or death) and favorable outcomes (absence of mechanical ventilation or death). A transitional cough per hour rate value was defined as the cough frequency below or above which all unfavorable outcomes could be predicted. Comparing cough rates to this transitional rate provided a simple predictive model whose performance (sensitivity, specificity, positive and negative predictive value) was analyzed. Since the clinical value of such a predictive model is greater the earlier it can be applied after initial contact with patients, the analysis was replicated strictly using the first 6 and 24 h of observation to predict the same longer-term outcomes.

3. Results

3.1. Study population

Between December 17, 2020 and June 15, 2021, 98 patients were enrolled at UFHSH and 25 patients were enrolled at CHUM. Study population characteristics, comorbidities and COVID-19 disease severity are presented in Table 1. At UFHSH, 14 patients were transferred to the intensive care unit (ICU), nine of whom subsequently died during the hospitalization. Three more patients died without ICU transfer after pursuing palliative care. At CHUM, two patients were transferred to the ICU, one of whom died.

3.2. Cough monitor validation

The mean study enrolment period was 3·18 days at UFHSH and 6,0 days at CHUM. Coughs were recorded from patients for an average of 106·91 h per patient (Q1 = 66·3 h, median = 96·67 h, Q3 = 144·17 h) in Gainesville and for an average of 121·28 h per patient (Q1 = 49·8 h, median = 72,17 h, Q3 = 180·84 h) in Montreal. The cough monitoring totaled 549·52 days (13,188·54 h) of monitoring and captured a total of 47·409 coughs (26·847 Florida; 20·562 Montreal), for an average of 395 coughs recorded per patient (282 per Florida patient; 822 per Montreal patient). Mean cough rates calculated over the complete enrollment period were higher in Montreal cohort than the Gainesville cohort (Supp. 3). 291,684 explosive putative cough sounds were recorded. Of those, 150,954 were randomly sampled and labelled as cough or non-cough sounds by trained human observers. Using this as the gold standard for cough detection, the Hyfe Research CNN model was calculated to be 94·1% sensitive and 97·4% specific (AUC 0·986) (Supp. 2).

3.3. Natural evolution of cough in COVID-19 disease

In both cohorts, cough was shown to be on a rapid increasing trend immediately following hospital admission before regressing with time and reaching a plateau (Fig. 1). Circadian cycle cough pattern analysis revealed lower cough rates at night than during the day (Supp. 5).

Table 1
Study population demographic characteristics.

	Gainesville (n = 98)	Montreal (n = 25)
Demographic		
Age - mean (SD)	61 [16]	55 (20)
Male sex – n (%)	51 (52)	15 (60)
Race – n (%)		
White	60 (61)	19 (76)
Black	37 (38)	1 (4)
Asian	0 (0)	1 (4)
Native American and other	1 (1)	4 (16)
Hispanic	4 (4)	2 (8)
Comorbidities and risk factors - n (%)		
Active smoking	33 (34)	0 (0)
Immunosuppression	16 (16)	7 (28)
Diabetes	34 (35)	3 (12)
Cardiac disease	36 (37)	5 (20)
Hypertension	73 (75)	8 (32)
COPD	20 (20)	2 (8)
Asthma	16 (20)	4 (16)
Obesity	60 (61)	5 (20)
Mean BMI (SD)	33·8 (9.8)	29·7 (7.8)
Clinical features and outcomes		
Mean hospital stay – days (SD)	8·3 (5.8)	9·2 (5.3)
Mean enrollment period – days (SD)	3·6 (3.2)	7.3 (5.5)
Final outcomes		
Discharged – n (%)	81 (81)	22 (88)
Left against medical advice – n (%)	0 (0)	1 (4)
Transferred to ICU – n (%)	14 (14)	2 (8)
Died without ICU transfer (palliative) – n (%)	3 (3)	0 (0)
Mean ICU stay - days	13·6	20·0
Intubation – n (%)	14 (14)	2 (8)
Mean invasive ventilation days - days	12·5	17·5
Death – n (%)	12 (12)	1 (4)

Gainesville and Montreal demographic characteristics, comorbidities and COVID-19 disease clinical severity and outcome. BMI; body mass index, COPD; chronic obstructive pulmonary disease, ICU; intensive care unit, SD; standard deviation.

3.4. Cough as a prognosis biomarker

In the Gainesville cohort, the transitional cough rate (maximum cough rate per hour among those participants who eventually required mechanical ventilation or died from COVID-19) for the total enrollment period was 3·40 coughs per hour; no patients coughing more than 3·40 times per hour experienced unfavorable outcomes. The transitional cough rates for the first 24 h and 6 h of monitoring, respectively, were 3·42 coughs per hour and 9·50 coughs per hour (Fig. 2). Although thresholds vary, all three-time frame analyses suggest that higher coughing rates were associated with fewer unfavorable outcomes. When varying transitional cough rates in ROC curve analyses, areas under the curve were 0·761, 0·792 and 0·715, respectively for the full, first 24 h and first 6 h periods of monitoring suggesting that limited early monitoring is a comparable predictor of clinical outcomes (Fig. 3). We conducted 500 5-fold cross validation runs for each of the binary predictive models. As expected, the empirical AUCs agreed with the mean and median AUCs obtained from cross validation. We assessed the performance of cough rate-based models with the above reported transitional cough rates as thresholds to predict clinical outcomes. By design, those models are 100·0% sensitive and have 100·0% negative predictive value given that all patients experiencing unfavorable outcomes exhibit cough rates inferior to the transitional rates. Models specificity and positive predictive values respectively ranged from 23·3 to 32·9 and 27·0 to 30·0 (Table 2). Specificity and positive predictive value could be improved at the cost of sensitivity and negative predictive value by choosing a different transitional cough rate threshold as shown on the ROC curves.

To assess for potential confounders, we assessed the potential contribution of demographic or medical co-variates in both cohorts of hospitalized COVID-19 patients and found no relationship between biological sex, race, smoking status, diabetes, hypertension, cardiac disease, chronic obstructive pulmonary disease or asthma and the discrepancies between cough rates among patients with favorable or unfavorable outcomes (Supp. 6). Only older patients were more likely to experience unfavorable outcomes (Supp. 7).

Given the limited number of patients experiencing unfavorable outcomes in the Montreal cohort (n = 3), a site-specific prediction model could not be built for this cohort. When combining data from both cohorts, we observed the same transitional cough rate on the total enrollment period and the ROC curve AUC was found to be 0·748 (Supp. 8). All analyses combining both cohort data reinforced the same biological signal of higher coughing rates being associated with more favorable clinical outcomes.

4. Discussion

Objective measurement of cough in acute care setting is feasible. In our study, more frequent coughing being associated with better outcomes. Although we showed that cough was naturally down trending in all hospitalized COVID-19 patients, those presenting with a lower cough per hour rate were at a higher risk of evolving towards intubation or death. Both site-specific and pooled data from two independent cohorts supported this finding.

One interesting finding of our study is the significant discrepancy in cough rates between both cohorts. The recording technology, cough detection algorithm and recording protocols were identical in both sites. We hypothesize that this difference could be explained by the time

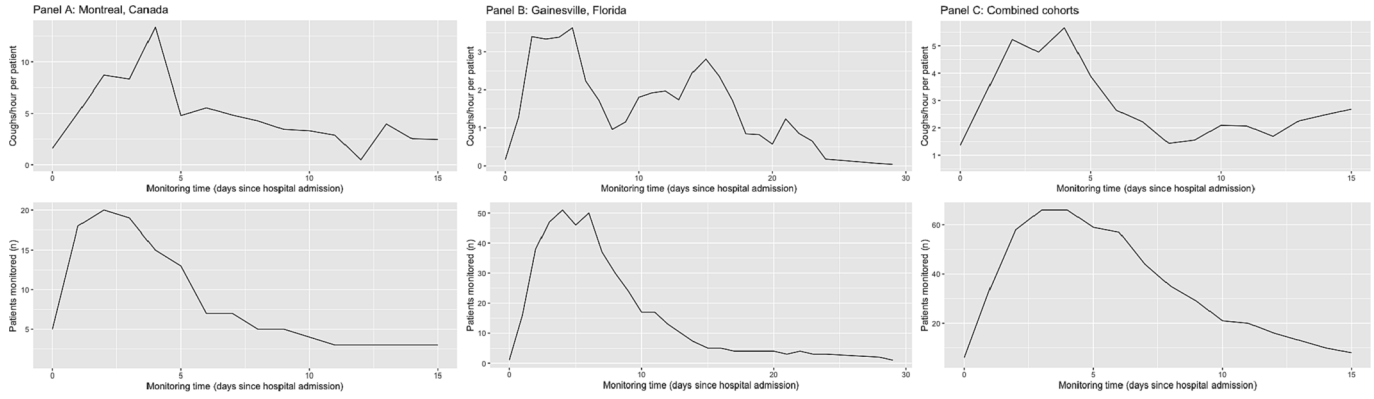

Fig. 1. Natural Evolution of Cough in Hospitalized COVID-19 disease. Natural evolution of cough in hospitalized COVID-19 patients from hospitalization to hospital discharge, intubation, or death in Montreal (Panel A - Left), Gainesville (Panel B - Center) and both patient cohorts (Panel C - Right). The evolution of cough in cough per participant per hour (up) and the total number of enrolled participants contributing to the data set at any given timepoint (down) is displayed.

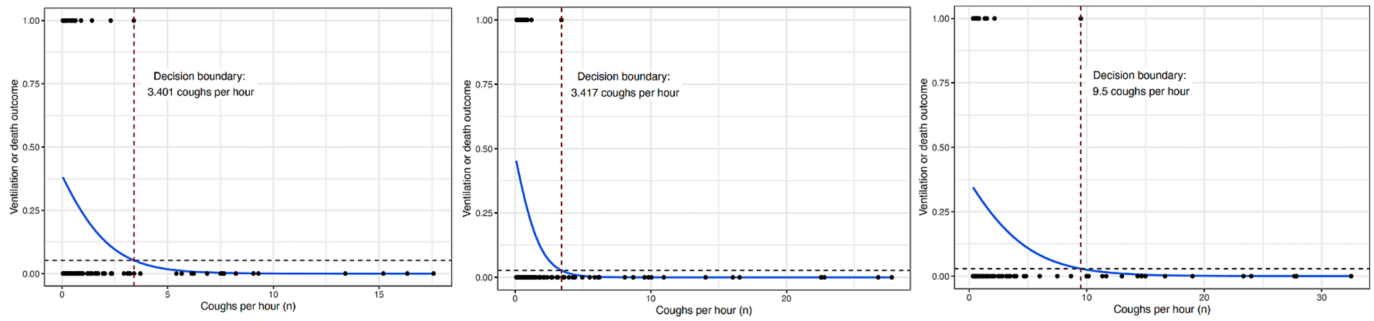

Fig. 2. Cough rates and clinical outcome in hospitalized COVID-19 patients. Relationship between cough per hours and clinical outcomes (mechanical ventilation or death – 1·00, favorable outcome – 0·00). Transitional cough rates, or maximum cough rates per hour among those with bad outcomes are 3·40 for the total enrollment period (Left) 3·42 for the first 24 h of monitoring (Middle) and 9·50 for the first 6 h of monitoring (Right).

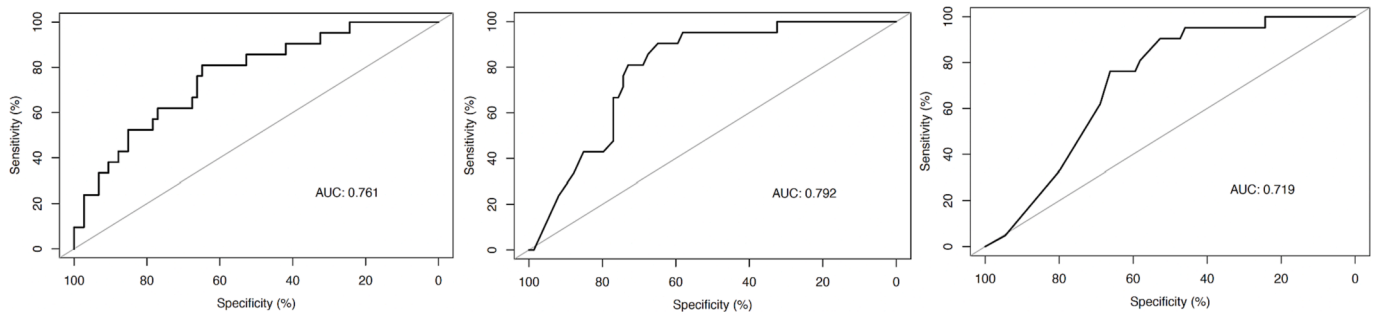

Fig. 3. Receiver operating characteristic curve of the cough-based clinical prediction models. ROC curve of the cough prediction models describing the trade-off in models' sensitivity when increasing specificity for the total enrollment period (Left), the first 24 h of monitoring (Middle) and the first 6 h of monitoring (Right).

Table 2
Baseline cough-based prognosis score performance.

	Total enrollment period	First 24 h	First 6 h
Sensitivity (%)	100·0	100·0	100·0
Specificity (%)	23·3	32·9	24·7
Positive predictive value (%)	27·3	30·0	27·6
Negative predictive value (%)	100·0	100·0	100·0

between hospitalization and study enrollment which was longer in the Gainesville cohort. As show on Fig. 1 Panel A (Montreal) and B (Gainesville) lower graphs, the number of patients monitored peaked earlier in Montreal. We may have captured Montreal patients earlier in the course of disease leading to higher cough rates given the general downward trend of cough following hospitalization.

Except for age which was correlated with unfavorable outcomes, no comorbidities or demographic factors were found to be independent predictors of intubation or dead, or potential biases in our analysis. This is most likely because enrolled patients were already severely ill and requiring hospitalization. Previously described risk factors for severe disease such as metabolic syndrome features would likely have emerged as significant predictors in an ambulatory population. Our study should be validated in independent cohorts given its limited power (n = 123). Our conclusions should also be tested in a broader range of COVID-19 infected patients including outpatients not requiring hospitalisation. A digital cough monitoring prognosis model would have high value in this population although it is unlikely that the cough observed patterns and decision thresholds would be similar to those described here. Antitussive drugs or airway clearance physiotherapy treatments may impact patients' cough rates. Such medication was not part of COVID-19 clinical management protocols and physiotherapy was not allowed because of infection control measures.

In a pandemic context, where health resources allocation requires prioritization, rapidly triaging patients and protecting hospitalization capacity for those at higher risk of complications is critical. Other studies, including some using machine learning approaches on large cohorts of hospitalized COVID-19 patients, have developed composite prognosis scores to predict mechanical ventilation, ICU admission and mortality. He et al. reported such composite scores having an AUC of 0·850. [12] With AUCs ranging from 0·719 to 0·792, cough represents a promising independent predictor which could complement previously developed scores or be used as a stand-alone, easy to implement strategy. In our study, the initial 6 h and 24 h of cough monitoring had similar performance for predicting unfavorable outcomes, suggesting that cough monitoring over an early observation period could support clinical decision making. This finding is also of particular interest for low- and middle-income settings with limited hospitalization and patient monitoring capacity.

To date, the use of digital cough monitoring in COVID-19 has been limited to AI cough classification algorithms aimed at screening for, or diagnosing, COVID-19. [13–16] Those models were reported to be highly sensitive and specific but their validation in external cohorts is still needed as their performance is highly contingent on their respective training and validation datasets. [17] Conversely, our approach strictly relies on human cough detection for which AI algorithms have been robustly validated as part of this trial and in independent settings. [7–8] In this study, the Hyfe cough detection model was found to be highly sensitive (94·1%) and specific (97·4%) when assessed against human observation on a subset of 150,954/291,684 putative explosive cough sounds randomly selected from both study sites. Although cough classification and cough detection represent different approaches and challenges, they could be combined to increase prediction models performance. That is, augmenting our model by taking into account the acoustic signature of coughs and recognizing the specific features of those coughs associated with unfavorable outcomes could be attempted in the future.

Analyzing longitudinal cough time series represents a challenge since clinically significant signals or changes in cough pattern may vary

between individuals and respiratory diseases. Although our study is the first in COVID-19, cough frequency was previously shown to correlate with disease-specific prognosis or severity and contagiousness markers in other conditions such as tuberculosis. [5,18] Proano et al. previously reported on the impact of tuberculosis treatment initiation on cough longitudinal patterns. [5] Similarly, to our approach, they assessed correlations between median cough per hour rates and clinically meaningful outcomes. Turner et al. rather measured the number of coughs per 24 h at initiation of TB treatment to predict contagiousness as measured by incident latent TB infection among household contacts. [18] Our study together with other evidence from those distinct medical conditions confirms the potential role of objective cough assessment in the clinical management of respiratory diseases.

We achieved implementation of digital cough monitoring technology within routine clinical care in tertiary care hospitals where cough was monitored longitudinally as a vital sign. Our study suggests that in hospitalized COVID-19 patients, although is not a perfectly accurate predictor of unfavorable clinical outcomes, limited coughing is associated with higher risks of intubation or death. If validated in future studies, this could support patient care and more strategic resource allocation.

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Ethics approval

This study received ethics board approval from the Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM) and the Emerging Pathogens Institute.

Consent to participate

Written informed consent was obtained from all individual participants included in the study.

CRediT authorship contribution statement

Ellery Altshuler: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Bouchra Tannir:** Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Gisèle Jolicoeur:** Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Matthew Rudd:** Formal analysis, Methodology, Software, Validation, Visualization, Writing – review & editing. **Cyrus Saleem:** Data curation, Writing – review & editing. **Kartikeya Cherabuddi:** Formal analysis, Methodology, Software, Writing – review & editing. **Dominique Hélène Doré:** Data curation, Writing – review & editing. **Parav Nagarsheth:** Formal analysis, Writing – review & editing. **Joe Brew:** Conceptualization, Writing – review & editing. **Peter M. Small:** Conceptualization, Methodology, Writing – review & editing. **J. Glenn Morris:** Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing. **Simon Grandjean Lapierre:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: EA, BT, GJ, CS, KC, DHD, JGM and SGL declare no financial interests. Co-authors MR, PN, JB and PMS are employees of Hyfe Inc. which provides a free of charge mobile application which was used during this study. No authors received financial compensation for participation in this work.

Data availability

All primary cough data is publicly available on Synapse Storage public repository under project name syn40812221. [19].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbi.2023.104283.

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