Physiological signal entropy in patients with chronic respiratory disease: a systematic review

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Further research is needed to facilitate the development of entropy analysis of physiological signals in chronic respiratory diseases into a fully effective tool for clinical practice.
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Abstract

Background Chronic respiratory diseases (CRDs) such as COPD and asthma have a substantial impact on patients and healthcare systems. Recent research on diagnosing and monitoring CRDs highlights the potential of continuous measurement of physiological parameters using nonlinear measures such as entropy analysis. Entropy measures the irregularity and complexity of physiological signals, reflecting the engagement of physiological control mechanisms. This systematic review examines the current evidence on changes in the entropy of physiological signals in CRDs.

Methods The review follows Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) guidelines and includes studies from databases such as Scopus, Medline, CINAHL and Embase. Quality assessment was conducted using the Newcastle–Ottawa Scale. Evidence was qualitatively synthesised, taking into account entropy signals, entropy type and results.

Results 11 studies met the inclusion criteria. Entropy in signals including heart rate variability (HRV), airflow, peripheral oxygen saturation (S_{pO_2}), inter-breath interval and tidal volume were evaluated. The findings indicated that patients with COPD and asthma exhibit lower entropy in HRV and airflow compared to healthy controls, with entropy decreasing as disease severity increases. Conversely, S_{pO_2} entropy values were increased during an exacerbation compared to stable COPD.

Conclusion The review highlights the potential of entropy analysis of physiological signals for early detection of COPD exacerbations and for differentiating between various levels of disease severity in both COPD and asthma. Additionally, it identifies research gaps, particularly in relation to other CRDs such as bronchiectasis and interstitial lung diseases. Further research is needed to facilitate the development of this approach into a fully effective tool for clinical practice.

Introduction

Chronic respiratory diseases (CRDs) represent a spectrum of conditions that adversely affect the lungs and airways. These conditions have a profound impact not only on the individuals affected but also on their families and the healthcare system. CRDs include, but are not limited to, COPD, asthma, bronchiectasis and interstitial lung diseases (ILDs) [1]. A hallmark symptom of these conditions is dyspnoea, which indicates an increased work of breathing due to impaired respiratory function. In many cases, prolonged hypoxia is a common consequence of CRD, triggering adaptive changes in integrative physiological control mechanisms. These adaptations alter the dynamic of physiological signals, potentially compromising respiratory efficiency and disrupting homeostasis.

The incidence of CRDs is influenced by several prevalent risk factors, including exposure to biomass fuel burning, which affects over two billion individuals worldwide, outdoor air pollution, impacting one billion

people, and tobacco smoking, which directly affects one billion people and an additional billion through passive exposure [2]. It is estimated that CRDs contribute to the premature deaths of approximately four million individuals annually [3].

While CRDs cannot be cured, available treatments can alleviate symptoms, enhance patients' quality of life and prevent adverse outcomes such as frequent healthcare utilisation, increased morbidity, disability and mortality [1]. However, diagnosing CRDs poses significant challenges; testing and appointments can be time-consuming, the required equipment is often costly in terms of equipment or expertise [4], and the tests are volitional, requiring patient effort and coordination. This can be particularly difficult for individuals with severe respiratory impairment, cognitive limitations or anxiety, which may hinder their ability to perform the necessary manoeuvres reliably [5].

Lung function tests are crucial for screening and identifying potential CRDs. Among these tests, spirometry is commonly used to measure airflow obstruction. However, spirometry has limitations when it comes to assessing the ongoing biological processes or changes occurring within a patient's lungs over time. It primarily measures airflow obstruction but does not capture the underlying dynamic changes in lung tissue or inflammation that may be occurring, making it unsuitable for evaluating the complex and evolving nature of a patient's condition [6, 7].

Current research on diagnosing and monitoring CRDs highlights the potential of continuous measurement of physiological parameters using nonlinear measures such as entropy analysis [8–11]. Entropy has been used in statistical physics to describe the degree of disorder in a system. In 1948, Shannon expanded the concept beyond statistical physics, applying it to signal processing to quantify the information content of a signal. This expansion paved the way for entropy's use in various fields such as information theory [12] and the analysis of physical and physiological time-series [13].

Entropy is a measure of the irregularity and complexity of physiological signals and quantifies the unpredictability within these signals. When the entropy of physiological signals is reduced, it can be interpreted as decreased engagement of the physiological network or partial uncoupling of its components [14]. In the context of dynamic physiological systems, several extended entropy concepts have been developed with potential clinical application. These include approximate entropy (ApEn), which was initially introduced to assess variability in physiological time-series data. However, a notable limitation of ApEn lies in its dependence on sequence length, which can affect the reliability of its estimations [15]. To overcome this limitation, sample entropy (SampEn) was developed as an improved alternative, offering greater consistency and reduced sensitivity to data length [16]. Furthermore, to analyse data at different resolutions and to better distinguish between randomness and complexity, multiscale entropy (MSE) was developed [17]. These measures have been comprehensively explained in a previous systematic review [18].

The entropy of physiological signals relevant to CRDs, including dynamical changes of air flow [9], peripheral oxygen saturation (S_{pO_2}) [19], inter-breath interval (IBI) [10], tidal volume [10] and heart rate variability (HRV) [20, 21], have been studied. It is known that the entropy of physiological signals differs in patients with obstructive sleep apnoea compared to healthy individuals [18]. Given that the entropy of physiological signals reflects the engagement of physiological control mechanisms, alterations in entropy are anticipated in CRDs due to the complexity of these disorders [20–22]. This systematic review aims to critically evaluate current evidence on entropy alterations in physiological signals, appraising findings from relevant studies and identifying knowledge gaps that warrant further investigation.

Methods

This systematic review followed the Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23] and was registered *a priori* with PROSPERO (registration number: CRD42023439931).

Search strategy and criteria for inclusion

The Scopus, Medline, CINAHL and Embase databases were searched for keywords and titles of papers published up to July 2024. The detailed strategy can be found in supplementary appendix 1. The search results were inputted into Rayyan software (www.rayyan.ai) and two researchers (M. Cheung and N. Alotaibi) assessed articles independently. Any disagreements were resolved by discussion, with the senior researcher (S. Mandal) having the final say. The initial search yielded 461 articles, which was reduced to 214 following the elimination of duplicates and the removal of those which were not pertinent based on titles and abstracts. Of these, 54 papers satisfied the criteria for full-text eligibility assessment. The result of this was that 11 studies ultimately satisfied the criteria for inclusion and were processed according to the workflow shown in figure 1.

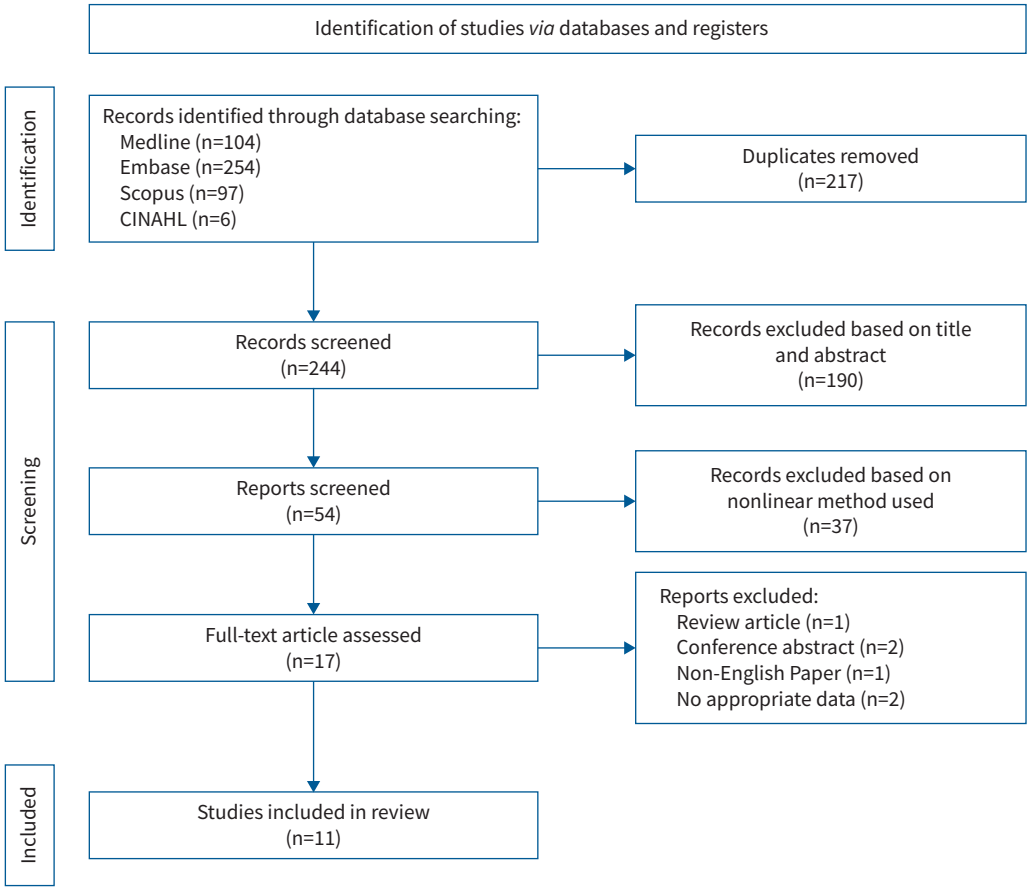

FIGURE 1 Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

The studies included in this review satisfied the following conditions: 1) studies involving human subjects; 2) adult participants >18 years of age; 3) patients diagnosed with CRDs; 4) utilisation of entropy for the analysis of physiological signals; 5) published in English; and 6) published articles, excluding conference abstracts. A SPIDER (sample, phenomenon of interest, design, evaluation, research type) format was used to include or exclude studies (table 1) [24]. No other restrictions were applied in terms of date or publication status specifications.

Data extraction and assessment of quality

We recorded the following parameters from the studies selected: physiological signals studied, gender and ages of subjects, study location, entropy types, and entropy results. The quality of the studies was assessed with the Newcastle–Ottawa Scale (NOS), which is designed to evaluate nonrandomised studies in systematic reviews (see supplementary appendix 2). We selected a form of the NOS which is adapted for

TABLE 1 The SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, Research type) tool applied to the review questions

Criteria	Definition
Sample	Adult with CRD
Phenomenon of interest	Analysis of entropy signals in patients with CRD
Interest	Entropy with CRD
Design	All observational studies, *e.g.* cross-sectional studies
Evaluation	Entropy signals, type of entropy, length of the time series
Research type	Original studies

CRD: chronic respiratory disease.

use in cross-sectional studies [25] (see supplementary appendix 3 for full details). This analysis gives a point score, where ⩾7 is considered "good", 2–6 "fair" and ⩽1 "poor".

Results

Following the application of our inclusion criteria, a total of 11 studies remained for analysis (figure 1), which were subsequently evaluated according to the procedure detailed in supplementary appendix 2. Of these, seven demonstrated good methodological quality, as indicated by their NOS scores. A number of physiological signals were measured in the studies, including air flow, IBI, tidal volume, S_{pO_2} and HRV time-series (see tables 2 and 3). The following sections describe each of these physiological signals specifically in relation to the entropy studies conducted on COPD and asthma. No studies examined the entropy of physiological signals in bronchiectasis or ILD.

Studies of COPD and entropy

Entropy of HRV

Four studies examined HRV entropy in COPD patients using electrocardiograms (ECG) with varying sample rates and degrees of severity [11, 20, 26, 27]. Caliskan *et al*. [26] observed that HRV measured by ApEn was significantly lower in patients with moderate to severe COPD compared to healthy subjects. Álvarez *et al*. [27] reported lower irregularity (lower SampEn) in overnight HRV recordings from patients with COPD alone compared to those with overlap syndrome (COPD and obstructive sleep apnoea syndrome).

A study by Ma *et al*. [20] explored the daytime differences in HRV between COPD patients and healthy subjects. The study revealed that older people and those with COPD exhibited reduced HRV, as well as diminished diurnal variations in HRV measurements when using MSE analysis. There was an increase in HRV using Shannon entropy in COPD patients compared to healthy control subjects of similar ages [11].

Entropy of S_{pO_2}

One study investigated night-time S_{pO_2} measured in 11 COPD patients using a pulse oximeter with 0.25 Hz sample recording. The results showed that the SampEn of S_{pO_2} increased during an exacerbation compared to stable COPD. Furthermore, the study showed that S_{pO_2} entropy exhibited reasonable sensitivity and specificity for the early detection of COPD exacerbations, as demonstrated by an analysis using receiver operating characteristic (ROC) curves [19].

Entropy of airflow

Two studies investigated airflow entropy as a potential marker for identifying alterations in airflow complexity caused by airway obstruction in COPD [9, 22]. Both studies utilised SampEn to measure airflow entropy, observing a reduction in entropy with increasing airway obstruction in COPD patients. ROC analysis demonstrated the sensitivity of SampEn for detecting respiratory system changes, achieving clinically acceptable values even in cases of mild obstruction, with an area under the curve (AUC) of 0.84 [9]. Yentes *et al*. [22] observed a significant difference in airflow between the groups and postures. COPD patients had more regular airflow than the control group in the three postures of standing, sitting and walking. In both groups, the airflow while walking showed significantly greater irregularity than that while seated or standing. Standing airflow was also more irregular than sitting in both groups. The studies of entropy and physiological signals in COPD are summarised in table 2.

Studies of asthma and entropy

Entropy of HRV

Garcia-Araújo *et al*. [21] analysed HRV in lying and seated positions, as well as respiratory sinus arrhythmia in asthma and healthy subjects. They employed nonlinear analysis methods including SampEn, ApEn and Shannon entropy to assess the complexity and irregularity of HRV (table 3). Those with asthma had a higher SampEn of cardiac rhythm when lying down compared to when seated. However, they had a significantly lower ApEn value whilst performing the respiratory sinus arrhythmia manoeuvre than the control group.

Entropy of airflow

Two studies explored respiratory pattern complexity using entropy [10, 28]. Veiga *et al*. [28] included patients with asthma, exhibiting varying degrees of airway obstruction, and a healthy control group. They found a significant decrease in airflow ApEn in the asthma patients, which was significantly correlated with the indices of airway obstruction in relation to forced expiratory volume in 1 s. The airflow ApEn values proved acceptable for use in the clinical determination of airway obstruction (AUC>0.8) as assessed by ROC plots.

TABLE 2 Studies on entropy comparing COPD patients and healthy subjects

Physiologic time-series	Study, year	Equipment used/sample rate/duration	Entropy type	Country of data collection	Sample size (COPD/ comparator)	Age in years as mean±SD or range	Gender ratio (male/ female)	Pulmonary function as mean±SD or range	Entropy result	ROC analysis used
HRV	Caliskan *et al.* [26] 2018	ECG/200 Hz	ApEn	Turkey	24 (16/8)	Moderate COPD: 60.63±2.22 Severe COPD: 68.13±2.95 Control: 58.88±1.99	NA	FEV_1/FVC Moderate COPD: 78.56±0.80 Severe COPD: 77.77±0.95 Control: 80.00±1.18 FEV_1 (% pred) Moderate COPD: 62.45±0.84 Severe COPD: 40.04±1.46 Control: 77.00±1.14	HRV entropy is lower in moderate to severe COPD patients than in the control group	No
	Álvarez *et al.* [27] 2019	Pulse oximeter/ 1 Hz/10 min	SampEn	Spain	84 (22/62)	COPD: 60.5 (57–64) COPD+OSAS: 66 (60–75)	74/10	FEV_1/FVC COPD: 59.4 (50.1–65.2) COPD+OSAS: 60.9 (52.0–65.4) FEV_1 (%) COPD: 68.5 (55.0–83.2) COPD+OSAS: 62.5 (54.3–73.0)	HRV entropy is lower in COPD patients compared to overlap syndrome	No
	Serrao *et al.* [11] 2020	ECG/250 Hz/ 10 min	Shannon entropy	Italy	74 (54/20)	COPD: 66±8.99 Control: 65±8.59	61/13	FEV_1/FVC COPD: 0.43±0.10 Control: 0.77±0.06 FEV1 (% pred) COPD: 34.42±9.67 Control: 101.66±16.83	HRV entropy is higher in COPD patients compared to control group	No
	Ma *et al.* [20] 2023	ECG/256 Hz/24 h	MSE	USA	194 (16/178)	COPD: 68.4±8.9 Younger healthy: 34.5±8.9 Older healthy: 61.6±9.1	96/98	NA	HRV entropy is lower in day–night differences in COPD compared to healthy individuals	No

Continued

TABLE 2 Continued

Physiologic time-series	Study, year	Equipment used/sample rate/duration	Entropy type	Country of data collection	Sample size (COPD/ comparator)	Age in years as mean±SD or range	Gender ratio (male/ female)	Pulmonary function as mean±SD or range	Entropy result	ROC analysis used
S_{pO_2}	Al Rajeh *et al.* [19] 2021	Pulse oximeter/ 0.25 Hz/90 min	SampEn	UK	11 (11/0)	71.8±10.4	7/4	FEV_1 (%): 47.7±18.8	S_{pO_2} entropy is higher during exacerbation compared to stable COPD	Yes
Airflow	Dames *et al.* [9] 2014	Spirometers/ 5 Hz	SampEn	Brazil	75 (59/16)	Mild: 62.1±10.7 Moderate: 64.8±10.2 Severe: 70.8±10.8 Very severe: 67.3±8.9 Controls: 61.4±13.6	NA	FEV_1/FVC Mild: 68.3±2.5 Moderate: 65±11.2 Severe: 39.7±10.1 Very severe: 40.2±10.2 Controls: 78.5±6 FEV_1 (% pred) Mild: 90.6±9 Moderate: 68.4±7.2 Severe: 39.5±6 Very severe: 25.2±0.2 Control: 94±18.9	Airflow pattern complexity is reduced with moderate and very severe airway obstruction in COPD compared to control group	Yes
	Yentes *et al.* [22] 2020	Portable metabolic unit/ 25 Hz	SampEn	USA	37 (16/21)	COPD: 64.3±7.9 Control: 60.2±6.8	14/23	FEV_1/FVC COPD: 0.54 Control: 0.79 FEV_1 (% pred) COPD: 52 Control: 97	Airflow entropy is lower in COPD compared to control group	No

ApEn: approximate entropy; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; HRV: heart rate variability; MSE: multiscale entropy; NA: not applicable/available; OSAS: obstructive sleep apnoea syndrome; ROC: receiver operating characteristic; SampEn: sample entropy; S_{pO_2}: peripheral oxygen saturation.

TABLE 3 Studies on entropy comparing asthma patients and healthy subjects

Physiologic time-series	Study, year	Equipment used/ sample rate/duration	Entropy type	Country of data collection	Sample size (asthma/ control)	Age in years as mean±SD or range	Gender ratio (male/ female)	Pulmonary function as mean±SD or range	Entropy result	ROC analysis used
HRV	GARCIA-ARAÚJO *et al.* [21] 2015	Cardio frequency meter/24 min	ApEn SampEn Shannon entropy	Brazil	24 (14/10)	Healthy: 31±8.7 Asthma: 28±8.5	21/3	FEV_1/FVC (%) Control: 102.1±8.0 Asthma: 70.0±13.0 FEV_1 (% pred) Control: 97.2±13.4 Asthma: 86±15	HRV entropy is lower in asthmatic patients during respiratory sinus arrhythmia manoeuvre compared to healthy subjects	No
Airflow	VEIGA *et al.* [28] 2012	Spirometer	ApEn	Brazil	51 (40/11)	Healthy: 54.4±15.1 Mild: 51.1±13.5 Moderate: 54.2±10.7 Severe: 60.5±12.5	NA	FEV_1/FVC (%) Control: 80.8±5.0 Mild: 68.6±5.3 Moderate: 53.4±4.7 Severe: 37.6±8.7 $FEF_{25–75\%}$ (%) Control: 88.9±22.9 Mild: 47.1±13.1 Moderate: 21.8±7.5 Severe: 8.4±3.4	Airflow entropy is lower in asthmatic patients with different levels of airway obstruction compared to healthy subjects	Yes
Inter-breath interval and tidal volume	RAOUFY *et al.* [10] 2016	Plethysmography/ 70 min	SampEn	Iran	40 (30/10)	Control: 27.6±5.3 Controlled atopic asthma: 30.8±9.8 Controlled atopic asthma: 31.1±7.2 Nonatopic asthma 32.7±8.1	NA	NA	Entropy of inter-breath interval is lower in asthmatic patients, particularly in UAA and UNAA compared to healthy control group Entropy of tidal volume time-series is not different in nonatopic asthma compared with healthy control group, but it is reduced in UAA	Yes
Airway resistance	GONEM *et al.* [29] 2012	Impulse oscillometry system/5–35 Hz/150 s	SampEn	UK	96 (66/30)	Control: 47.0±2.2 GINA4: 51.0±2.3 GINA5: 56.5±1.9	43/53	NA	Airway resistance is higher in asthmatic patients with frequent exacerbations	No

ApEn: approximate entropy; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; GINA: Global Initiative for Asthma; HRV: heart rate variability; NA: not applicable/available; ROC: receiver operating characteristic; SampEn: sample entropy; UAA: uncontrolled atopic asthma, UNAA: uncontrolled non-atopic asthma.

IBI and tidal volume

Raoufy *et al*. [10] employed SampEn to compare respiratory complexity patterns between asthma patients and healthy individuals. Continuous measurements of tidal volume and IBI were recorded, revealing a significant reduction in SampEn for both parameters in the asthma patients, in comparison with the healthy control group. This study also compares IBI and tidal volume time-series between patients with atopic and nonatopic asthma. The results showed no significant differences in the SampEn of tidal volume between nonatopic asthma patients and healthy subjects, whereas nonatopic asthma patients exhibited more regular IBI series (*i.e.* reduced entropy). These findings suggest that entropy measures of respiratory time series may distinguish between atopic and nonatopic asthma and provide insights into the pathophysiology of nonatopic asthma.

Entropy of airway resistance

One study explored SampEn patterns in airway resistance in both patients with asthma and control subjects and examined the correlation with asthma symptom exacerbation frequencies. The study found that the SampEn of airway resistance was significantly higher in severe asthma patients compared to the control group, both at baseline and after bronchodilation. Additionally, there was a significant correlation between higher SampEn and the frequency of exacerbation (table 3). The only one independently linked to frequent exacerbations (defined as two or more exacerbations in the previous year) was a SampEn of R5–R20, which is the difference between resistance at 5 Hz and that at 20 Hz, a measure of the diversity of bronchial tree obstruction [29].

Discussion

The present review identified 11 studies that explore the entropy of physiological signals in patients with CRDs, specifically COPD and asthma. To the best of our knowledge, no studies have investigated the entropy of physiological signals in other CRDs, such as bronchiectasis and ILD. Thus, there is a gap in knowledge and understanding of the entropy of physiological signals in ILD and bronchiectasis, which awaits further investigation.

The findings of this review demonstrate that the change in entropy patterns in CRDs are dependent on the specific physiological signals being monitored. A key tool in the evaluation of physiological processes is HRV. The findings demonstrate that individuals with asthma and COPD exhibit lower entropy values compared to healthy controls in both HRV and airflow. Furthermore, entropy decreases progressively with greater disease severity in these physiological signals [20, 21, 26, 27]. Alterations in HRV patterns serve as an early and sensitive, though nonspecific, indicator of critical illness [30]. In healthy individuals, adequate HRV indicates proper engagement and efficient autonomic mechanisms. Conversely, low HRV suggests an uncoupling of the autonomic mechanisms that modulate heart rate [3]. Since COPD and asthma are chronic conditions, they involve the release of proinflammatory cytokines, such as interleukin (IL)-1β and IL-6 [31]. These cytokines are known to interact with the autonomic control pathways, contributing to a decreased in HRV [32]. Furthermore, patients with COPD may develop arrhythmia, heart failure, pulmonary vascular disorders and ischaemic heart disease, all of which can influence autonomic control and HRV [33, 34]. The absence of detailed comorbidity information in certain studies limits our ability to fully understand the impact of these additional factors on HRV outcomes in COPD and asthma patients. Thus, HRV provides only nonspecific information regarding underlying physiological dysfunctions. Consequently, further investigation is necessary to obtain a more detailed and comprehensive insight into the mechanism of lower HRV entropy in CRDs.

While most studies have demonstrated a reduced entropy of HRV, one study reported an increase in entropy of HRV in COPD [11]. However, Shannon entropy was the methodology employed the latter studied to estimate entropy. Shannon entropy is a concept which is fundamental to information theory. When considering a data source, this method measures the average quantity of information which it produces. This gives rise to a number of limitations; for example, its sensitivity to noise which can produce inaccurate results due a distortion of the entropy calculation. Furthermore, while Shannon entropy exhibits uncertainty or randomness as a whole, it does not take into consideration local structures or patterns arising in the data, which means that the method is not so appropriate for physiological time-series analysis [35]. In addition, Shannon entropy assumes stationarity of the data, *i.e.*, that the statistical properties of data remain constant, which is not the case with such datasets derived from physiological processes. Thus, the estimates produced by Shannon entropy for data sequences that are short may not be reliable because they lack the quantity of data required to make accurate estimates of probabilities [13].

In terms of airflow, entropy is significantly reduced in patients with early-stage COPD and asthma compared to both healthy individuals and those with more advanced stages of these diseases. This

reduction in entropy indicates a loss of complexity in the respiratory dynamics of affected patients. The theory outlined by GOLDBERGER *et al*. [12] provides a compelling framework for interpreting these results. According to this theory, pathophysiological states are often associated with a reduction in the complexity ("de-complexification") of physiological processes. In such states, physiological signals may display either increased regularity (*i.e.*, reduced entropy) or a shift toward randomness (*e.g.*, the development of arrhythmias, which is linked to increased entropy). Therefore, the entropy of physiological signals alone is not a direct measure of complexity and should be interpreted with caution. It is advisable to complement entropy analysis with more advanced methods such as MSE, which can differentiate between random and truly complex time-series data [17]. The observed reduction in airflow entropy in patients with early-stage COPD and asthma compared to healthy individuals may reflect a decline in the complexity of the physiological control system, potentially correlating with disease progression and severity [9, 28]. However, further analytical approaches, such as physiological network mapping [36] and MSE, are necessary to fully understand and interpret these findings.

Airflow obstruction increases in asthma patients cause altered system resistance in respiration. The most common clinical method of measuring the physiology of respiratory tract flow resistance is the forced oscillation technique (FOT). One kind of FOT is impulse oscillometry, which uses external pressure oscillation based on impulses to estimate airway resistance. The results of this demonstrate that airway resistance leads to an inverse change in entropy; reduced entropy in airflow, airway resistance and HRV are associated with increased obstruction of airways [29].

Several studies performed ROC analysis to assess the diagnostic accuracy of a test. The highest AUC value, 0.95, was observed with SampEn in IBI measurements when comparing asthma patients with healthy subjects. However, SampEn did not yield sufficiently high discriminating power when differentiating between controlled and uncontrolled asthma patients or between atopic (allergic) and nonatopic asthma, with AUC values below 0.8. According to the literature, airflow ApEn exhibited acceptable AUC values when comparing healthy individuals to asthma patients with moderate or severe airway obstruction [37]. However, an AUC>0.8 was observed when comparing patients with mild airway obstruction to healthy individuals [28]. Patients with nonatopic asthma exhibited distinct patterns in ventilation dynamics compared to those with atopic asthma, specifically in terms of the entropy of tidal volume time-series [10]. This finding aligns with other reports on the dynamic aspects of ventilation physiology in nonatopic asthma [2, 38] and may provide insights into the pathophysiology of different asthma types.

Differences between control subjects and COPD patients could be detected by entropy in various physiological signals, but the degree of COPD severity could not be distinguished. Thus, entropy analysis for identifying CRD progression has not been utilised to any extent in prior research and evaluation of this methodology deserves further studies. One study reported the potential for early detection of COPD exacerbations 1 day before clinical diagnosis through overnight S_{pO_2} entropy analysis [19]. This proof-of-concept report suggests the potential of home monitoring for COPD patients, as early diagnosis of exacerbations is known to prevent hospitalisations and support the efficient use of rescue packs [19]. However, further studies with larger sample sizes are needed before S_{pO_2} entropy analysis can be implemented clinically for home monitoring of COPD patients.

Our review highlights the potential value of entropy as a novel metric for assessing disease progression at the individual level. However, further research is needed before it can be fully developed as an effective tool for clinical practice. Firstly, the over-arching patterns of entropy variation need to be investigated according to different disease stages. Secondly, the results of entropy analysis vary according to individual differences, so that there is a need to develop standardised value ranges for healthy individuals, based on their biological characteristics (weight, height, age, sex, *etc*.), in order to provide a benchmark for the identification and classification of CRD status. In addition, longitudinal studies would be valuable in revealing relationships between entropy changes and the progression of patients' conditions over time.

Limitations

This systematic review and narrative analysis has some limitations. The primary weakness lies in the heterogeneity of the included studies, which precluded the possibility of conducting a meta-analysis. There is high variability in the physiological time-series measurement methodology, which may introduce inconsistencies across studies and limit our ability to draw definitive conclusions or compare findings effectively. In the context of our research synthesis, it is important to note that some of the studies included were not grouped according to disease severity. This methodological choice has significant implications for the homogeneity and comparability of the data, which can introduce potential bias, particularly if the severity of the disease influences the outcomes.

Additionally, the potential for publication bias exists due to the exclusion of unpublished grey literature and non-English language studies, which may have resulted in the omission of supplementary evidence. This may also have led to a bias in favour of studies reporting positive outcomes. Furthermore, conference abstracts were excluded, despite the fact that a significant portion of entropy-related research originates from engineering literature, where researchers often prioritise conference papers over full reports.

Conclusion

This systematic review may offer new insights into the application of entropy analysis as a tool for assessing disease progression and enhancing diagnostic methods in chronic respiratory diseases. We found reports of significant relationships between changes in the entropy of physiological signals and disease severity in patients with COPD and asthma. Most of the physiological signals examined in the reviewed literature, such as airflow and HRV, show a decrease in entropy with both diseases. Thus, this work lays a foundation for using entropy measurements as indicators to assist in the early recognition of COPD exacerbation and to distinguish between levels of severity in both COPD and asthma. The results of our review suggest valuable avenues for future research on entropy of physiological time-series in CRDs.

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