

Temporal Fluctuations of Electronic Nose Signatures from breath in Patients with Asthma and Healthy Controls before and after challenge with Rhinovirus.

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Rationale

- Point-of-care breath analysis → useful for diagnosing and phenotyping patients with chronic airway diseases [De Vries et al. ERJ, 2018].
- Integration of electronic nose (eNose) to spirometer (SpiroNose) at clinic → effective for exhaled breath analysis [De Vries et al. JBR, 2015].
- Time series fluctuations of eNose signals from exhaled breath, in stable and unstable disease could provide insights → pathophysiology of asthma with episodic loss of control predominantly due to viral exposures.

Hypothesis

Temporal behavior of exhaled breath signatures differs between healthy and asthmatic subjects representing differences in airway pathophysiology, particularly after destabilization by RhinoVirus Challenge (RVC).

Aim

Comparing temporal fluctuations of eNose signatures in exhaled breath of asthmatic and healthy subjects before and after Rhinovirus (RV) challenge.

Methods

Subjects in the study:

- 12 asthmatics (GINA-criteria) - mild to moderate:
 - - atopic, not using steroids, aged 18-35 years.
- 12 healthy volunteers:
 - - non atopic, aged 18-35 years
- Non-smokers or ex-smokers (< 5 pack years)
- Design: (Part of the larger project)
- 3 months - prospective, observational, follow-up study with rhinovirus intervention after 2 months → (33+ visits).
- Exhaled breathprints collected in duplicate consisted of signals from 7 different metal oxide semiconductor sensors (SpiroNose).
- Data analysis involved signal processing, ambient correction and conventional statistics and non-linear time-series analysis.

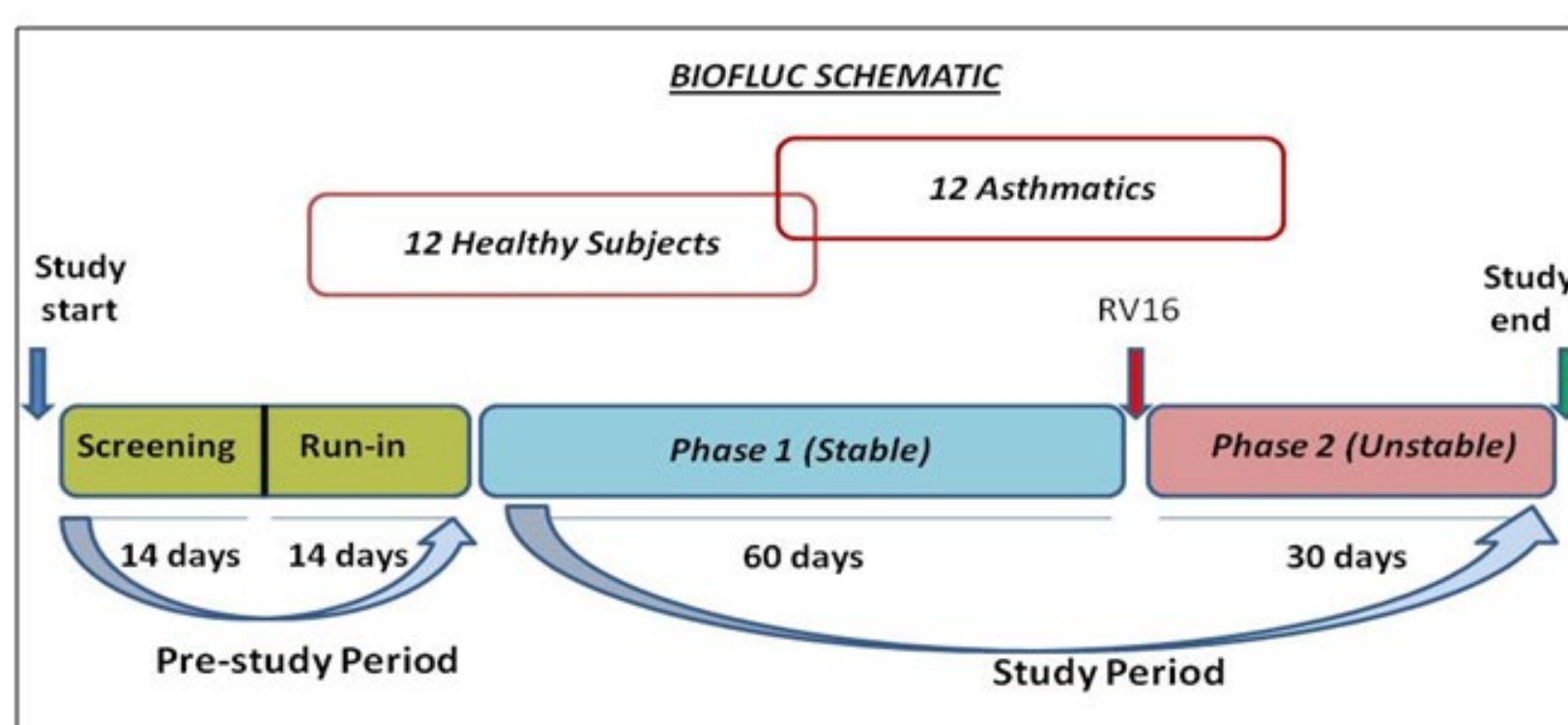
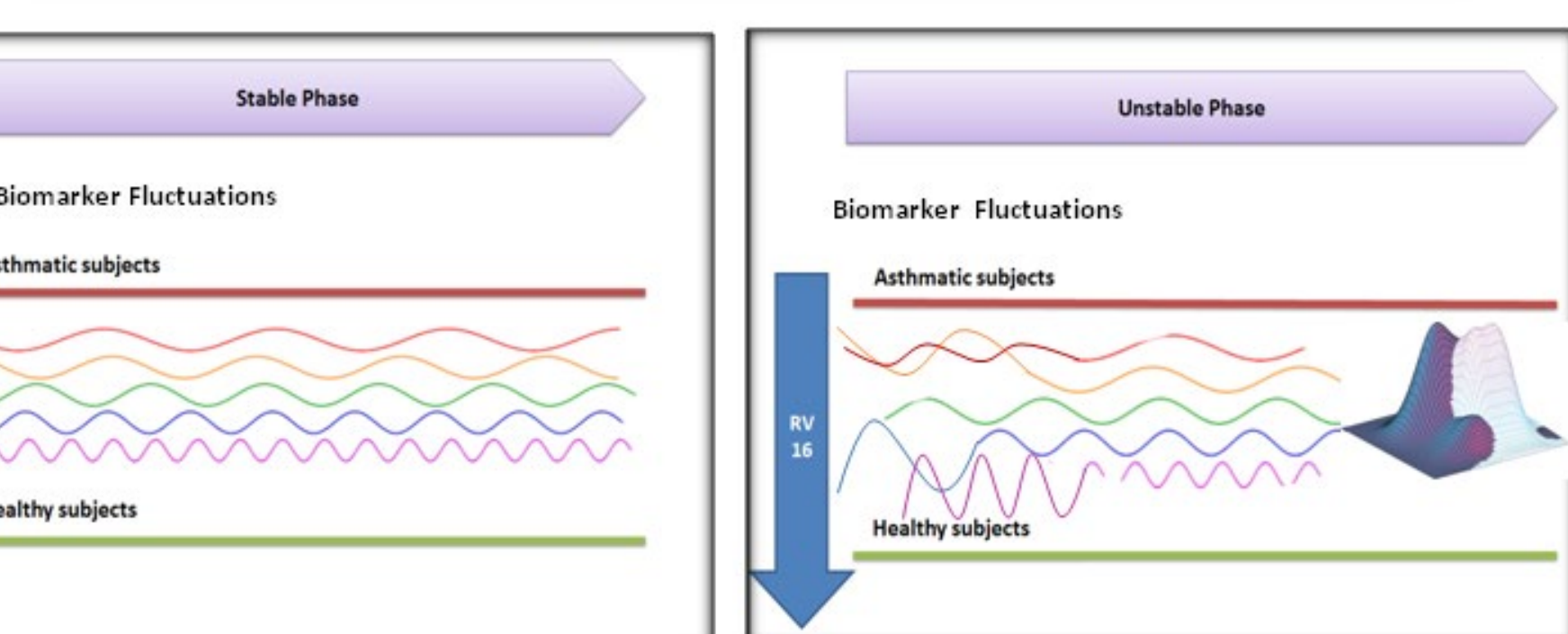


Fig 1: The upper panel shows the design of the study including phases 1 and 2 and the repeated assessments during these episodes. The lower two panels are showing the schematic representation of fluctuation patterns of markers before and after rhinovirus challenge. The frequency of sampling is 3 x weekly



Rhinovirus Intervention: The study participants are challenged with a standardized, validated & low dose of RV16 (100 TCID₅₀) after 2 months into the study to induce loss of control/exacerbation.

Results

I. Comparison of eNose time-series b/w Healthy and Asthma groups: CV and Mean

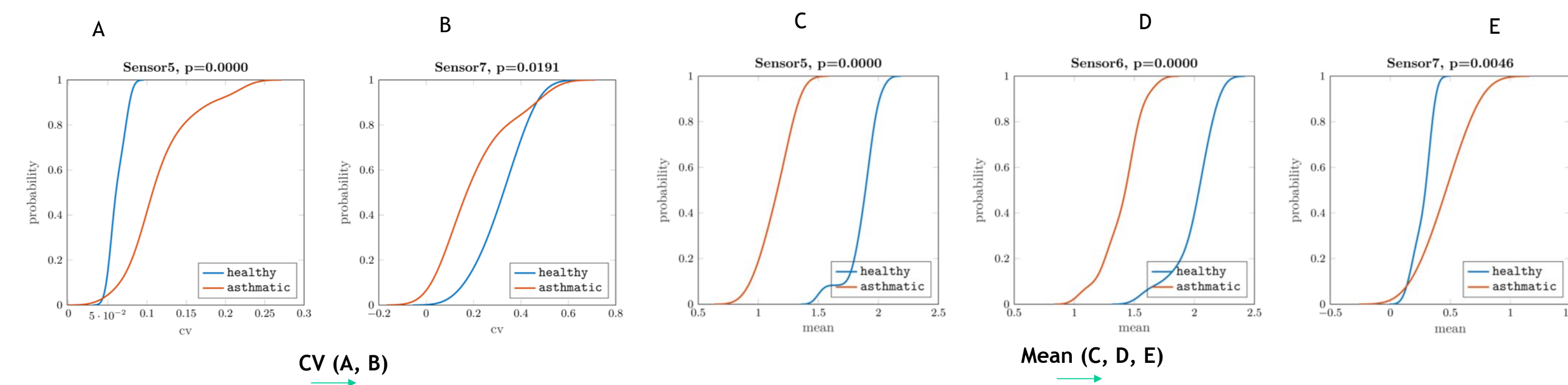


Fig. 2: Kolmogorov-Smirnov (KS) test indicated by Kernel density plots comparing distributions of time series clearly demonstrates significant differences between Healthy and Asthmatic groups for breath signals

II. Non-Linear Time Series Analysis: Comparison of sensor signal fluctuations between Healthy and Asthmatic groups

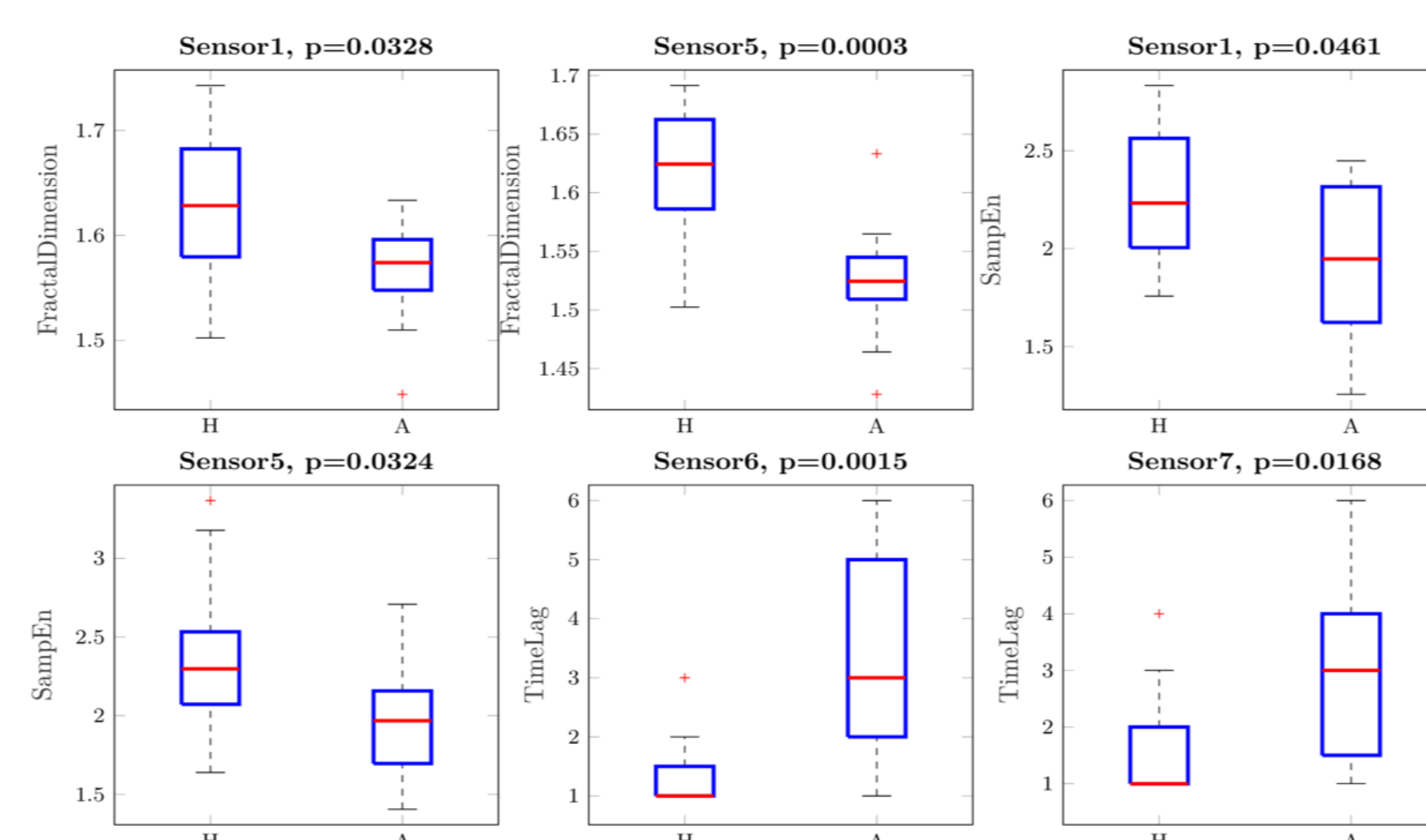


Fig. 3: Fractal Dimension, Sample Entropy and Time lag calculated from eNose sensors clearly distinguishes Healthy from Asthmatic groups

III. Changed pattern of fluctuations b/w pre & post RV challenge

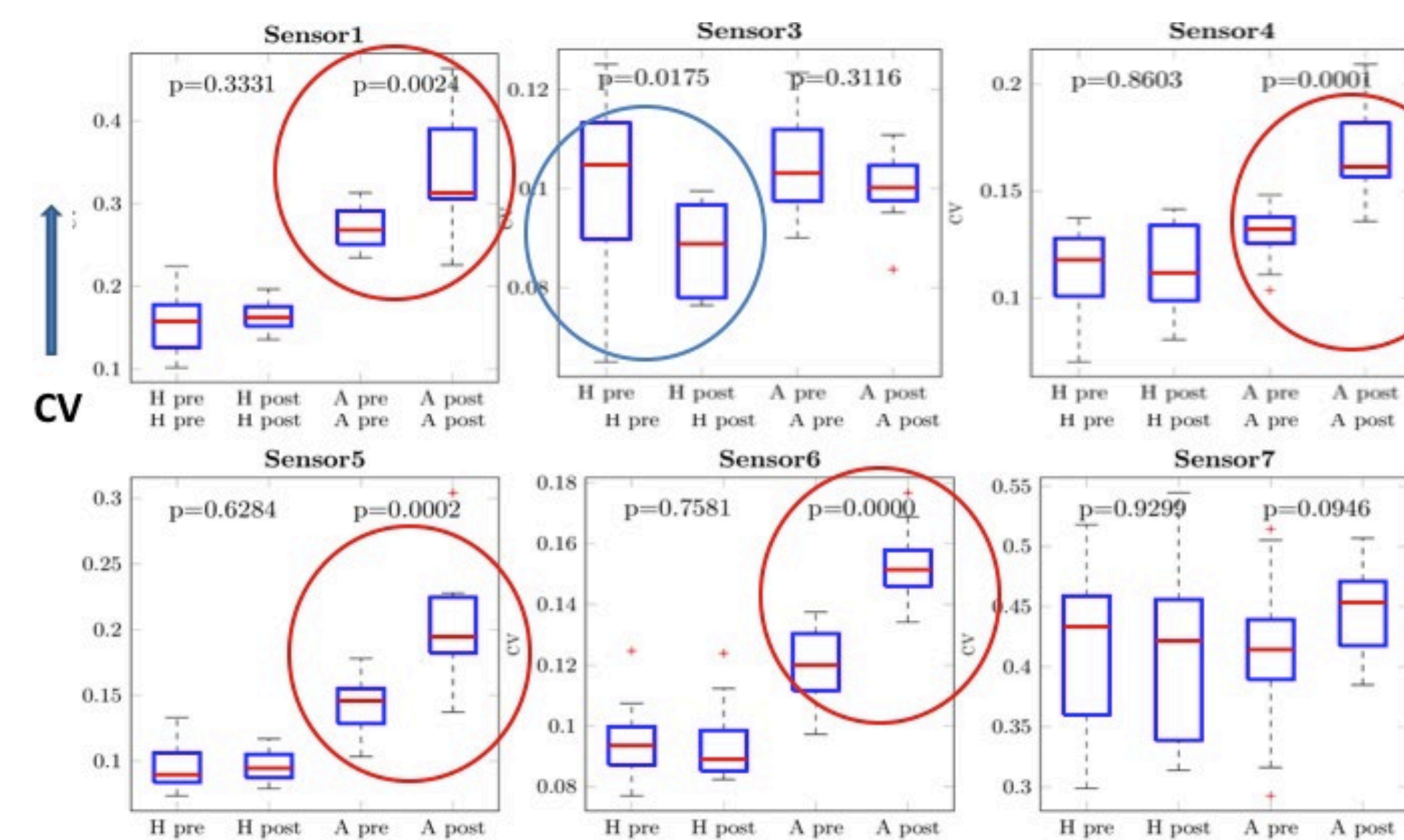


Fig. 4: Coefficient of Variation (CV) differences between pre vs post challenge states compared using Kruskal-Wallis test. CV of asthmatic subjects increase post challenge whereas it decreases post challenge in healthy subjects.

IV. Phase Space Analysis: Comparison of eNose sensor fluctuations between Pre vs Post RV challenge states

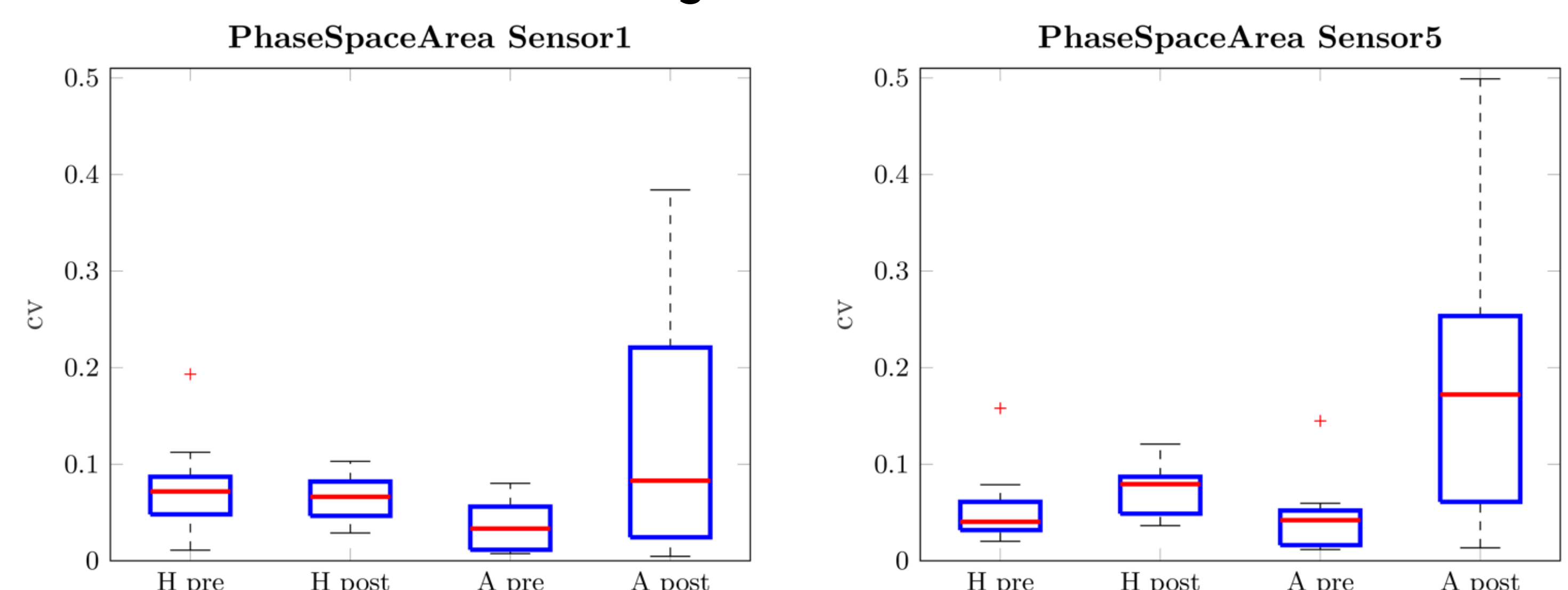


Fig 5: Phase space area of asthmatic subjects after challenge is significantly greater than before challenge indicating larger fluctuations and lesser stability in comparison due to the viral challenge.

Conclusion

Temporal Fluctuations of eNose differ between

1. Healthy and Asthmatic subjects
2. Stable and Unstable states of disease
3. Differences in stability/adaptive capacity of physiological system

Implications

- 1. Point-Of-Care diagnostic in disease monitoring and outcome prediction.
- 2. Variations of exhaled biomarkers provide pathophysiological finger-prints.