The impact of time of day on the diagnostic performance of tests for asthma

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To the Editor:

Asthma affects almost 10% of people worldwide, but up to a third of patients are misdiagnosed [1]. Asthma is a highly rhythmic disease; the majority of patients experience pronounced nocturnal symptoms [2]. Despite almost all the key diagnostic tests showing diurnal variability [2], tests carried out at unspecified times of day are used for clinical decision making. The American Thoracic Society and European Respiratory Society (ATS/ERS) technical statements for spirometry and fractional exhaled nitric oxide (F_{ENO}) acknowledge diurnal variation observed in these tests and recommend the documentation of timing whenever possible [3, 4], but no specific advice is given on how this information should influence interpretation of results. Current asthma diagnostic strategies also do not take into account diurnal variation in tests, likely due to the lack of evidence on how the time of day impacts diagnostic decisions. We investigated the impact of the time of day on the diagnostic performance of tests in asthma.

The Rapid Access Diagnostics for Asthma (RADicA) Study (Research Ethics Committee number 18/NW/0777; ISRCTN 11676160; https://www.radica.org.uk [5]) provides a research platform where symptomatic and untreated (defined as no inhaled corticosteroids use for at least 4 weeks prior to consent) individuals with clinician-suspected asthma are recruited and after giving written, informed consent undergo extensive physiological testing. Using data from RADicA, we describe how the performance of diagnostic tests is influenced by the time of day. Briefly, clinical history and physical examination was carried out. Participants were asked about within-day symptom patterns using a structured questionnaire which was interviewer-administered. Key asthma diagnostic tests, including spirometry and bronchodilator reversibility (BDR), F_{ENO}, methacholine and mannitol bronchial challenge tests, were performed [5]. Participants were skin prick tested and blood eosinophils measured before inhaled corticosteroids (ICS) (Flixotide Accuhaler, 250 µg twice daily) were commenced. Asthma diagnosis was confirmed or refuted by a panel comprising at least two asthma specialists following 6–8 weeks of ICS and taking into account all clinical information and test results. Bronchodilators were withheld for at least 8 h, caffeine intake avoided for 8 h and antihistamines for 3 days prior to all clinical visits. The time of the appointments was allocated based on patients' preference and clinic availability between 09:00 and 17:00, reflecting clinical practice. The time at which the tests were performed was recorded. Positive tests were defined according to the UK National Institute for Health and Care Excellence 2017 asthma diagnostic guidance [6].

Tests performed prior to the initiation of ICS were included in the analysis. Time variable was either treated as a continuous variable (over 24 h) or split into two hourly time slots (09:00–11:00, 11:00–13:00, 13:00–15:00 and 15:00–17:00). Quantile regression was used where a linear relationship was assumed during the investigated timeframe based on existing literature (*e.g.* in F_{ENO}, BDR and bronchial challenge tests). Where a non-linear relationship was assumed (*i.e.* in spirometry parameters, which typically peak during early afternoon), descriptive statistics and a one-way analysis of variance were used. The relationships between timing of measurements and positive/negative test results were assessed using logistic regression. Missing data were excluded. All statistics were performed using R version 4.1 (RStudio version 1.4.1106).

140 symptomatic adults (>16 years) were recruited, of which 118 (84.3%, median (IQR) age: 32.0 (26.0–42.8) years, 37.3% male) had definitive diagnostic outcomes (59.3% asthma and 40.7% not asthma). 84%

Shareable abstract (@ERSpublications)
Performing fractional exhaled nitric oxide and bronchodilator reversibility tests in the morning is more likely to lead to a positive test result than when performed in the afternoon. Therefore, time of day should be considered during test interpretation. https://bit.ly/4b79e5J

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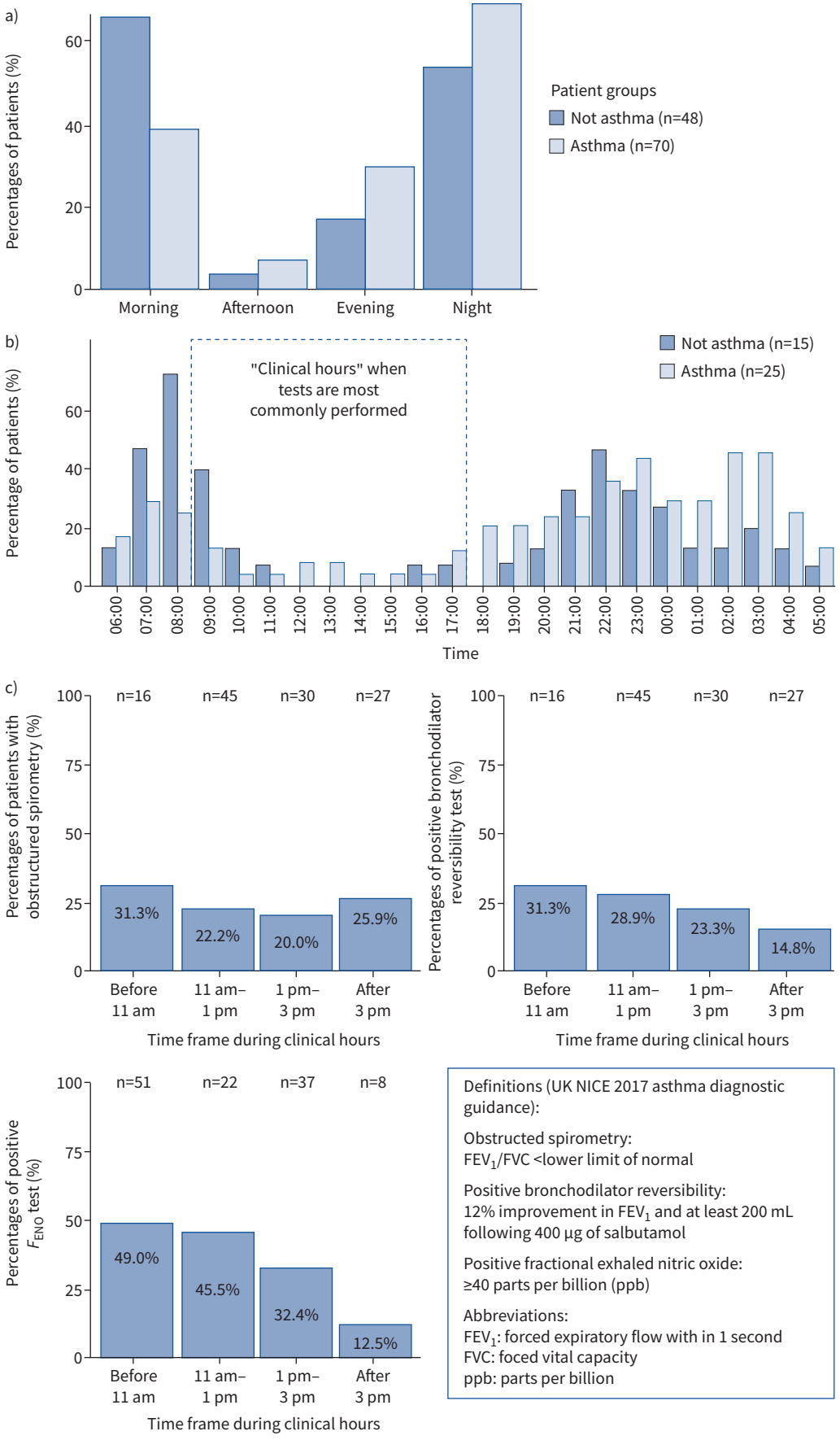

Definitions (UK NICE 2017 asthma diagnostic guidance):

Obstructed spirometry:
FEV_1/FVC <lower limit of normal

Positive bronchodilator reversibility:
12% improvement in FEV_1 and at least 200 mL following 400 µg of salbutamol

Positive fractional exhaled nitric oxide:
≥40 parts per billion (ppb)

Abbreviations:
FEV_1: forced expiratory flow with in 1 second
FVC: foced vital capacity
ppb: parts per billion

FIGURE 1 a) Self-reported symptom pattern in response to the question "Is there any variability of your symptoms through the day?" and "If yes, when are your symptoms worse usually? (Circle all relevant): Morning, afternoon, evening, night"; b) Self-reported symptom patterns of patients specifying the hours during which the symptoms worsened; c) Proportion of obstructive spirometry, positive bronchodilator reversibility and fractional exhaled nitric oxide tests at different time frame during clinical hours. F_{ENO}: exhaled nitric oxide fraction; FEV_1: forced expiratory volume in 1 s; exhaled nitric oxide fraction; FVC: forced vital capacity; ppb: parts per billion.

of those with asthma and 68% not asthma reported same-day variation in symptoms. Most individuals reported worsening symptoms in the morning and/or overnight, and fewest symptoms between 09:00 and 17:00 (figure 1a-b).

There were no differences in baseline characteristics (age, sex, smoking status, blood eosinophilia, skin prick test sensitisation, Asthma Control Questionnaire score and self-reported same-day variability in symptoms) between participants attending the morning or afternoon clinics. Of 28 patients with baseline obstructive spirometry, 92.9% were subsequently diagnosed with asthma; all participants with positive BDR were diagnosed with asthma. Obstructive spirometry was least commonly found during early afternoon (figure 1c), and median % change in forced expiratory volume within 1 s (FEV_1) following bronchodilation significantly fell as the day went on (β=−0.91, 95% CI: (−1.52, −0.15), p=0.018). The prevalence of positive BDR tests decreased during the day (figure 1c). However, the likelihood of having an obstructive spirometry (OR: 0.97, 95% CI: [0.42, 2.33], p=0.953) or a positive BDR (adjusted for baseline airflow obstruction, OR: 0.47, 95% CI: [0.15, 1.37], p=0.173) in the afternoon was not significantly different compared to tests in the morning.

Of 48 patients who had a positive *F*ENO test, 85.4% were subsequently diagnosed with asthma. The median *F*ENO levels were also negatively associated with the timing of measurements (β=−5.0, 95% CI: [−9.3 −0.7], p=0.009) in the univariate quantile regression. Following the adjustment for atopy and blood eosinophilia, timing of test remained significant. The effect of timing was pronounced with a fall of 6.2 ppb (95% CI [−10.4, −2.1]) per hour as the day went on in atopic individuals, although this association was not observed in non-atopic individuals. The proportion of positive *F*ENO tests fell as the day went on (figure 1c) and performing *F*ENO in the morning was more likely to give a positive result than performing in the afternoon (odds ratio [95%CI]: 3.35 [1.33−9.05], p=0.013) in the multivariate logistic regression model. We did not find the time of day affected the bronchial challenge tests (afternoon methacholine challenge compared to morning tests: OR: 0.88, 95% CI: [0.40, 1.98]; mannitol challenge: OR: 1.40, 95% CI: [0.48, 4.17]).

We found that the timing of performing *F*ENO and BDR is likely to affect test results in the diagnostic setting. Performing these tests in the morning may improve test sensitivity and have health-economic implications.

The diurnal pattern observed in *F*ENO and bronchodilator response were consistent with previous reports [2, 7, 8]. Lung function peaks during early afternoon [9], consistent with the observed fall in the prevalence of obstructive spirometry during this time. We have previously found that over 30% of severe asthma patients had same-day variability in *F*ENO exceeding the minimal clinically significant difference [10]. Importantly, *F*ENO has recently been recommended by the ATS to monitor asthma treatment [11]; we would advocate that the time of day is taken into account to improve the usefulness of *F*ENO in this setting. As self-reported time-of-day symptom patterns coincide with airflow obstruction in patients with asthma, it is plausible that assessing the airflow obstruction and associated inflammation at the time of day when patients are most symptomatic may improve diagnostic efficiency. Although domiciliary spirometry and *F*ENO has been evaluated for asthma self-management [12], its utility for diagnosis is unclear and should be investigated as the next step.

Our study is limited by small sample size and large interpersonal variations, making subgroup analyses difficult. The lack of statistical significance may also have been a result of our study being underpowered. No assessment of intra-individual diurnal variation could be made in the current study; a future longitudinal study with intra-individual repeated measurements at different time of day will be needed to validate our findings and establish the optimal timing of tests.

As asthma is such a common and frequently misdiagnosed disease, these findings suggest a significant impact of timing on clinical decision making, particularly in those with borderline results.

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This study is registered at https://www.isrctn.com/ with identifier number 11676160. Individual participant data that underlie the results reported in this article, after deidentification, will be shared 3 years following the completion of the RADicA study and following the publication with investigators whose proposed use of data has been approved by the study sponsors. Proposals should be directed to research.sponsor@mft.nhs.uk. To gain access, data requestors will need to sign a data access agreement.

Ethics statement: This study was approved by the Research Ethics Committee (GM East REC, 18/NW/0777). All participants provided informed written consent.

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