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PSYCHIATRIC DISORDERS

Hyperventilation in asthma: A validation study of the Nijmegen Questionnaire – NQ

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Abstract

Introduction: The Nijmegen questionnaire (NQ) has previously been used for screening the hyperventilation syndrome (HVS) in asthmatics. However, no validity study has been reported so far. *Objective*: To examine the validity and reliability of the NQ in asthma patients and identify the prevalence of HVS. *Methods*: The NQ ($n = 162$) was examined for translation, construct, cross-sectional and discriminant validity as well as for internal consistency and test–retest reliability. *Results*: Principal component analysis and exploratory factor analysis revealed a single factor solution with 11 items and 58.6% of explained variability. These 11 NQ items showed high internal consistency (Cronbach's alpha = 0.92) and test–retest reliability ($IR = 0.98$). Higher NQ scores were found in the following subgroups: women versus men ($p < 0.01$); participants with moderate versus mild asthma ($p < 0.001$) or uncontrolled versus controlled asthma ($p < 0.001$), and participants with breath-hold time (BHT) < 30 versus ≥ 30 s ($p < 0.01$) or end-tidal CO_2 ($ETCO_2$) ≤35 versus >35 mmHg ($p < 0.001$). A cut-off score of >17 discriminated the participants with regard to the presence of HVS. The NQ showed 92.73% sensitivity and 91.59% specificity. The total NQ score was found significantly correlated with $ETCO_2$ ($r = -0.68$), RR ($r = 0.66$) and BHT ($r = -0.65$). The prevalence of HVS was found 34%. *Conclusion*: The NQ is a valid and reliable questionnaire for screening HVS in patients with stable mild-to-moderate asthma.

Keywords

Hyperventilation, Nijmegen questionnaire, reliability, validity

History

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Introduction

Hyperventilation syndrome (HVS) is the most recognized form of dysfunctional breathing (DB) that is strictly related to biochemical factors [1–3]. According to Gardner, HVS is defined physiologically as "breathing in excess of the body's metabolic requirements that results in a reduction in arterial pCO2, respiratory alkalosis, and wide ranging symptoms" [1]. The syndrome may include hyperventilation related to psychogenic (anxiety/depression, panic, air hunger, sighing), organic (respiratory diseases, pain) and physiologic (progesterone effect, speech, pyrexia) factors [1].

The relation between hyperventilation and asthma remains unclear [1]. Buteyko stated that "hidden" hyperventilation is the basic cause of asthma [4], without, however, presenting any scientific evidence. Acute and chronic hyperventilation are most likely to be associated with asthma [2]. Acute hyperventilation often occurs in acute asthma attacks, leads to hypocapnia and reverses with appropriate treatment [2,5]. Limited relevant data, however, are available for patients with stable asthma [6–8]. Patients clinically diagnosed with chronic hyperventilation showed a high prevalence (80%) of asthma, which in turn was suggested as the most common cause of confounding illness [2,9].

The absence of a gold standard for the diagnosis of HVS, apart from clinical assessment confirmed by physiological testing [2,5,10], makes asthma treatment difficult. Many asthma symptoms due to hyperventilation could be improved by appropriate intervention, such as breathing retraining [11]. Further, several measures, such as the cardio-pulmonary exercise test [12], hyperventilation provocation test [13,14], end-tidal carbon dioxide ($ETCO_2$) [15], breath-hold time (BHT) [16], respiratory rate (RR), the Nijmegen questionnaire (NQ) [17,18], etc., have been used to assess the presence of the HVS. The NQ is the most commonly used screening tool for dysfunctional breathing and specifically for hyperventilation. The questionnaire incorporates a 16-symptom checklist grouped under three factors and has been validated in the

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general population with a clinical diagnosis of HVS [17,18] by discriminating individuals with and without dysfunctional breathing [17]. It has been suggested that an NQ total score of 23 and above is positive for HVS in a non-asthma population [17] as well as in patients with asthma (ranging from 20 to 66%) although no reports of validity testing have been published [5,19–23]. The validity of the NQ in asthma has been questioned because of the absence of an accepted gold standard for the diagnosis of HVS, the lack of validity evidence in asthma patients, and the possible overlap between anxiety and asthma symptoms [12,24]. Finally, according to the theory of sample-specific validity and reliability [25–29] and to relativism, an orientation in cross-cultural psychology, researchers cannot use standard instruments across cultures but only local instruments [26].

The aim of the present study was to contribute to knowledge about HVS, by providing validity and reliability evidence for the NQ in Greek patients with stable asthma and identify the prevalence of HVS in this specific group of patients. This will help health providers to screen HVS in asthma, and provide conventional and effective interventions.

Methods

Study population

The present study included 162 patients, all with stable asthma (30), 68 (42%) men and 94 (58%) women, aged from 20 to 68 years old (Mean = 46.65, SD = 12.94) who were recruited from the outpatients of the Asthma Department of the "Amalia Fleming" General Hospital in Athens, Greece, during 2009. Asthma severity ranged from mild to moderate. Patients with severe asthma were not included in the present study because they exhibited unstable asthma [30]. Participants were excluded if they, suffered from chronic obstructive pulmonary disease (COPD), cardiovascular disease, neurological disorders or physical disability, or were unable to comprehend or complete questionnaires in Greek. All patients were clinically diagnosed and had at least a 12% improvement in FEV1 after inhalation of 200–400 μg of salbutamol [30]. The patients were symptomatic during the previous 12 months, under a specialist's care and under controlled medications including inhaled glucocorticosteroids, long-acting inhaled β2-agonists, and other medication according to Global Initiative for Asthma (GINA) [30]. Asthma severity ranged from mild to moderate [30]. 110 (67.9%) patients had suffered from asthma for more than eight years, while 52 (32.1%) had asthma for less than eight years [31]. 42 (25.9%) patients (aged 20–59) were smokers, while 120 (74.1%) patients (aged 20–68) were non-smokers [32]. All patients gave their informed consent prior to their inclusion in the study, and the study protocol was approved by the Research Ethics Committee of the "Amalia Fleming" General Hospital of Athens.

Data collection

The following measures were assessed at two scheduled visits to the Asthma Department of the "Amalia Fleming" General Hospital, between 10 to 12 a.m.:

- a questionnaire regarding the demographic information
- the NQ
- the asthma control test (ACT)
- the Borg scale
- the oxi-capnography comdek MD-660P
- the Spiro sense spirometry system
- BHT after exhalation up to tidal volume
- RR at rest

The NQ is a screening questionnaire for DB and consists of 16 items, grouped under three factors named: (a) shortness of breath, (b) peripheral tetany and (c) central tetany [17]. The 16 NQ items include symptoms common to both anxiety and asthma [33] and related to different systems, such as cardiovascular, neurological, respiratory, gastro-intestinal and psychological factors [17]. The NQ evaluates the frequency incidence of the 16 items with a five-point ordinal scale (from 1 = never to 5 = very frequently). The NQ showed acceptable ($r = 0.70$) test–retest reliability [18], high sensitivity (91%) and high specificity (95%) for healthy people with HVS [17]. Cut-off scores of 20, 22 and 23 have been reported for the identification of DB/HVS [3,17]. However, no validation study for the NQ and respective cut-off scores have been reported, so far, for patients with asthma.

The diagnosis of HVS, was confirmed by a specialist in pneumology and a physiotherapist, through: (a) the presence of a dominant high costal breathing pattern at rest and (b) at least five out of 10 symptoms such as difficult inspiratory breathing, unable to take deep breaths, increased breathing frequency (>16 breaths/min), frequent sighing/yawning, frequent need to clear the throat, muscle and joint tenderness in the upper part of the chest, hacking cough, chest tightness, sensation of lump in the throat and previous or current effects of stress (DB criterion list) [23]. The physician was blinded to each patient's NQ score.

The ACT was used for the evaluation of asthma control [34]. The questionnaire consists of five items. The total ACT score ranges from 5 (poorly controlled) to 25 (completely controlled). The ACT is suggested valid and reliable for the Greek asthma patients [35].

A *portable capnograph* (oxi-capnography comdek MD-660P) with a nasal canula was used for the measurement of the mean $ETCO_2$ and breathing rate at rest, over a 10-min period [15]. Participants were instructed to breathe through their nose and not speak during the measurement [3]. In the present study, a cut-off score of 35 mmHg was used to classify participants regarding $ETCO_2$ [3,5].

BHT: Participants, in a sitting position, were instructed to breathe up to tidal volume and at the end of this gentle exhalation to pinch their nose and hold their breath until the first involuntary movement of the respiratory muscles occurred (BHT-IRM) [16]. This type of respiratory pause is reproducible and physiologically stable compared to the subjective sensation of the urge to breathe [36]. Three repetitions were conducted for the BHT-IRM measurement and finally the mean BHT-IRM (in seconds) was recorded [16]. In the present study, validity evidence of the BHT-IRM was provided through the difference between groups [37]. Specifically, BHT-IRM was higher for 25 adults without asthma (22.36 ± 4.63 s) compared to 25 adults with asthma (18.16 ± 6.57 s) ($t = 2.12$, $p < 0.012$). In the present study, a cut-off score of 30 s was used to classify asthma patients [3,5].

Pulmonary Function Testing tested the predicted values of FEV_1% for the assessment of bronchospasm [30]. According to GINA [30] recommendations, the participants indicated no use of bronchodilators at least 4 h before the spirometry test (Spiro sense spirometry system; Burdick, Inc., Deerfield, WI). Three valid efforts were conducted for the FEV_1 measurement and finally the mean FEV_1 (in % predicted values) was recorded [30].

The perceived degree of dyspnea was evaluated using the Borg scale, with responses varying from a minimum score of 0 to a maximum score of 10. The Borg scale is considered valid and reliable [38,39].

The administrations as well as data collection for the NQ, ACT and Borg scale were conducted by the primary researcher. Physiological assessments and clinical diagnosis of hyperventilation were conducted by the same specialist. All measurements were performed in a random order. During $ETCO_2$ and RR measurement, participants were encouraged to complete the NQ, ACT or Borg scale as a means of distracting their attention from breathing [3].

Statistical analysis

The Statistical Package for the Social Sciences (IBM Corp., SPSS, Version 19, Armonk, NY) was used for data analysis. The validity and reliability of the NQ were tested through: (a) translation validity, (b) construct validity, (c) cross-sectional validity, (d) convergent validity, (e) discriminant validity and (f) test–retest reliability and internal consistency [37].

The translation validity of the NQ was established according to the guidelines for the cross-cultural adaptation of self-reported measures [28,29].

The construct validity of the NQ was reported for a sample of adults from the "general" population, with 16 items classified under the three factors (shortness of breath, peripheral tetany and central tetany) [17]. In the present study, however, the sample examined consisted of asthmatic patients. Therefore, we were not aware whether the same factorial structure was evident for our sample of patients with asthma. Hence, we decided to explore the construct validity of the NQ for our sample of Greek asthmatics through a principal component analysis (PCA) in order to identify the respective factors. To identify the number of extracted factors, the following criteria were used: (a) eigen values above 1.00, (b) scree plot, (c) percentage of explained variability, and (d) content of extracted factors [40]. The criteria used to retain the respective items were high factor loading (>0.30) and communality above 0.30 [41]. In the present study, the recruited sample size ($n = 162$) was adequate, according to pre-determined factor analytic criteria [41,42].

In addition, construct validity was examined using *t*-tests to evaluate the differences between groups [37].

Reliability testing: (a) the internal consistency of the NQ was tested through Cronbach's alpha reliability coefficients while *(b) test–retest reliability* was tested with intraclass correlation coefficient (IR) between the two measurements (0, 2 months) for the total sample [35,43].

The cross-sectional validity was tested through the correlation between the NQ total score and ACT, $ETCO_2$, BHT, FEV1%, RR and Borg scale with the Pearson's *r* correlation coefficient [37].

The convergent validity was examined through the correlation of the NQ total score with the specialist's rating with the Pearson's *r* correlation coefficient.

The discriminant validity was examined through the receiver operating characteristic (ROC) analysis. The criterion used for the *ROC curve analysis* was the expert's rating [23]. Sensitivity and specificity statistics, positive and negative predictive values and likelihood ratios were estimated at each cut-off score.

Results

Study population

The total sample of 162 participants exhibited the following mean scores: (a) NQ 16.97 (±7.85), (b) $ETCO_2$ 35.93 mmHg (±3.23), (c) BHT 19.04 s (±7.81), (d) RR 14.33 breaths/min, (e) ACT 19.31 (±3.09), (f) FEV1% predicted 84.68 (±9.45) and (g) Borg scale score 1.99 (±1.68).

Construct validity

Principal components analysis

The Bartlett test of sphericity (1462, *df* 120, $p < 0.001$) and the KMO criterion (0.873) supported a single-factor model, with 41.31% of explained variability. Eleven items (No1, No2, No4, No5, No6, No7, No8, No9, No11, No13, No16) showed high factor loadings and communalities at the appropriate range (above 0.30). The decision to retain a single-factor solution was further supported by the scree plot.

Subsequently, the above 11 items were used for exploratory factor analysis, with a pre-hypothesized single factor. The Bartlett test of sphericity (Bartlett = 1290, *df* 55, $p < 0.001$) and the KMO criterion (KMO = 0.926) supported the single-factor model, with 58.6% of explained variability. Cronbach's alpha for the 11 items with a single-factor model was 0.92, while the test–retest reliability was IR = 0.98 [41]. Loadings and item communalities of the 11 items are presented in Table 1.

Table 1. Item loadings and item communalities of the 11-item NQ.

Items	Item loadings	Item communalities
9 (Bloated abdominal sensation)	0.89	0.80
6 (Accelerated or deepened breathing)	0.89	0.80
11 (Unable to breath deeply)	0.89	0.79
7 (Shortness of breath)	0.86	0.75
8 (Constricted chest)	0.85	0.72
13 (Tightness around the mouth)	0.83	0.68
5 (To be confused, losing touch with environment)	0.80	0.65
16 (Anxiety)	0.76	0.58
4 (Dizzy spells)	0.56	0.32
1 (Chest pain)	0.46	0.21
2 (Chest pain)	0.42	0.18
Eigen value	6.47	
% explained variance	58.86	

Table 2. Means, SD, and p values for the 11-item NQ total score between patients of different gender, duration of asthma, asthma control, asthma severity, smoking behavior, BHT, $ETCO_2$ and follow-up visits.

Variables	N	Mean (SD) NQ score	t	p
Gender				
Male	68	11.88 (6.67)	−2.98	0.003
Female	94	19.28 (6.24)		
Duration of asthma				
<8 yrs	52	11.00 (7.14)	−3.52	0.001
≥8 yrs	110	15.21 (4.81)		
Asthma control (ACT)				
No (≤19)	58	10.17 (5.99)	−5.12	<0.001
Yes (≥20)	104	15.91(7.27)		
Asthma severity				
Mild	86	11.25 (6.41)	−5.16	<0.001
Moderate	76	16.80 (7.28)		
Smoking				
No	42	11.83 (6.53)	2.09	0.03
Yes	120	14.57 (7.52)		
BHT				
≥30 s	91	10.21 (5.71)	−2.63	0.01
<30 s	71	18.53 (6.57)		
$ETCO_2$				
≤35 mmHg	66	23.06 (6.06)	−12.08	<0.001
>35 mmHg	96	12.49 (5.44)		
Follow-up				
Every 1-2 months	95	10.82 (6.20)	−8.62	<0.001
On symptom deterioration	67	18.53 (6.57)		

Differences between groups

The construct validity of the NQ was examined through differences in the NQ total score between: (a) men/women with asthma, (b) patients with controlled/uncontrolled asthma, (c) mild/moderate asthma, (d) patients who suffered from asthma for ≤8/>8 years, (e) patients with BHT-IRM ≤30 s/>30 s, (f) patients with $ETCO_2$ ≤35 mmHg/>35 mmHg, (g) smokers/non-smokers and (h) patients who underwent follow-up regularly/only on deterioration of symptoms (Table 2).

Cross-sectional validity testing

Moderate positive correlations were found between the total NQ score and the Borg scale ($r = 0.43$) and RR ($r = 0.66$), showing that the higher the RR and dyspnea, the higher the NQ score. Moderate negative correlations (ranging from $r = -0.47$ to $r = -0.68$) between the total NQ score and ACT, $ETCO_2$, BHT and FEV1%, demonstrated that the lower the asthma control, $ETCO_2$, BHT-IRM and FEV1%, the higher the NQ score. The results of cross-sectional validity testing are presented in Table 3.

Convergent validity testing showed a high correlation of the NQ score with the specialists' rating ($r = 0.81$, $p < 0.001$).

Discriminant validity testing

Based on the ROC curve analysis, point >17 was defined as the ideal cut-off score and as the nearest point to the upper left corner (Figure 1). The area under the ROC curve (AUC) was 0.952 ($p < 0.0001$), significant different from AUC = 0.05, providing evidence of discriminant accuracy to the NQ. In conclusion, the NQ with a cut-off score > 17 can discriminate asthma patients with hyperventilation from those with no hyperventilation (Table 4).

Table 3. Inter-correlations between the 11-item NQ total score and ACT, $ETCO_2$, RR, Borg scale and FEV1%.

	NQ	ACT	$ETCO_2$	BHT	RR	Borg scale	FEV1%
NQ	1.00	−0.47*	−0.68*	−0.65*	0.66*	0.43*	−0.48*
ACT		1.00	0.45*	0.48*	−0.38*	−0.52*	0.58*
$ETCO_2$			1.00	0.88*	−0.86*	−0.53*	0.59*
BHT				1.00	−0.88*	−0.61*	−0.68*
RR					1.00	0.51*	−0.59*
Borg scale						1.00	−0.87*
FEV1%							1.00

*$p < 0.01$.

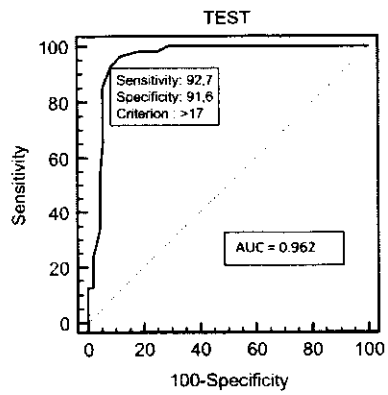

Figure 1. ROC curve for the NQ.

Prevalence of HVS

Based on the cut-off score >17 for the 11-item NQ, HVS was detected in 55 (34%) patients with stable asthma. Those patients scoring >17 were more likely to be female (81.4%) than male (18.6%) ($p < 0.001$), to have moderate (72.9%) rather than mild asthma (27.1%) ($p < 0.001$), $ETCO_2$ ≤35 mmHg (86.4%) rather than $ETCO_2$ >35 mmHg (13.6%) ($p < 0.001$), and to exhibit uncontrolled (81.4%) rather than controlled asthma (18.6%) ($p < 0.001$). The mean RR and FEV1% scores for the asthmatics with HVS were higher compared to those without HVS (18 versus 12 breaths/min and 79 versus 88%, respectively) ($p < 0.001$).

Predictors of HVS

Multivariate logistic regression analysis was performed to examine the relation of hyperventilation with gender, severity and control of asthma, $ETCO_2$ and FEV1. The analysis resulted in a high protection of HVS for men with asthma (odds ratio [OR]: 0.23, 95% confidence interval [CI]: 0.08–0.71) and for the asthma patients with $ETCO_2$ >35 mmHg (odds ratio [OR]: 0.035, 95% confidence interval [CI]: 0.01–0.10).

Discussion

The present study examined the validity and reliability of the NQ in a sample of Greek out-patients with mild-to-moderate stable asthma under a specialist's care. The statistical analyses revealed one single factor solution with the following 11 NQ

Table 4. Screening accuracy of the 11-item NQ based on different cut-off points.

Cut-off points	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio	Positive predictive value (%)	Negative predictive value (%)
>13	100.00	71.03	3.45	0.00	64.00	100.00
>14	98.18	74.77	3.89	0.024	66.70	98.80
>15	98.18	81.31	5.25	0.022	73.00	98.90
>16	96.36	87.85	7.93	0.041	80.30	97.90
>17*	92.73	91.59	11.02	0.079	85.00	96.10
>18	85.45	94.39	15.24	0.15	88.70	92.70
>19	65.45	94.39	11.67	0.37	85.70	84.20
>20	54.55	95.33	11.67	0.48	85.70	80.30
>21	34.55	95.33	7.39	0.69	79.20	73.90
>22	30.91	96.26	8.27	0.72	81.00	73.00
>23	23.64	98.13	12.65	0.78	86.70	71.40
>24	18.18	98.13	9.73	0.83	83.30	70.00
>25	12.73	98.13	6.81	0.89	77.80	68.60
>26	12.73	100.00		0.87	100.00	69.00

* identifies the cut-off score of any questionnaire.

items describing HVS in asthma: chest pain (No1); feeling tense (No2); dizzy spells (No4); to be confused, losing touch with environment (No5); accelerated or deepened breathing (No6); shortness of breath (No7); constricted chest (No8); bloated abdominal sensation (No9); unable to breathe deeply (No11); tightness around the mouth (No13); and anxiety (No16).

Regarding the content of the aforementioned 11 items, six of them "chest pain", "feeling tense", "accelerated or deepened breathing", "shortness of breath", "constricted chest" and "unable to breathe deeply" comprise the majority of the component "shortness of breath". These are respiratory symptoms common to both asthma and DB [25], as well as to complaints of HVS in asthma [23]. "Bloated abdominal sensation" in asthma may be a sense of pulmonary hyperinflation [1]. "Anxiety" coexists in anxiety disorders and asthma [44], and has shown a prevalence of 56% in patients with BD compared to 24% in patients with controlled asthma [23]. "Anxiety" comprises the major asthma co-morbidity [20], increasing the risk of hyperventilation in the disease [12,45]. "Dizzy spells", "tightness around the mouth" as well as "to be confused, losing touch with the environment" are not respiratory symptoms but peripheral and central tetany symptoms, respectively, related to anxiety and hypocapnia [17].

The above findings are in line with the literature, since HVS symptoms start with a subjective obstruction of breathing [17] and are followed by symptoms of hypocapnia, respiratory alkalosis and neuronal hyperexcitability [2]. However, two items ("chest pain" and "feeling tense") showed low item communalities (below 0.30). "Chest pain" is not usual in stable asthma [46]. Of the present sample with stable asthma, 77% of the patients chose the option "never" in the "chest pain" item, while the remaining 23% chose the option "rarely". "Feeling tense" is a symptom of both hyperventilation and panic, which overlap [47], and more common in patients with asthma, than in a normal population [48]. In the present study, 58% of patients reported "never" with respect to "feeling tense", 38% answered "rarely", while nearly 4% of the participants responded "sometimes".

Five items were excluded from the NQ: (a) one item ("palpitations") from the 1st factor ("shortness of breath"), (b) three ("tingling fingers", "stiffness of fingers or arms" and "cold hands or feet") from the 2nd factor ("peripheral tetany") and (c) one item ("blurred vision") from the 3rd factor ("central tetany"). The excluded items are related to hypocapnia [49,50], which is usually present in acute asthma [51–53]. In particular, "palpitations" were observed in patients admitted to hospital with an exacerbation of asthma, and their degree was correlated with asthma severity [51]. "Tingling sensations" were grouped in the "Hyperventilation-Hypocapnia" cluster in the study of Kinsman et al. [52] with a sample of acute asthma. "Cold hands or feet" and "blurred vision" were reported by patients with asthma-like symptoms without physiological signs of asthma [53]. "Stiffness of fingers or arms" is a neuromuscular symptom related to hypocapnia [49]. The present sample consisted of patients with diagnosed stable asthma and a mean $ETCO_2$ of 35.93 mmHg (±3.23), a higher value than the pCO_2 threshold of 20 mmHg for hypocapnia symptoms [1,51,54,55].

The 11 NQ items explained 58.6% of the variability which is satisfactory for the social sciences [41,52]. Our findings are inconsistent with those of previous studies that defined NQ as multidimensional [17]; this is probably due to: (a) the different sample used, with a non-asthma population; (b) the exception of the "anxiety" item in their analysis, as a cause rather than a symptom of HVS; and (c) the individual characteristics of our patients' culture. The responses to items may have different meanings in different cultures and places; even in the same place, they may vary across time because of historical events, economic conditions, etc [28,29,56]. Overall, for the specific sample of Greek asthmatics, the NQ had a different meaning, which was mainly expressed by "shortness of breath" items related more to anxiety and less to hypocapnia, which in turn is related to the excluded items. So, we can say that the NQ in patients with stable asthma reflects breathing-related tension.

The psychometric properties of the 11-item NQ cannot be compared directly to those of the NQ. The NQ was developed in the Netherlands and validated in non-asthmatic patients with diagnosed HVS. The 11-item NQ is the result of validity testing, in a sample of out-patients with stable asthma in Greece. As we know, the validity and reliability of measures varies by sample [28]. Researchers should always present updated validity evidence of the measures used [28], and

avoid generalizing validity to all samples examined, which can lead to misinterpretation of their findings [25].

In the present study, men with asthma were less likely to develop HVS. The observation that women with asthma had higher NQ scores is in line with that of previous studies [19,20] and may be explained by the effect of progesterone that reduces pCO_2 in the second half of the menstrual cycle [1]. It is, however, interesting to note that 74.5% of women participants, in the present study, aged beyond 50 years. As for asthma severity, our findings are not in agreement with those of previous studies [19,20], perhaps because of the different sample (patients with no objective evidence of asthma) and the NQ cut-off score used, which had not been validated in asthma patients [19,20].

Higher NQ scores were reported by patients who had uncontrolled asthma and follow-up visits upon deterioration of symptoms, probably because of the relation between: (a) rare follow-up visits with uncontrolled asthma [57] and (b) uncontrolled asthma with DB as well [21].

This is the first study that showed a high positive correlation between $ETCO_2$ and BHT scores for the specific population with asthma; thus, supporting the claim of Buteyko that BHT can determine hypocapnia and chronic hyperventilation [4]. Moreover, our results indicated asthma patients with $ETCO_2$ >35 mmHg at rest as the most protected group from developing HVS. So, one can realize the utility of breathing retraining techniques aiming at reducing hyperventilation in asthma patients and raising carbon dioxide levels [11,45].

The discriminant analysis demonstrated a cut-off score of >17 that is inconsistent to previous studies. Specifically, other researchers used the NQ cut-off scores of 20, 22 and 23 in asthma patients, though with no validity report [3,5,9,19–22]. This discrepancy may be due to the absence of a validated screening questionnaire for HVS and the different sample used [24]. The sensitivity of 92.7% found in the present study means that 7.3% of asthmatics with HVS were not detected through the NQ; the 7.3% misclassification may be due to: (a) missing items of certain psychosocial attributes related to HVS and (b) the subjective perception of patients (undergoing cultural adaptation procedure, some patients complained for misunderstanding of item 5).

The prevalence of HVS (34%) in the present study was within the wide range observed in previous studies; cultural differences, over-diagnosis of asthma by physicians, and the different samples, measures, cut-off scores and non-validated tools used, might be responsible for this variation [5,19–23]. Specifically, Hagman et al. [23], in Sweden, screening HVS based on the presence of a dysfunctional breathing pattern with at least five symptoms associated with DB, observed HVS in 20% of patients with a diagnosis of controlled asthma. Thomas et al. [20], in the UK, using the NQ with a cut-off score of 23, found an HVS frequency of 29% in patients with no objective evidence of asthma who had received one or more prescriptions for inhaled or oral bronchodilator or prophylactic asthma medication in the past year. Agache et al. [21], in Romania, found that 30% of patients diagnosed with severe asthma had a positive NQ score (>23), confirmed by progressive exercise testing. Martinez-Moragon et al. [22], in Spain, evaluating consecutive outpatients with stable asthma of varying degrees of severity, found that the HVS was present in a percentage of 36%. Stanton et al. [5] reported an HVS prevalence of 66% in patients attending the Problem Asthma Clinic at Glasgow Royal Infirmary over a 5.5-month period, most of whom were in British Thoracic Society (BTS) step 4 or 5 of asthma treatment.

The present study had some potential limitations: (a) the sample was recruited and not randomly selected; (b) no patients with severe asthma or asthma attack participated, preventing the generalization of our findings to such populations; (c) no gold standard for the diagnosis of HVS was available, which casts possible doubt upon the validity of the clinicians' diagnosis; (d) anxiety disorders were not evaluated to support the relation of the 11 NQ items to anxiety in patients with stable asthma; and (e) no confirmatory factor analysis was conducted to show the fit of the 11-item model.

Despite the above limitations, this is the first study to provide validity and reliability evidence for the NQ and to report the prevalence of HVS in stable asthma patients. The strength of the present study lies in the wide sample and the valid measures used. However, future researchers should provide additional validity and reliability evidence, possibly through confirmatory factor analysis, to support the present findings.

Clinical and research implementation

In clinical practice, the use of the valid NQ in asthma will confirm the clinicians' suspicion that HVS is present, or think HVS as a possibility to be seriously considered [17]. Therefore, health care providers will proceed to reduction of unnecessary medication, provide non-pharmaceutical treatment, such as physiotherapy-based breathing retraining [11], and protect asthma patients from asthma attacks [21]. Breathing retraining in patients with asthma, with a slow RR and breath hold, has been shown to lead to a significant reduction in RR [11,58], an improvement in $ETCO_2$ [11,58], a reduction of hyperventilation symptoms [11,59,60] and bronchodilators [61], as well as an improvement in asthma control [11,58] and quality of life [11,59,60]. Moreover, beyond the valid NQ, the use of predictor variables, such as those found in the present study (gender and $ETCO_2$) may help in the diagnosis and treatment of HVS [21]. Particularly in patients with mild and moderate stable asthma, the use of the NQ along with other validated tools, such as the ACT, Asthma Quality of Life Questionnaire (Standardized) [62], and the GINA guidelines will raise the quality of the assessment, treatment and overall clinical services provided for asthma management in both primary and secondary care, leading to economic and social benefits.

In research, the use of a valid HVS screening tool will strengthen the internal validity and help researchers (a) recruit samples of asthma patients with HVS and (b) evaluate the effectiveness of breathing techniques on HVS symptoms in asthma across time [2,33].

Conclusion

The present study provided validity and reliability evidence for the NQ in Greek out-patients with stable mild-to-moderate

asthma under a specialist's care. The NQ is a clinical and research tool that may facilitate health professionals to screen for HVS, while also provide adequate treatment beyond pharmacology.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Author contribution

All authors provided the final agreement and approval of the draft to be submitted.

All authors have made substantial contributions:

- Eirini Paschalis Grammatopoulou: designed research study, collected data, analyzed data, interpreted data, wrote the paper.
- Emmanouil Skordilis, Georgoudis Georgios and Panagiotis Kalagiakos: analyzed data.
- Aikaterini Haniotou: diagnosed hyperventilation.
- Afroditi Evangelodimou and Theodoros Katsoulas: conducted physiological assessments.
- George Fildissis: revised critically the paper.

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