Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2024;33:17-22
doi: 10.15570/actaapa.2024.7

Diagnostic accuracy of a short-form version of the diagnostic criteria for primary hyperhidrosis

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Abstract

Introduction: The gold standard method for diagnosing primary hyperhidrosis (PHH) is based on seven patient-reported criteria. By determining an individual criterion's diagnostic accuracy, one can identify short-version classification models.
Methods: In this cross-sectional study, data were collected from Danish blood donors in 2021. Cohen's kappa and diagnostic accuracy were determined by comparing each criterion with the gold standard method.
Results: The study included 1,039 participants. Of them, 59 (5.7%) had PHH and 980 (94.3%) were classified as control individuals. The PHH major criterion "focal visible excessive sweating for at least 6 months without an apparent cause" had the highest prevalence in the participants with PHH compared to the control individuals (100% vs. 0.6%; $p < 0.0001$). The agreement between this criterion and PHH was Cohen's kappa = 0.95 (95% confidence interval [CI] 0.91–0.99), and its sensitivity was 1.00 (95% CI 0.94–1.00) and specificity 0.99 (95% CI 0.99–1.00). The other criteria showed lower agreement and diagnostic accuracy.
Conclusions: The PHH major criterion showed near-perfect agreement and near-equal diagnostic accuracy compared with the gold standard method. This single criterion can be used as a short-form version to screen for PHH. Determination of reproducibility in independent populations is warranted.

Keywords: diagnostic accuracy, primary hyperhidrosis, sensitivity, short-form version, specificity

Received: 9 January 2024 | **Returned for modification:** 9 March 2024 | **Accepted:** 11 March 2024

Introduction

Primary hyperhidrosis (PHH) is a skin disease that presents with unexplained localized excessive sweating for at least 6 months (1). PHH has a heavy disease burden (2–5). A recent review confirmed that patients with PHH experience reductions in their wellbeing (6). Likewise, patients with PHH more often than others have psychiatric diseases, including depression and anxiety, and somatic diseases, including skin infections and dermatitis (2, 3, 7–12). Therefore, early diagnosis and initiation of treatment are imperative to prevent these undesired outcomes (13–18). To ascertain the diagnosis, the gold standard, which has remained unchanged since 2004, is fulfilling the major criterion "focal visible excessive sweating for at least 6 months without an apparent cause" plus two of six minor criteria (1). These consensus criteria were established by a multidisciplinary task force of experts following a review of the literature (1). The distribution of the criterion in individuals with and without PHH, and thereby how well they can differentiate between participants with and without PHH, remains unknown. Therefore, the objective of this study was to determine the ability of the individual criteria to diagnose PHH by comparing the occurrence of the diagnostic criteria in individuals with and without PHH. This method allows for the identification of short-version classification models. In clinical practice, a single criterion with high diagnostic accuracy can be especially valuable in screening for PHH in primary healthcare facilities. In research, such a criterion is ideal to include in larger questionnaires designed for epidemiological research, in which the number of items can be a limiting factor.

Methods

Setting

This is a cross-sectional study using questionnaires to collect data from voluntary blood donors. The study inclusion was conducted between June and December 2021 at blood banks in Denmark's Zealand region. The study follows the statement Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and the guideline Standards for Reporting Diagnostic Accuracy Studies (STARD) (19, 20).

PHH consensus criteria

The consensus criteria were created by an international group of experts, as described by Hornberger et al. (1). Briefly, the authors reviewed English-language literature published between 1966 and 2002 (1). Then, each article was ranked from 1 to 5 based on the criteria of 1) diagnostic test, 2) diagnostic criteria, 3) reproducibility, 4) patient selection, and 5) at least 50 participants with and 50 participants without PHH (1). Finally, clinical recommendations on recognition, evaluation, and treatment were reached (1). The recommendation for diagnosing focal PHH (i.e., the PHH consensus criteria) is that the patient meets the major criterion, meets two of six minor criteria, and does not have secondary hyperhidrosis (SHH). The major criterion is "focal visible excessive sweating for at least 6 months without an apparent cause." The minor criteria are 1) "bilateral and relatively symmetric," 2) "impairs daily activities," 3) "frequency of at least one episode per week," 4) "age of onset

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less than 25 years," 5) "positive family history," and 6) "cessation of focal sweating during sleep." SHH is caused by concurrent exposures, most often diseases, medication use, or drug abuse (1).

Source population

The source population was voluntary adult blood donors. Upon blood donation at blood banks located in urban areas in Denmark's Zealand region, eligible participants were offered study inclusion based on convenience sampling. Those that accepted first provided informed consent and then completed the study questionnaire. Blood bank nurses and a medical student distributed the questionnaires and then collected them from the study participants.

Participants with PHH and control individuals

Participants that fulfilled the consensus criteria in the absence of SHH were classified as having PHH. Participants that did not fulfill the consensus criteria and that did not have SHH were classified as control individuals. Participants with SHH were excluded. SHH was assessed in the questionnaire by including items on concurrent diseases or medication use that induces sweat production.

Eligibility criteria

The eligibility criteria were identical to the Danish blood donation criteria. Briefly, the study participants were 18 to 70 years old, not receiving medications or with diseases that precluded blood donation, and had no alcohol or substance misuse (21). The list of diseases is extensive and includes infections, autoimmune diseases, anemia, coagulopathies, neurologic diseases, diabetes, circulatory diseases, and cancer (21). Likewise, many medications preclude donation, including antibiotics and immunosuppressants (21).

Demographic variables

The demographical variables encompassed sex, age, height, and weight. Sex was considered a binary variable indicating female and male sex, and age, height, and weight were continuous variables. Body mass index (BMI) was calculated using height and weight and was also considered a continuous variable.

Diagnostic accuracy

Each of the seven PHH major and minor consensus criteria was used as an index test. For each index test, the presence of the criteria (i.e., a positive answer) was considered a positive result, and the absence of the criteria (i.e., a negative answer) was a negative result. The answer "I do not know" was considered an indeterminate answer and not included in the analysis of accuracy. Fulfilling the PHH consensus criteria, as described above, was considered a positive reference test result. The index and reference test algorithms were prespecified before the study inclusion. The conductors of the study inclusion were blinded to the diagnostic algorithm and results of the index and reference tests. Data extraction from the questionnaires and interpretation was undertaken by the first author. The data from the index tests were extracted and interpreted first, and then the reference test.

Descriptive statistics

Categorical variables were presented as frequency distributions with percentages. The distribution of the continuous variables was assessed using histograms. Normally distributed variables were presented as means (standard deviation [SD]), and non-normally as medians (interquartile range [IQR]). The differences between the demographic variables were assessed using the chi-squared test for binary variables, Student's *t*-test for normally distributed continuous variables, and the Mann-Whitney *U* test for non-normally distributed continuous variables. The alpha level was set to < 0.05.

Analytical statistics

Cohen's kappa was calculated to evaluate the performance of each criterion compared with the diagnosis of PHH. Then the diagnostic accuracy was determined by comparing each criterion with PHH, as defined by the consensus criteria. A secondary diagnostic accuracy analysis was conducted, in which the individual criterion was compared with the diagnosis of PHH, defined as the presence of the major criterion plus two of the minor criteria excluding the individual criterion investigated. The results were reported using positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity with 95% confidence intervals (CIs).

Data availability statement

The data that support the findings of this study are not shared to protect the anonymity of the participants.

Sample size calculation

The prevalence of PHH based on the consensus criteria remains non-reported. Therefore, the sample size calculation was based on the 60 first participants, in whom the prevalence was 6.7% ($n = 4$). The anticipated sensitivity was 75% or 80% and the specificity 95% (22). Employing the method described by Buderer et al., with a precision of 0.10 and confidence level of 0.95, it was necessary to include 1,029 participants to reach a sensitivity of 0.80 and 879 participants to reach a sensitivity of 0.75. With the same expectations, it was necessary to include 20 participants to reach a specificity of 0.95 (23).

Ethics

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Research based solely on anonymized questionnaires, such as this study, does not require institutional review board approval or data protection approval in Denmark.

Results

Demographics

Overall, 1,039 participants were included. Of them, 59 (5.7%) had

PHH and 980 (94.3%) were classified as control individuals. In addition, two individuals had SHH and they were excluded; see Figure 1. Of the 59 participants with PHH, 33 (55.9%) were females and 26 (44.1%) males. Their median age was 39.0 (IQR 32.5–52.0) and their median BMI 27.1 (IQR 23.7–28.7). Of the 980 control individuals, 390 (39.8%) were females and 584 (59.6%) males. Their median age was 48.0 (IQR 39.0–57.0) and their median BMI 26.2 (IQR 23.9–29.1). Only age was significantly different between the participants with PHH and the control individuals ($p = 0.0030$).

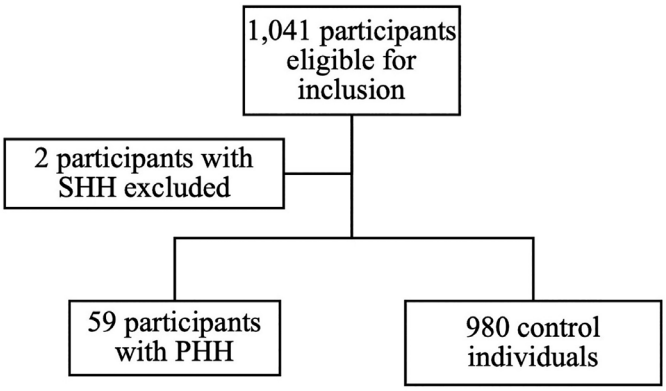

Figure 1 | Flowchart of participant inclusion process.
PHH = primary hyperhidrosis, SHH = secondary hyperhidrosis.

Distribution of the criteria

The distribution of the criteria and their demographics are presented in Table 1. The following criteria were more common in the participants with PHH than in the control individuals: "focal visible excessive sweating for at least 6 months without an apparent cause" (100% vs. 0.6%; $p < 0.0001$), "frequency of at least one episode per week" (69.5% vs. 8.2%; $p < 0.0001$); "age of onset less than 25 years" (57.6% vs. 8.5%; $p < 0.0001$); "impairs daily activities" (57.6% vs. 9.5%; $p < 0.0001$); and "positive family history" (45.8% vs. 10.6%; $p < 0.0001$). The criterion "bilateral and relatively symmetric" was equally common in the two groups (90.0% vs. 89.9% $p = 0.97$). The criterion "cessation of focal sweating during sleep" was more common in the control individuals than in the participants with PHH (52.8% vs. 37.3%; $p = 0.028$). The co-occurrence of the criteria with other criteria is presented in Table 2.

Cohen's kappa

Cohen's kappa analyzed the agreement between the individual criteria and PHH, and is presented in Table 1. The results showed almost perfect agreement with the criterion "focal visible excessive sweating for at least 6 months without an apparent cause," moderate agreement with the criterion "frequency of at least one episode per week," and fair agreement with the criteria "age of onset less than 25 years," "impairs daily activities," and "positive family history." A negative agreement was observed with the criterion "cessation of focal sweating during sleep."

Diagnostic accuracy

The diagnostic accuracy measurements are presented in Table 3. The highest diagnostic accuracy was observed for the criterion "focal visible excessive sweating for at least 6 months without an apparent cause" with a PPV of 0.91 (95% CI 0.81–0.97), an NPV of 1.00 (95% CI 1.00–1.00), a sensitivity of 1.00 (95% CI 0.94–1.00),

Table 1 | Distribution of the primary hyperhidrosis criteria and their descriptive statistics.

Criterion	With PHH, $n = 59$	Female (%)	Age, median, IQR	BMI, median, IQR	Without PHH, $n = 980$	Female (%)	Age, median, IQR	BMI, median, IQR	Cohen's kappa (95% CI)
1. Focal visible excessive sweating for at least 6 months without an apparent cause	59 (100.0)	33 (55.9)	39.0 (32.5–52.0)	27.1 (23.7–28.7)	6 (0.6)	2 (33.3)	51.5 (49.0–57.0)	25.5 (22.8–29.1)	0.95 (0.91, 0.99)
2. Bilateral and relatively symmetric	53 (89.8)	29 (54.7)	40.0 (33.0–52.0)	27.0 (23.7–28.7)	882 (90.0)	342 (39.0)	48.0 (39.0–57.0)	26.2 (23.9–29.1)	−0.00066 (−0.0066, 0.0053)
3. Impairs daily activities	34 (57.6)	18 (52.9)	35.5 (32.0–45.5)	26.6 (22.7–29.0)	93 (9.5)	44 (47.3)	42.0 (27.0–50.0)	27.2 (24.5–30.2)	0.32 (0.23, 0.41)
4. Frequency of at least one episode per week	41 (69.5)	24 (58.5)	43.0 (33.0–53.0)	27.1 (23.8–28.9)	80 (8.2)	50 (62.5)	51.0 (38.0–57.0)	26.5 (24.3–30.2)	0.42 (0.32, 0.51)
5. Age of onset less than 25 years	34 (57.6)	17 (50.0)	34.5 (29.0–45.5)	26.5 (22.9–28.3)	83 (8.5)	38 (45.8)	34.0 (26.0–45.4)	27.3 (24.4–30.1)	0.35 (0.26, 0.45)
6. Positive family history	27 (45.8)	14 (51.2)	36.0 (32.0–50.0)	27.2 (23.9–29.2)	104 (10.6)	59 (56.7)	44.0 (36.0–50.3)	25.8 (23.6–29.2)	0.25 (0.16, 0.34)
7. Cessation of focal sweating during sleep	22 (37.3)	16 (72.7)	39.5 (32.0–57.5)	27.1 (23.5–27.7)	517 (52.8)	208 (40.5)	48.0 (40.0–57.0)	25.9 (23.6–28.8)	−0.035 (−0.063, −0.0076)

BMI = body mass index, CI = confidence interval, IQR = interquartile range, PHH = primary hyperhidrosis.

Table 2 | **Co-occurrence of consensus criteria.**

	Focal visible excessive sweating for at least 6 months without an apparent cause, *n* = 59	Bilateral and relatively symmetric, *n* = 53	Impairs daily activities, *n* = 34	Frequency of at least one episode per week, *n* = 41	Age of onset less than 25 years, *n* = 34	Positive family history, *n* = 27	Cessation of focal sweating during sleep, *n* = 22
Focal visible excessive sweating for at least 6 months without an apparent cause, *n* = 59	59	53	34	41	34	27	22
Bilateral and relatively symmetric, *n* = 53	53	53	29	38	31	25	19
Impairs daily activities, *n* = 34	34	29	34	24	22	16	15
Frequency of at least one episode per week, *n* = 41	41	38	24	41	24	17	15
Age of onset less than 25 years, *n* = 34	34	31	22	24	34	18	16
Positive family history, *n* = 27	27	25	16	17	18	27	9
Cessation of focal sweating during sleep, *n* = 22	22	19	15	15	16	9	22

Table 3 | **Diagnostic accuracy of the individual primary hyperhidrosis criteria.**

Criterion	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
1. Focal visible excessive sweating for at least 6 months without an apparent cause	0.91 (0.81–0.97)	1.00 (1.00–1.00)	1.00 (0.94–1.00)	0.99 (0.99–1.00)
2. Bilateral and relatively symmetric	0.057 (0.042–0.074)	0.93 (0.78–0.99)	0.96 (0.87–1.00)	0.031 (0.021–0.044)
3. Impairs daily activities	0.27 (0.19–0.35)	0.97 (0.96–0.98)	0.60 (0.46–0.72)	0.90 (0.88–0.92)
4. Frequency of at least one episode per week	0.34 (0.26–0.43)	0.98 (0.97–0.99)	0.72 (0.58–0.83)	0.92 (0.90–0.93)
5. Age of onset less than 25 years	0.29 (0.21–0.38)	0.98 (0.97–0.99)	0.65 (0.51–0.78)	0.91 (0.89–0.93)
6. Positive family history	0.21 (0.14–0.29)	0.98 (0.96–0.99)	0.66 (0.49–0.80)	0.85 (0.83–0.88)
7. Cessation of focal sweating during sleep	0.041 (0.026–0.061)	0.92 (0.89–0.94)	0.39 (0.27–0.53)	0.43 (0.40–0.46)

The PHH consensus criteria require that the participants fulfill criterion number 1 and at least two of criteria 2-7. The PPV, NPV, sensitivity, and specificity were calculated by comparing each criterion with the consensus criteria.
CI = confidence interval, NA = information not available, NPV = negative predictive value, PPV = positive predictive value, PHH = primary hyperhidrosis.

Table 4 | **Secondary analysis of the diagnostic accuracy of the individual primary hyperhidrosis criteria.**

Criterion	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
1. Focal visible excessive sweating for at least 6 months without an apparent cause	NA	NA	NA	NA
2. Bilateral and relatively symmetric	0.18 (0.16–0.21)	0.76 (0.56–0.90)	0.96 (0.92–0.98)	0.028 (0.018–0.042)
3. Impairs daily activities	0.27 (0.19–0.36)	0.97 (0.95–0.98)	0.52 (0.38–0.65)	0.91 (0.89–0.93)
4. Frequency of at least one episode per week	0.34 (0.25–0.43)	0.98 (0.97–0.99)	0.64 (0.50–0.77)	0.92 (0.91–0.94)
5. Age of onset less than 25 years	0.33 (0.24–0.44)	0.91 (0.86–0.94)	0.59 (0.45–0.72)	0.77 (0.71–0.82)
6. Positive family history	0.21 (0.14–0.30)	0.98 (0.96–0.99)	0.64 (0.47–0.79)	0.87 (0.84–0.89)
7. Cessation of focal sweating during sleep	0.047 (0.031–0.069)	0.91 (0.87–0.93)	0.40 (0.28–0.54)	0.41 (0.38–0.44)

The PHH consensus criteria require that the participants fulfill criterion number 1 and at least two of criteria 2-7. The PPV, NPV, sensitivity, and specificity were calculated by comparing each criterion with the consensus criteria, but by omitting the criterion in question from the consensus criteria to avoid overestimating the diagnostic properties. For example, for criterion number 2, "bilateral and relatively symmetric," we compared its occurrence in participants with and without PHH, in which PHH was defined as the presence of criteria 1 and at least two of criteria 3–7. The accuracy was not calculated for criterion 1 because PHH cannot be diagnosed if this criterion is omitted.
CI = confidence interval, NA = information not available, NPV = negative predictive value, PPV = positive predictive value, PHH = primary hyperhidrosis.

and a specificity of 0.99 (95% CI 0.99–1.00). The results of the secondary diagnostic accuracy analysis are presented in Table 4. The diagnostic accuracy of combinations of the major criterion and each of the minor criteria are presented in Table S1.

Discussion

Establishing a diagnosis is a prerequisite for selecting adequate treatments. PHH is confirmed if the patient meets the diagnostic consensus criteria. This cross-sectional study has shown that the single major criterion has near-perfect agreement using Cohen's kappa and can confirm and reject the diagnosis with near-perfect accuracy. Therefore, this single major criterion can accurately identify individuals with and without PHH.

Because the presence of the major criterion is mandatory, its absence rules out PHH, yielding a sensitivity of 1.00. The major criterion's ability to confirm PHH (i.e., specificity), however, depends on the copresence of at least two minor criteria, which was 0.99 in this study. In the literature, only one study has presented the accuracy of a novel hyperhidrosis classification item (22). Research using this item as a case definition has studied comorbidities, human leucocyte antigen genetic dispositions, socioeconomic development, and the experience of the COVID-19 pandemic, showing the potential of a validated questionnaire item (2, 3, 7, 8, 24).

The criterion "bilateral and relatively symmetric" was the second most common criterion and equally frequent in the participants with and without PHH. The diagnostic accuracy analysis showed that this criterion can be used to rule out PHH but it cannot by itself confirm the diagnosis. An ideal classification item should have both a high sensitivity and specificity. Thus, on its own, this criterion has limited diagnostic value.

The four criteria "impairs daily activities," "frequency of at least one episode per week," "age of onset less than 25 years," and "positive family history" occurred in 45% to 70% of the participants with PHH and 8% to 10% of those without. These results rendered fair to moderate agreement on Cohen's kappa. Of their diagnostic accuracy measurements, the sensitivities were between 0.60 and 0.72 and specificities above 0.85, meaning that they can only be used to confirm the PHH diagnosis. As stated above, an ideal classification item should have both a high sensitivity and specificity. Although the consensus developmental study does not describe the reason for including these four criteria, the former two may capture participants with severe symptoms, whereas the latter two capture those with a genetic predisposition toward PHH (1).

The final criterion, "cessation of focal sweating during sleep," occurred in a minority of patients with PHH and was in fact more common in the control population, which led to a negative Cohen's kappa. The diagnostic accuracy analysis showed that it cannot be used to confirm or reject PHH. Potentially, this criterion can exclude causes of SHH such as malignancies or other systemic diseases (1). In the literature, however, there is little evidence to support the assumption that patients with PHH stop sweating while asleep. Research including participants from the general population or dermatology departments has shown that this criterion occurred in zero to 38% of the participants with PHH (25–27). Furthermore, a study reported that PHH was associated with sleep disturbances, which could support this study's observation that most patients with PHH do not experience relief of symptoms while asleep (2). In contrast, another study that collected data from a dermatological department found that nightly sweating was absent in 97% of patients with PHH (28). A tentative reason for the diverging results of this study is that the authors determined the occurrence of nightly sweating and not symptoms while asleep. Furthermore, a possible selection bias may also explain this observation because the patients included already had a confirmed PHH diagnosis upon inclusion, in which cessation of sweating while asleep is one of the minor criteria. The results of this study question the use of this criterion, which warrants additional research.

A combination of two criteria could retain important information that may be overlooked in a single-criterion version. Of the two-criteria versions, the combination of the major criterion with the minor criterion "bilateral and relatively symmetric" had the highest accuracy. When compared to the major criterion alone, the combination of these two criteria had a lower sensitivity of 0.96 (vs. 1.00) and only a marginally higher specificity of 1.00 (vs. 0.99). Because the confidence intervals overlapped, the difference between these two criteria and the major criterion alone was nonsignificant. Therefore, a two-item short form is not suggested.

The study population was overweight, with PHH-positive individuals having a BMI 0.9 points higher than the control individuals. This difference between the two groups was statistically nonsignificant and, in addition, it is similar to the BMI reported for Danish blood donors and the general population (29, 30). Therefore, the analysis of this study—that is, a comparison of those with and without PHH—is unlikely to be affected by overweight, and, moreover, the study population reflects the composition of the Danish population today.

Strengths and limitations

The major limitation is that an individual criterion was validated against the diagnosis of PHH based on the consensus criteria. This approach may overestimate the diagnostic accuracy. A secondary analysis therefore also determined the accuracy of an individual criterion by comparison with PHH, defined as the presence of the major criterion plus two of the minor criteria excluding the criterion we were investigating. This secondary analysis showed no difference in the sensitivities and only a reduction in the specificity for the criterion "age of onset less than 25 years," which suggests that the results are valid. It should be noted that the major criterion was not investigated separately in the secondary analysis because PHH cannot be diagnosed if this criterion is omitted. Furthermore, the exclusion of participants in this secondary analysis may have reduced the power and thereby negatively affected the ability to detect a statistical difference when compared with the primary analysis. SHH was excluded by using questionnaire items and by including blood donors that must not have the common causes of SHH, including having chronic diseases, using systemic medications, or having substance misuse. We did not conduct investigations such as blood samples or diagnostic imaging for the identification of SHH, which is not a requirement (1). Furthermore, although blood donors are an ideal cohort of patients because of the low risk of SHH, it may limit the external validity. Therefore, future validation studies in other populations are warranted. Finally, self-reported data were used, which may be subject to recall bias. This is likely; however, a non-differential bias affected the entire study population equally because the inclusion of participants was not subject to PHH disease status. Furthermore, the consensus criteria of PHH rely on patient-reported

data. Therefore, the use of questionnaires for validating the diagnosis of PHH is adequate.

Implications

This study shows that the use of a single patient-reported item can accurately both confirm and reject PHH. The brevity makes it an ideal screening tool in clinical practice. Importantly, this can allow a timely diagnosis and thereby early treatment initiation and referrals to dermatologists, which can prevent undesired co-occurring outcomes of PHH (13–18). In research, this item is advantageous because it can easily be included in questionnaires and provide a high degree of accuracy.

Conclusions

This study shows that the single major criterion of PHH has both near-perfect agreement on Cohen's kappa and near-equal diagnostic accuracy compared to the gold standard consensus method. Thus, this single item can be used as a short-form version to screen for PHH in clinical practice and research. Applying a validated screening tool can increase the quality of PHH research by strengthening the case definition. This research would profit from further validation in the general population and secondary care facilities to determine its external validity. In addition, future research avenues should include determination of reproducibility in independent populations.

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