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TITLE: The ability of the Bristol Impact of Hypermobility questionnaire to discriminate between people with and without Joint Hypermobility Syndrome: a known-group validity study.

RUNNING TITLE: Known group validity of the BIoH questionnaire.

AUTHORS: Shea Palmer[a]*, Samuel Macconnell[a], Alison Willmore[a]

AFFILIATIONS: [a]Faculty of Health & Applied Sciences, University of the West of England, Bristol, UK.

CORRESPONDING AUTHOR DETAILS:

*Professor Shea Palmer, Professor of Musculoskeletal Rehabilitation, Department of Allied Health Professions, University of the West of England, Blackberry Hill, Bristol, BS16 1DD

Tel: +44 117 3288919

Email: shea.palmer@uwe.ac.uk

ORCID: https://orcid.org/0000-0002-5190-3264

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TITLE

The ability of the Bristol Impact of Hypermobility questionnaire to discriminate between people with and without Joint Hypermobility Syndrome: a known-group validity study.

ABSTRACT

Introduction: A number of psychometric properties of the Bristol Impact of Hypermobility (BIoH) questionnaire have previously been demonstrated, including strong concurrent validity and test-retest reliability. This study aimed to identify whether it can discriminate between those with and without Joint Hypermobility Syndrome (JHS).

Methods: The wording of a small number of BIoH questionnaire items was adapted to create a generic version that asked about 'general health' rather than 'hypermobility'. The generic questionnaire was distributed online to university students and staff. A sampling frame was used to create age and sex-matched samples from the non-JHS respondents in the current study and a pre-existing JHS cohort. Questionnaire scores were then compared between samples.

Results: 790 responses were received. 414 were excluded, mainly due to self-reported generalised joint hypermobility or a JHS diagnosis. The sampling frame was applied to the remaining non-JHS responders (n=376) and the pre-existing JHS cohort (n=448), resulting in 206 age and sex-matched participants in each sample. The median (IQR) BIoH scores (out of a maximum 360) were 81 (57.25) and 231.5 (74.25) in the non-JHS and JHS samples respectively ($p<0.001$). There was a very strong correlation between BIoH score and the number of painful areas ($r=0.867$, $p<0.001$).

Conclusions: The BIoH questionnaire discriminates between those with and without JHS. The median difference (151.5 points) far exceeds the smallest detectable change of 42 points previously identified. The results provide further evidence of the psychometric properties of the BIoH questionnaire and its potential to support research and clinical practice.

KEY WORDS

Psychometrics; Joint laxity, familial; Surveys and Questionnaires

INTRODUCTION

Joint hypermobility syndrome (JHS) is a heritable connective tissue disorder (HCTD) characterised by joint laxity and pain (Grahame et al., 2000). It was originally understood to be purely an articular problem of excessive joint range that leads to localised problems such as pain, dislocation and early osteoarthritis (Kirk et al., 1967). However, people with JHS suffer a wide variety of symptoms, such as fatigue, skin and cardiovascular abnormalities (Hakim & Grahame, 2003a); gastrointestinal symptoms (Bolasco et al., 2015); autonomic dysfunction (Hakim & Grahame, 2004); altered proprioception (Mallik et al., 1994); muscle weakness (Sahin et al., 2008); and sleep apnoea and restless leg syndrome (Castori et al., 2012). Anxiety, depression (Smith et al., 2013a) and other psychiatric conditions are also more common in JHS (Cederlof et al., 2016). There have been recent changes to the nosology and associated diagnostic criteria in this area (Castori et al., 2017; Malfait et al., 2017). However, the current study pre-dated their introduction and the older term JHS will therefore be used throughout.

Understanding related to the diagnosis, assessment and treatment of JHS is limited (Grahame, 2008), with inconsistent epidemiological information (Remvig et al., 2007),

poor use of diagnostic criteria (Palmer et al., 2015), limited knowledge of the condition (Rombaut et al., 2015) and problems distinguishing it from other similar disorders (Castori et al., 2017). The previous Brighton criteria for JHS had major diagnostic criteria of ≥4 on the 9-point Beighton score of generalised joint hypermobility (GJH) (Beighton et al., 1973) and pain for longer than 3 months in 4 or more joints (Grahame et al., 2000). 30% of patients accessing a musculoskeletal triage service in the United Kingdom (UK) were found to meet the Brighton criteria (Connelly et al., 2015). Similarly, 46% of women and 31% of men referred to a UK rheumatology clinic (Hakim & Grahame, 2004), and 55% of women seen in a musculoskeletal outpatient department in Oman (Clark & Simmonds, 2011) fulfilled the JHS criteria. The condition is therefore likely to be very prevalent in musculoskeletal services.

Despite its likely prevalence, there is poor understanding of the condition by physiotherapists and other health professionals (Rombaut et al., 2015). For example, 33.5% of Flemish physiotherapists reported having no idea about the impact of JHS on patients' lives (Rombaut et al., 2015) and 51% of UK physiotherapists reported having no training in hypermobility (Lyell et al., 2016). When diagnosing JHS, physiotherapists most frequently used the Beighton score in conjunction with other assessment questions, with only 31% using the Brighton criteria (Palmer et al., 2015). And, although the Beighton score is widely accepted as a measure of GJH, there are inconsistencies in how the tests are performed and utilised (Remvig et al., 2014).

This lack of knowledge and understanding of the condition has meant that assessment and treatment of JHS patients has been problematic. Both health professionals and patients have expressed a need for JHS to be treated holistically, as often only a single aspect or single joint is considered (Palmer et al., 2016). People with JHS present with such a wide array of signs and symptoms that they cannot be treated with one singular

intervention (Malfait et al., 2017). Indeed, current treatment options include a very wide variety of pharmacological and non-pharmacological interventions (Castori et al., 2012; Rombaut et al., 2015; Smith et al., 2013b). Evidence for the effectiveness of many interventions is either non-existent or very limited (Castori et al., 2012; Engelbert et al., 2017; Palmer et al., 2014; Smith et al., 2013b) but they are still frequently employed (Rombaut et al., 2015), mainly based upon clinical experience and patient feedback (Keer & Simmonds, 2011). JHS is considered difficult to manage (Castori et al., 2012; Englebert et al., 2017) but physiotherapy is a mainstay of treatment and aims to reduce pain, improve joint stability and facilitate self-management (Keer & Simmonds, 2011).

Assessment of JHS has been identified as an area where clinical practice could be improved, with a mismatch between what physiotherapists state as the aims of management and the outcome domains they assess to identify the success of management (Palmer et al., 2015). The Bristol Impact of Hypermobility (BIoH) questionnaire is the first condition-specific tool to assess the impact of JHS (Palmer et al., 2016). It was developed in close partnership with people with JHS, researchers and clinicians. It consists of 55 scored items assessing a wide range of impairments, activity limitations and participation restrictions, including items such as joint pain, fatigue, joint instability and the effects on activity. The BIoH questionnaire provides a score out of 360, with a higher score representing a greater impact of JHS (Palmer et al., 2017a). The BIoH questionnaire aims to better represent the difficulties experienced by people with JHS and thus underpin future research and clinical practice.

The BIoH questionnaire has demonstrated strong concurrent validity with the physical component score of the SF-36 ($r = -0.725$) (Palmer et al., 2017a) and has also shown excellent test-retest reliability (Interclass Correlation Coefficient = 0.922) (Palmer et al., 2017b). The smallest detectable change, beyond which changes are likely to be

greater than measurement error, has been calculated as 42 points (Palmer et al., 2017b). A qualitative evaluation of the questionnaire by patients and therapists has also strongly supported its appropriateness, validity, acceptability, feasibility and interpretability (Manns et al., 2018). However, other psychometric properties still need to be evidenced.

Construct validity describes the degree to which a tool measures what it is intended to measure, including the ability to distinguish between people with and without a health condition, a concept called ‘known-group validity’ (Bolarinwa, 2015). Determining the known-group validity of the BIoH thus formed the primary aim of the current investigation. A secondary aim was to explore the concurrent validity of the BIoH score with the number of painful areas reported by respondents (as a surrogate of condition severity).

METHOD

The original BIoH questionnaire (Palmer et al., 2017a) was adapted slightly to make it relevant to people without JHS. As few changes as possible were made, limited to removing reference to ‘hypermobility’, in most cases replacing this with ‘your general health’. Only a very small number of changes were required, as detailed in Table 1. The generic questionnaire was piloted with some university students (n=8). Feedback confirmed that questions were easily understood and that no further adjustments were required.

TABLE 1 HERE

The generic questionnaire was transferred to an online questionnaire platform (Qualtrics, Provo, UT) and was supplemented with some further brief questions that collated

information relating to age, sex, ethnicity and relevant medical history. This included the 5-part questionnaire for identifying generalised joint hypermobility (Hakim & Grahame 2003b).

Inclusion criteria: Adults ≥18 years old.

Exclusion criteria: A diagnosis of JHS, Ehlers-Danlos Syndrome (EDS), another HCTD, or another condition causing multiple joint pain (such as Rheumatoid Arthritis or Fibromyalgia); a score ≥2 on the 5-part questionnaire for identifying GJH (Hakim & Grahame 2003b).

A link to the generic questionnaire was distributed via email and an online newsletter to students and staff at UWE Bristol. Recipients were encouraged to further distribute the questionnaire to friends and family. A participant information sheet and consent form were provided online. All participants were asked to provide informed consent before completing the online questionnaire. All data was collected anonymously.

There was no formal sample size calculation but the intention was to match or exceed the existing JHS cohort. That cohort constituted 448 participants who completed the baseline BIoH questionnaire as part of a previous test-retest reliability study (Palmer et al., 2017b). Those participants had a self-declared formal diagnosis (by a healthcare professional) of JHS or EDS hypermobility type and/or scored ≥2 on the 5-part hypermobility questionnaire (Hakim & Grahame 2003b).

The current research involving non-JHS participants was approved by the Faculty of Health & Applied Sciences Research Ethics Committee at the University of the West of England, Bristol (HAS/16/12/076). Previous ethical approval was in place for the collection and use of data from the JHS cohort (HAS/15/01/99), as described by Palmer et al. (2017b).

Data Analysis

Responses to the generic questionnaire were compared to existing BIoH questionnaire data from a cohort of people with JHS (Palmer et al., 2017b).

Data collected from non-JHS participants was exported from Qualtrics into a Microsoft Excel spreadsheet. Participants that fulfilled the exclusion criteria were then removed. A sampling frame was used to match non-JHS participants and people with JHS on the basis of age and sex, as both are associated with joint hypermobility (Remvig et al., 2007). The original JHS cohort (Palmer et al., 2017b) was not very ethnically diverse and therefore it was decided not to match on the basis of ethnicity. Non-JHS and JHS participants were divided into women and men and then into age groups (18-29, 30-39, 40-49, 50-59, 60-69, 70+ years). The sample size for each age/sex category was determined by the lowest number of participants in each category. A matching number of participants in the same category in the other group were then selected at random. A random sample was achieved using the =RAND() function in Microsoft Excel to assign a random number to each participant. Participant numbers were then ordered smallest to largest and the first participants were chosen in the required quantity. For example, there were 81 women aged 18-29 years in the JHS group and 141 in this category in the non-JHS group. 81 non-JHS women were thus randomly selected from the 141 available. This process was repeated for all age/sex categories and resulted in samples from both groups that were comparable on the basis of sample size, age and sex.

The sampled data from each group were then exported to IBM SPSS Statistics (Version 25.0). Data distributions were tested for normality using Kolmogorov-Smirnov tests. Descriptive statistics were calculated for participant characteristics, total questionnaire scores (maximum score 360), the number of painful areas (Section A), average pain (Question 1) and average fatigue (Question 5). Pain and fatigue were

explored separately as these are commonly reported by people with JHS (Terry et al., 2015). Known-group validity was determined using non-parametric tests for independent samples (Mann-Whitney U Tests) to see if there were statistically significant differences between the two samples for the total questionnaire score, number of painful areas, average pain and average fatigue. Additional tests were performed on all individual questionnaire items questions (Mann-Whitney U Tests and Independent-Samples Median Tests for scale and ordinal data respectively). Analysis of concurrent validity used the combined non-JHS and JHS samples. A Spearman's rank order correlation coefficient was calculated to explore the concurrent validity of the total BIoH score against the number of painful areas reported by respondents.

RESULTS

A total of 790 respondents completed the generic online questionnaire. Of these, 414 were excluded (see Table 2), leaving a potential cohort of 376 non-JHS participants. There were data available for 448 people with JHS (Palmer et al., 2017b).

TABLE 2 HERE

Application of the sampling frame created two age and sex-matched groups, each with n=206 participants. The median BIoH scores in the non-JHS and JHS groups before and after sampling (81 and 238 before, 81 and 231.5 after, respectively) were comparable, suggesting that the samples were representative of the original larger groups in terms of condition severity. Kolmogorov-Smirnov tests revealed that all data deviated from a normal distribution, with the exception of the JHS participants' BIoH data. It was therefore decided to conduct non-parametric analyses throughout.

The participant characteristics of both samples are presented in Table 3. Sex was perfectly matched (9.7% men in each sample). The median age was very slightly lower in the non-JHS sample (32 years versus 34 years in the JHS sample), although this was not statistically significant. The non-JHS sample was also slightly more ethnically diverse than the JHS sample (9.7% versus 3.9% respectively indicated ethnicity other than 'white'), although again the differences were not statistically significant. The JHS sample scored a median of 4 on the 5-point questionnaire for GJH.

TABLE 3 HERE

Table 4 presents some of the BIoH questionnaire results. The median total BIoH score was significantly higher in the JHS sample, exceeding the score of the non-JHS sample by 150.5 points. The number of reported painful areas in the past 7 days (Section A), average pain (Question 1) and average fatigue (Question 5) were also significantly higher in people with JHS than non-JHS controls. All 55 scored questionnaire items proved statistically significantly different between samples (all $p<0.001$).

TABLE 4 HERE

Finally, a very strong correlation was demonstrated between the number of painful areas and the total BIoH score in the combined non-JHS and JHS samples ($n=412$, $r=0.867$, $p<0.001$). Figure 1 graphically illustrates this relationship. The trendline suggests an increase of approximately 200 points on the BIoH score as the number of painful areas increases from 0 to 10.

FIGURE 1 HERE

DISCUSSION

The results demonstrate that the BIoH questionnaire clearly differentiates between those with and without JHS, thereby exhibiting known-group validity. The difference in median scores of 150.5/360 points is well in excess of the smallest detectable change of 42 points established by Palmer et al. (2017b). The observed difference, therefore, cannot be explained by measurement error and is likely to indicate a true difference. Known-group validity was also demonstrated by individual aspects of the questionnaire, namely the number of painful areas, average pain and average fatigue (Table 4). The very strong correlation between the number of painful areas and the total BIoH score provides further evidence of concurrent validity. The approximate increase of 200 points as the number of painful areas increases (Figure 1) also considerably exceeds the smallest detectable change and suggests that the questionnaire should be sensitive to changes in condition severity. It should be noted, however, that clinical importance and sensitivity to change are much more complex and nuanced than investigated in the current study and require specific investigation. Nevertheless, the findings further support the validity of the BIoH questionnaire and increase confidence in its utility for research and clinical purposes.

It should be pointed out that the non-JHS sample was not necessarily a ‘healthy’ control group in the current study, as evidenced by the observation that they experienced pain in a median of 2/10 body areas in the previous 7 days, with a median pain intensity of 1.5/10 and fatigue intensity of 3/10. It is therefore particularly notable that the BIoH questionnaire was able to discriminate people with JHS from this general population sample who had some concomitant symptoms.

The Chartered Society of Physiotherapy (CSP) (2016) in the UK have recommended the use of the EQ-5D-5L (Herdman et al., 2011) in addition to condition-specific patient-reported outcome measures for assessment in musculoskeletal services. The BIoH questionnaire could, therefore, be suitable as a condition-specific measure for conditions associated with joint hypermobility, specifically hypermobile EDS (hEDS) (Malfait et al., 2017) and Hypermobility Spectrum Disorders (HSDs) (Castori et al., 2017). These revised diagnostic categories are likely to encompass people previously diagnosed with JHS or EDS hypermobility type who contributed to the development of the BIoH questionnaire (Palmer et al., 2017a). There is no reason to believe that the BIoH questionnaire is not relevant to hEDS or HSDs, however specific validation in people who explicitly meet the diagnostic criteria for those conditions would be helpful.

The very high number of painful areas reported by people with JHS (a median of 9 out of 10 areas) has potential implications for assessment and management. Firstly, it is notable that the Beighton score, integral to the previous and revised diagnostic criteria, only assesses five joints and therefore may not detect problematic joints in this patient population. There has been recent interest in validating upper and lower limb assessment scales that account for a greater number of joints and planes of movement (Meyer et al., 2017; Nicolson and Chan, 2018) and it will be interesting to see if such scales can be incorporated into the diagnostic criteria in due course. Secondly, patients have reported that physiotherapists often only treat single joints in isolation, particularly if they have been referred with one particularly problematic joint (Palmer et al., 2016). It is clear that such a reductionist approach to management is unlikely to be successful and a much more holistic approach is required that considers the biomechanical relationships between body areas and addresses psychosocial factors.

48% of respondents were excluded on the basis of either scoring ≥2 on the 5-point questionnaire for GJH (32% of respondents) or because they self-reported a diagnosis of JHS, EDS hypermobility type or another HCTD (16%). This perhaps suggests that the participant information sheet was not sufficiently clear about recruiting people without symptomatic joint hypermobility or that some participants previously diagnosed with HCTDs did not adequately read the information. It might also simply indicate that there was a high prevalence of GJH and undiagnosed JHS in those who responded, reinforcing the notion that JHS is largely underdiagnosed (Grahame, 2008). Unfortunately, it is not possible to determine which of these potential explanations was responsible for the high number of exclusions. The online questionnaire might have been more effectively designed to prospectively identify exclusions and prevent participants having to complete the entire questionnaire. However, the criteria were clearly effective in allowing retrospective exclusion of those with JHS or GJH and creating appropriate comparator samples.

Although the BIoH questionnaire is not specifically designed to have separate component scores, comparison of some of the individual BIoH questions (for the number of painful areas, average pain and average fatigue) between samples in the current study (Table 4) indicates that they might give useful information when considered in isolation. Indeed, all 55 individual scored items were statistically significantly different between samples, suggesting that they all have some relevance, at least in terms of distinguishing between people with and without JHS. Such findings further support the known-group validity of the questionnaire.

Strengths and limitations

The questionnaire was distributed to university students and staff at a university, meaning that there was an imbalance in the age distributions between the original non-JHS and JHS

groups. Application of the sampling frame therefore excluded many participants from each group (n=170/376 and n=242/448 were excluded from the non-JHS and JHS groups respectively). However, a very robust process was followed to ensure that representatives from each age/sex category within the sampling frame were selected at random. This process provided a sound basis for comparison of the samples, which were still quite large (n=206 in each sample). However, it is acknowledged that the resultant samples are not necessarily representative of the original groups from which they were derived and therefore appropriate care needs to be taken in generalising the findings. For example, although the overall BIoH score was comparable between the JHS sample (n=206) and the original larger JHS group (n=448) (median 231.5 versus 238 points respectively), the sample was younger (median 32 years versus 43 years) and had a larger proportion of men (9.7% versus 4.5%) once the sampling frame had been applied. The samples, and indeed the original groups from which they were derived, were also not very ethnically diverse. This is important as hypermobility has been reported to be more prevalent in African and Asian groups as compared to white populations (Hakim & Graham, 2003a).

The present study has demonstrated the ability of the BIoH questionnaire to discriminate between those with and without JHS. However, further work needs to be conducted to determine if it can also discriminate between different diagnoses, for example between hEDS and HSD. Further information on its sensitivity to change is also required.

Conclusion

The BIoH questionnaire has demonstrated the ability to differentiate between those with and without JHS, an important element of construct validity. The difference between groups was well in excess of the smallest detectable change, suggesting that the difference cannot be explained by measurement error. Further evidence of concurrent validity has

also been demonstrated, with a very strong correlation observed between the number of painful areas and the total BIoH score. The findings further support the potential clinical and research utility of the questionnaire.

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TABLES

Table 1. Changes made to the BIoH questionnaire wording to make it applicable to a general population.

Original BIoH questionnaire wording	**Generic questionnaire wording**
Introduction: *"This questionnaire is designed to ask how hypermobility affects activities in your day to day life."*	**Introduction:** *"This questionnaire is designed to ask how your general health affects activities in your day to day life."*
Section B: *"We would like to know how often you have experienced pain and fatigue due to hypermobility during the* ***past 7 days****."*	**Section B:** *"We would like to know how often you have experienced pain and fatigue during the* ***past 7 days****."*
Section C: *"Please tick the box which best describes how much, during the* ***past 7 days****, hypermobility has affected..."*	**Section C:** *"Please tick the box which best describes how much, during the* ***past 7 days****, your general health has affected..."*
Section E: *"How much difficulty have you had with the following tasks during the* ***past 7 days*** *due to hypermobility?"*	**Section E:** *"How much difficulty have you had with the following tasks during the* ***past 7 days****?"*
Question 40: *"How frustrated you have felt with hypermobility during the* ***past 7 days****?"*	**Question 40:** *"How frustrated you have felt with your general health during the* ***past 7 days****?"*
Section H: *"Thinking about what you are usually able to do how much has hypermobility interfered with your activities during the* ***past 7 days****?"*	**Section H:** *"Thinking about what you are usually able to do how much has your general health interfered with your activities during the* ***past 7 days****?"*

Question 46: *"How much has hypermobility interfered with your daily activities during the past 7 days?"*	**Question 46:** *"How much has your general health interfered with your daily activities during the past 7 days?"*
Question 49: *"I am concerned about my condition getting worse"*	**Question 49:** *"I am concerned about my general health getting worse"*
Question 50: *"I feel frustrated with my condition"*	**Question 50:** *"I feel frustrated with my general health"*
Question 55: *"I feel that I can manage my condition"*	**Question 55:** *"I feel that I can manage my general health"*

Table 2. Reasons for exclusion of respondents to the generic questionnaire. EDS = Ehlers-Danlos Syndrome, GJH = generalised joint hypermobility, HCTD = heritable connective tissues disorder, JHS = Joint Hypermobility Syndrome.

	Number of respondents (total n=790), n (%)
Diagnosis of JHS	115 (15%)
Diagnosis of EDS	5 (<1%)
Diagnosis of another HCTD	3 (<1%)
Diagnosis of another multiple joint condition	19 (2%)
Scored ≥2 on 5 point GJH questionnaire	253 (32%)
Incomplete consent	18 (2%)
Entered incorrect year of birth	1 (<1%)
Total excluded	414 (52%)
Total included	376 (48%)

Table 3. Participant characteristics of the non-JHS and JHS samples. GJH = Generalised Joint Hypermobility, JHS = Joint Hypermobility Syndrome, IQR = Interquartile Range, N/A = Not Applicable.

		Non-JHS (n=206)	JHS (n=206)	p-value, statistical test
Women:Men, n		186:20	186:20	N/A
5-point Questionnaire for GJH (max 5), Median (IQR)		N/A	4 (3, 4)	N/A
Age (years), Median (IQR)		32 (22.5, 41.75)	34 (26, 42.75)	p=0.106, Mann-Whitney U Test
Ethnicity, n (%)	White	186 (90.3%)	198 (96.1%)	p=0.084, Pearson Chi-Square Test
	Mixed	5 (2.4%)	5 (2.4%)	
	Asian	5 (2.4%)	0 (0%)	
	Black	5 (2.4%)	1 (0.5%)	
	Chinese	1 (0.5%)	0 (0%)	
	Other	4 (1.9%)	2 (1.0%)	

Table 4. Median (IQR) BIoH total score, painful area count, average pain and average fatigue in the non-JHS and JHS samples. *Statistically significant (all Mann-Whitney U Tests). JHS = Joint Hypermobility Syndrome, IQR = Interquartile Range.

	Non-JHS (n=206)	JHS (n=206)	p-value
BIoH total score (max 360), Median (IQR)	81 (62.5, 119)	231.5 (193, 266.75)	p<0.001*
Section A: Painful area count (max 10), Median (IQR)	2 (1, 3)	9 (7, 10)	p<0.001*
Question 1: Average pain (max 10), Median (IQR)	1.5 (0.5, 3)	6 (4, 7)	p<0.001*
Question 5: Average fatigue (max 10), Median (IQR)	3 (1, 5)	7 (5, 8)	p<0.001*

FIGURE LEGENDS

Figure 1. Scatterplot of the relationship between the number of painful areas and the total BIoH score (n=412).

FIGURES

Figure 1. Scatterplot of the relationship between the number of painful areas and the total BIoH score (n=412).