Environmental Sciences Europe

RESEARCH

Open Access

The Brief Environmental Exposure and Sensitivity Inventory (BREESI): an international validation study

Raymond F. Palmer*, Rudy Rincon, Roger B. Perales, Tatjana T. Walker, Carlos R. Jaén and Claudia S. Miller

Abstract

Background: Chemical intolerance (CI) is a condition that may result in multisystem symptoms triggered by low levels of exposure to xenobiotics such as chemical inhalants, foods, and/or drugs. The population prevalence of self-reported chemical intolerance is estimated to be between 4 and 25% across several countries. Clinicians and researchers require a brief, practical screening tool for identifying chemical intolerance.

Objectives: We investigated the validity of a three-item screening questionnaire for CI, the Brief Environmental Exposure and Sensitivity Inventory (BREESI). The internationally validated, and widely used 50-item Quick Environmental Exposure and Sensitivity Inventory (QEESI) was used as the reference standard.

Methods: Five thousand individuals ($n = 1000$ in each of five countries: the US, Japan, Italy, Mexico, and India) responded to both the QEESI and the BREESI using an online research survey platform. We determined the statistical performance metrics for the BREESI, comparing the number of items chosen on the BREESI with QEESI scores for chemical intolerance. Logistic regression was used to determine the likelihood of chemical intolerance based on endorsing 0, 1, 2, or 3 items on the BREESI. We report the BREESI's sensitivity and specificity, positive and negative predictive values, and positive and negative likelihood ratios.

Results: Compared to the QEESI reference standard, the BREESI had excellent sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values for chemical intolerance in all countries except than in Japan, the negative predictive value was poor. Notwithstanding, logistic regression curves show that in all of the countries, for each one-unit increase in the number of BREESI items, there is a 4- to 5-fold increase in the odds of CI.

Discussion: This study confirms the results of two recently published validation papers in the US. The BREESI performs well as a screening tool for chemical intolerance. It is a practical screening tool for researchers, clinicians, and epidemiologists seeking to understand and address this important and prevalent condition.

Keywords: Chemical intolerance, Idiopathic environmental intolerance (IEI), Drug intolerance, Food intolerance, QEESI, BREESI, Multiple chemical sensitivity (MCS), Mexico, India, Japan, Italy, United States

Introduction

Chemical intolerance (CI) is characterized by multisystem symptoms initiated by a one-time acute high-dose, or persistent low-dose exposures to environmental toxicants [2], with new-onset intolerances often triggered by subsequent exposures to structurally unrelated chemicals [16, 34], foods [29, 30, 38], and/or drugs [19]. CI

*Correspondence: palmerr@uthscsa.edu
Department of Family and Community Medicine, Hoffman TILT Program, University of Texas Health Science Center at San Antonio, Texas, San Antonio, USA

symptoms include fatigue, headache, weakness, rash, mood changes, musculoskeletal pain, gastrointestinal, difficulties with memory and concentration (often described as "brain fog"), and respiratory problems [2, 12, 23, 24, 39]. There is growing international concern over CI and there is evidence of increasing 10-year prevalence rates in the US and Japan [16, 34].

Precise prevalence estimates for CI are difficult to obtain, due in part to the various names that differ across studies, and the lack of a universally accepted case definition. Further, the criteria and diagnostic tools used to assess CI differ across studies [21]. Prevalence rates in different population-based surveys also differ by whether CI is clinically diagnosed (between 0.5 and 6.5%) or self-reported (up to ~20%) [3–7, 17, 28, 36].

Recent reports indicate that at least one in ten US adults have well-documented food allergies, and one in five report food intolerances [13, 29, 30]. A large US electronic medical records study showed that 2.1% of health plan patients reported three or more drug intolerances [20]. Similarly, a UK survey of more than 25,000 inpatients with a documented drug intolerance showed that 4.9% had Multiple Drug Intolerance Syndrome, defined as 3 or more adverse reactions to drugs [26]. Despite its relatively high prevalence, chemical intolerance often goes undiagnosed as physicians and researchers have not had a rapid way to screen for CI.

The Quick Environmental Exposure and Sensitivity Inventory (QEESI) is the most widely used clinical and research tool for identifying CI. It has emerged as an international reference standard, used by researchers in over 17 countries with a collective *N* of ~32,000 (see [28] for a list of these studies using the QEESI). Although the 50-item QEESI can be completed in 15–20 min, clinicians and researchers need a rapid, accurate means to screen for CI. In response, we developed a three-question instrument called the Brief Environmental Exposure and Sensitivity Inventory (BREESI), derived from the QEESI.

The BREESI's three questions gauge an individual's tendency to react adversely to diverse substances representing the three major exposure categories (chemical inhalants, foods, and drugs) included in the QEESI.

The Brief Environmental Exposure and Sensitivity Inventory (BREESI)

Instructions: please answer these three questions by checking Yes or No

1. Do you feel sick when you are exposed to tobacco smoke, certain fragrances, nail polish/remover, engine exhaust, gasoline, air fresheners, pesticides, paint/thinner, fresh tar/asphalt, cleaning supplies, new carpet or furnishings? By sick, we mean headaches, difficulty thinking, difficulty breathing, weakness, dizziness, upset stomach, etc.
_Yes _No

2. Are you unable to tolerate or do you have adverse or allergic reactions to any drugs or medications (such as antibiotics, anesthetics, pain relievers, X-ray contrast dye, vaccines or birth control pills), or to an implant, prosthesis, contraceptive chemical or device, or other medical/surgical/dental material or procedure?
_Yes _No

3. Are you unable to tolerate or do you have adverse reactions to any foods such as dairy products, wheat, corn, eggs, caffeine, alcoholic beverages, or food additives (such as MSG, food dye)?
_Yes _No

In two prior studies, the BREESI demonstrated excellent positive and negative predictive values (97% and 95%, respectively) and good specificity and sensitivity (90% and 87%, respectively) in a clinical sample of 297 primary care patients [27]. Using a US population-based sample of over 10,000 Americans, the BREESI also demonstrated good positive and negative predictive values (83% and 97%, respectively) and good specificity and sensitivity (93% and 91%, respectively) [28].

Given the global relevance of CI and international use of the QEESI, we wanted to investigate the BREESI's performance as a screening instrument for CI in an international sample. We selected four countries other than the US in which to re-validate the BREESI using random, population-based survey methods. We selected India, Italy, Japan, and Mexico based upon our interest in their environmental trends and published literature (or lack thereof) on chemical intolerance. Although we investigated the BREESI's performance in the US in our previous study [28], it is also included here for comparison, using the same sampling methodology as the other four countries. This study provides the BREESI's sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios using the QEESI as the reference standard.

Materials and methods

Sample recruitment

Respondents were randomly recruited by email through a global research-literate, multi-lingual data collection specialist company that provides recruitment services for researchers (www.dynata.com). Dynata adheres to the European Society for Opinion and Marketing Research code of conduct. In this study, Dynata performed survey translation, including back-translation, for each country. Respondents were recruited from Dynata's nationally representative research panel in each country. Invitations to participate include e-mail, phone alerts, banners, and messaging on panel community sites to include those with a diversity of motivations to take part in research. Weighted randomization was used to assign surveys to participants. A review of the data was performed to ensure that answers were logical and not random responses, with additional logic checks built into the script to ensure participants could not continue if they tried to submit illogical answers. Overuse of item non-responses (e.g., 'Don't Know') were identified and removed from the final data during quality checks. Our sample was collected by stratifying approximately equal numbers of participants ($n=1000$) across seven age bands: 18–19, 20–29, 30–39, 40–49, 50–59, 60–69, and 70 and older, and by gender for approximately equal numbers of males and females.

QEESI scoring

The QEESI has 4 scales: Chemical Exposures, Other Exposures, Symptom Severity, and Life Impact. Each scale contains 10 items which are rated from 0 to 10 on a Likert scale: 0="not at all a problem" to 10="severe/disabling symptoms" (total scores for each scale have a potential range from 0 to 100). Only the Chemical and Symptom scales are used to classify individuals into severity groups [24, 25]. The cut-off criteria for "very suggestive" of CI is a score greater than or equal to 40 on both the QEESI Chemical Intolerance and Symptom Scales. The criteria for "not suggestive" of CI are scores less than or equal to 19 on each of those scales.

Statistical analysis

We calculated sensitivity and specificity, positive and negative predictive values, and likelihood ratios for the BREESI items.

Positive predictive value (PPV) is the probability that subjects with a positive screening test truly have CI. Negative predictive value (NPV) is the probability that subjects with a negative screening test truly do not have CI. Specificity, sensitivity, PPV, and NPV are measures that depend upon the prevalence of the clinical event in the population under study [14]. In contrast, positive likelihood ratios (PLR) and negative likelihood ratios (NLR) do not depend on disease prevalence and are therefore preferred and considered more accurate than NPV and PPV [1]. According to Sedighi [32]:

- Positive likelihood ratio (PLR): ratio between the probability of a positive test result given the presence of the disease and the probability of a positive test result given the absence of the disease: PLR = true positive rate/false positive rate = sensitivity/(1-specificity).
- Negative likelihood ratio (NLR): ratio between the probability of a negative test result given the presence of the disease and the probability of a negative test result given the absence of the disease: NLR = false negative rate/true negative rate = (1-sensitivity)/specificity.

A PLR greater than 10 is strong evidence for determining a disease condition is present. Conversely, an NLR less than 0.10 is strong evidence for ruling out a disease condition [22]. The accuracy statistic (e.g., the receiver operator curve), reflects the overall performance of the test.

Using logistic regression, we determined odds ratios (OR) with 95% confidence intervals and the c-statistics for the BREESI as a predictor of chemical intolerance. Age and gender were included in a multivariate model as covariates. All analyses were conducted using SAS statistical software [33].

Results

Table 1 shows population demographics. Age ranges and gender distribution were statistically equivalent across countries. However, mean ages differed and were highest in Italy and Japan, followed by the US, Mexico, and then India, which had the lowest mean age.

Figure 1 shows the average and the range of Chemical Exposures and Symptom Severity Scale scores for

Table 1 Age and gender by country

	Age range, years[2]	Mean ages, years (standard deviation)[1]	Percent female[2]
India	18–99	38.07 (14.12)[a]	48.50
Italy	18–88	48.14 (16.46)[b]	51.90
Japan	18–89	48.07 (16.65)[b]	51.80
Mexico	18–90	39.56 (15.44)[a]	51.70
United States[1]	18–88	45.76 (16.87)[c]	51.00

[1] Values with different letters indicate statistical differences at $p<0.05$

[2] No statistical difference by country Mantel–Haenszel Chi-square $p=0.13$

$N=1000$ per country

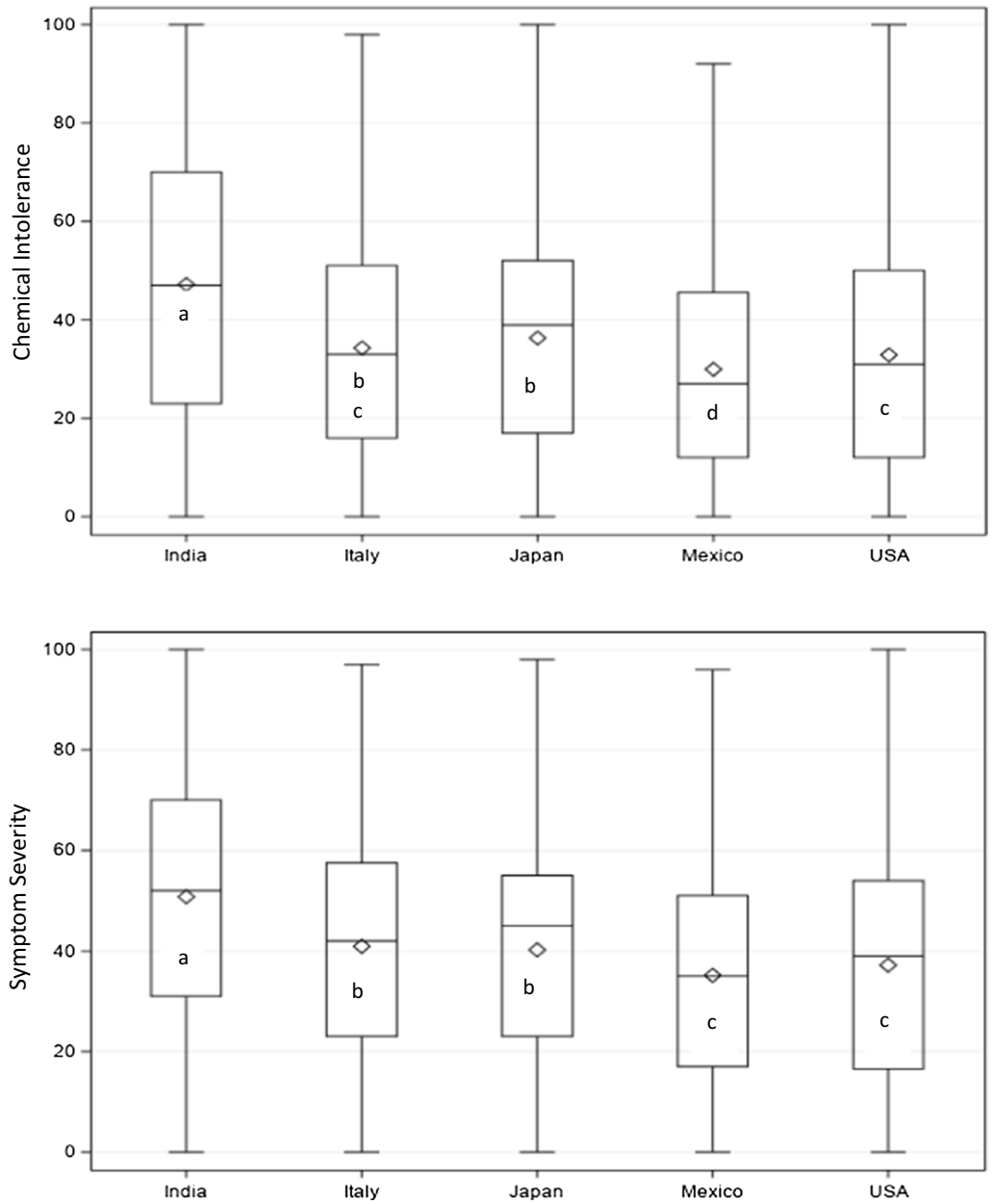

Fig. 1 Distribution of QEESI chemical intolerance and symptom scores by country. Values with different letters indicate statistical differences at $p < 0.05$

each country. Note that average scale scores for both scales exceed 40 for India. Italy and Japan both have average scores ≥ 40 on the Chemical Exposures Scale, but scores < 40 on the Symptom Severity Scale. Mexico and the US averaged scores below 40 on both scales.

The metrics in Table 2 indicate how well the BREESI correctly categorizes "very suggestive" and "not suggestive". True negatives should be congruent with "not suggestive" of CI (i.e., no BREESI items chosen), and true positive should be congruent with "very suggestive" (all three BREESI items chosen). Sensitivity indicates how well a test predicts true positive cases. Specificity indicates how well a test predicts true negative cases. Sensitivity ranged from 79 to 93% for all countries except Japan, which had 17% sensitivity due to the high number of false negatives. Specificity across countries ranged from 79 (India) to 99% (Japan, which has a low number of false positive cases).

Table 2 Performance metrics for BREESI by country

	Value	95% confidence intervals
India		
Sensitivity	91.58%	88.38–94.13%
Specificity	92.21%	83.81–97.09%
Positive likelihood ratio	11.75	5.45–25.36
Negative likelihood ratio	0.09	0.07–0.13
Positive predictive value	93.49%	86.94–96.87%
Negative predictive value	89.96%	86.53–92.59%
Accuracy	91.86%	89.01–94.17%
Italy		
Sensitivity	80.75%	74.36–86.14%
Specificity	96.97%	91.40–99.37%
Positive likelihood ratio	26.65	8.72–81.39
Negative likelihood ratio	0.2	0.15–0.27
Positive predictive value	93.21%	81.80–97.67%
Negative predictive value	90.72%	87.92–92.93%
Accuracy	91.45%	87.59–94.42%
Japan		
Sensitivity	17.22%	12.37–23.04%
Specificity	99.57%	97.65–99.99%
Positive likelihood ratio	40.48	5.60–292.67
Negative likelihood ratio	0.83	0.78–0.88
Positive predictive value	96.43%	78.87–99.49%
Negative predictive value	64.34%	62.90–65.76%
Accuracy	66.63%	62.04–71.01%
Mexico		
Sensitivity	92.50%	86.24–96.51%
Specificity	93.53%	88.06–97.00%
Positive likelihood ratio	14.29	7.58–26.93
Negative likelihood ratio	0.08	0.04–0.15
Positive predictive value	97.26%	94.98–98.52%
Negative predictive value	93.26%	89.49–95.99%
Accuracy	92.50%	86.24–96.51%
United States		
Sensitivity	78.71%	71.42–84.87%
Specificity	97.28%	93.18–99.25%
Positive likelihood ratio	28.93	10.96–76.31
Negative likelihood ratio	0.22	0.16–0.30
Positive predictive value	92.85%	83.13–97.17%
Negative predictive value	91.05%	88.24–93.23%
Accuracy	91.52%	87.79–94.41%

The PPV (probability of true positive cases) of the BREESI was between 75 (Mexico) and 97% (India). The NPV (percentage of true negative cases) for US, Mexico, India, and Italy ranged from 79 to 96%. These ranges indicate that in these countries the BREESI correctly classifies those without chemical intolerance. Japan's high number of false negatives is reflected in a low NPV of 57%.

Responses on individual BREESI items by country appear in Table 3. The outliers were India and Japan. In India, 44% endorsed all three BREESI items (chemical inhalants, foods, and drugs). In contrast, in Japan, only 5% endorsed all three.

Table 4 shows the odds of CI with each additional BREESI item chosen. The logistic regression probability graphs are shown in Fig. 2. The predicted probabilities of CI increase sharply with increasing BREESI items chosen. Each country shows a similar increase in the odds of CI with increasing number of BREESI items. The odds of CI increase are 4- to 5-fold with each additional BREESI item. Consistent with the poor NPV for Japan, with 0 items endorsed on the BREESI, the predicted probability of CI is 50%, yet the odds of CI still increases with each additional BREESI item.

Discussion

Our study of four non-US countries with 1000 respondents each confirms the BREESI's utility as a brief screening tool for chemical intolerance. The BREESI is not a substitute for the QEESI or physician-diagnosed CI, but a quick screening tool. Patients who might benefit from interventions to ameliorate CI could be deprived of the opportunity because many clinicians overlook CI as a clinical diagnosis. As always, in clinical practice it is important to consider and address alternative explanations for a patient's signs and symptoms, irrespective of the results of the QEESI.

As Table 2 depicts, all of the statistical performance metrics were excellent in the United States, Italy, Mexico, and India, confirming the BREESI as an efficient and reliable chemical intolerance screening tool. In Japan, however, there was a significant number of false negatives. For example 42% of those choosing none of the BREESI items had QEESI-defined CI, and therefore the negative predictive value and sensitivity were poor. On the other hand, the specificity and positive predictive value in Japan were excellent. Note that in Fig. 2, even in Japan, as the number of BREESI items increased, the greater the likelihood of CI. However, with zero BREESI items chosen, the probability of CI is much higher than the rest of the countries.

This anomaly in Japan might be explained by cultural response differences. Hui and Triandis [18] suggest that survey responses vary between cultures. For example, consistent with our findings, Roster et al. [31] and Chun et al. [10] show that Asians tend to demonstrate lower extreme response scores than westerners, tend to believe it is more important to be modest and respond

Table 3 Responses for individual BREESI items by country (N = 1000 for each country)

Number of BREESI items chosen	Country				
	India % (95% CI)	Italy % (95% CI)	Japan % (95% CI)	Mexico % (95% CI)	US% (95% CI)
0	19.6 (17.2–22.2)	33.3 (30.3–36.3)	59.4 (56.2–62.5)	23.4 (20.8–26.1)	32.3 (29.4–35.3)
1	18.3 (15.9–20.8)	26.7 (23.9–29.6)	27.1 (24.4–29.9)	29.4 (26.6–32.3)	29.5 (26.7–32.4)
2	17.9 (15.6–20.4)	18.7 (16.3–21.3)	8.9 (7.2–10.8)	26.4 (23.7–29.3)	19.1 (16.7–21.7)
3	44.2 (41.1–47.3)	21.3 (18.8–24.0)	4.6 (3.3–6.1)	20.8 (18.3–23.5)	19.1 (16.7–21.7)
Single BREESI Item[a]	**%**	**%**	**%**	**%**	**%**
None	19.6[a] (17.2–22.2)	33.3[b] (30.3–36.3)	59.4[c] (56.2–62.5)	23.4[a] (20.8–26.1)	32.3[b] (29.4–35.3)
Chemicals	71.4[a] (68.5–74.2)	57.7[d] (54.6–60.8)	35.7[b] (32.7–38.7)	66.2[c] (63.2–69.1)	56.5[d] (53.3–59.6)
Foods	55.3[a] (52.2–58.4)	34.2[d] (31.3–37.2)	9.2[b] (7.5–11.2)	39.5[c] (36.4–42.6)	32.9[d] (29.2–35.9)
Drugs	60.0[a] (49.7–69.6)	36.1[c] (33.1–39.1)	13.8[b] (11.7–19.1)	38.9[c] (35.8–42.0)	35.6[c] (32.6–38.6)

Superscripted letters are statistical comparisons of BREESI categories across countries. Countries with the same letters are not statistically different. Those with different letters are statistically different at $p < 0.05$

[a] *N* and percentages exceed 1000 or 100% due to respondents choosing multiple BREESI items

Table 4 Logistic regression of BREESI predicting chemical intolerance

	Odds ratios comparing Very Suggestive of CI to Not Suggestive of CI		
	Estimate (SE)	**Odds ratio**	**95% CI**
India	1.62 (0.14)	5.05	3.86–6.57
Italy	1.64 (0.16)	5.16	3.81–7.01
Japan	1.65 (0.14)	4.39	2.87–6.71
Mexico	1.64 (0.13)	5.21	3.97–6.82
US	1.45 (0.22)	5.22	3.93–6.92
	Odds ratios comparing Suggestive of CI to Not Suggestive of CI		
	Estimate (SE)	**Odds ratio**	**95% CI**
India	0.86 (0.13)	2.39	1.82–3.12
Italy	0.84 (0.14)	2.32	1.76–3.05
Japan	0.84 (0.21)	2.33	1.53–3.54
Mexico	1.01 (0.11)	2.74	2.23–3.36
USA	1.10 (0.13)	3.01	2.33–3.87

cautiously [9, 35]. In a review of studies on differences in cross-cultural response styles, Clarke [11] shows differences occur primarily with ordinal response formats (e.g., Likert scales). Asian cultures tend to choose more middle-level items on Likert scales than other cultures [37]. We checked this assertion in our data with responses from the 10-item chemical and symptom scales. Indeed, we found Japan's responses to be consistent with Wang et al. [37]. Figure 3 depicts this phenomenon. The bottom of Table 3 shows that the frequency of endorsements of the BREESI items differs by country. Japan had the lowest endorsement rates of all three items (inhaled chemicals, foods, and drugs), and India had the highest rates of endorsing all three BREESI items. Based on these results, we suggest that caution be taken when interpreting results from different cultures.

This current study is consistent with two previous US studies showing the BREESI to be an efficient and reliable CI screening tool [27, 28]. We are hoping that the BREESI will lead healthcare providers across the globe to consider how CI may underlie a wide range of chronic and acute health problems. When patients report new onset (or marked worsening) of chemical, food, and/or drug intolerances, healthcare providers can screen with the BREESI and confirm with the QEESI to help patients identify and avoid exposures that trigger symptoms.

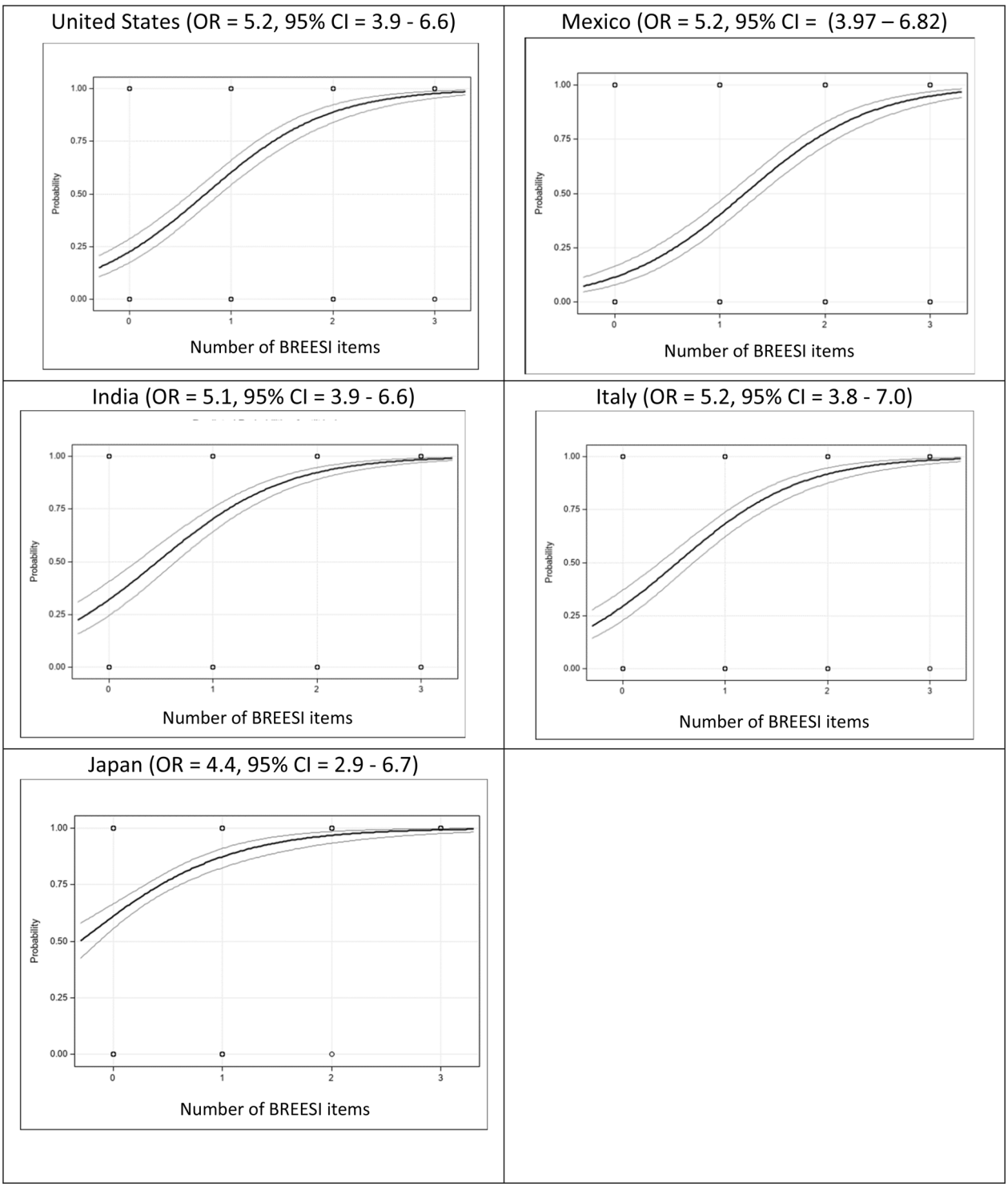

Fig. 2 Predictive probabilities of chemical intolerance by number of BREESI items endorsed. These are the Logistic model curves showing the probability of Chemical Intolerance on the Y axis given a one-unit increase of the number of BREESI items chosen (x axis). Odds ratio (OR) and 95% confidence interval (CI) are also given. The dependent variable compares the Very Suggestive vs Not Suggestive of CI groups

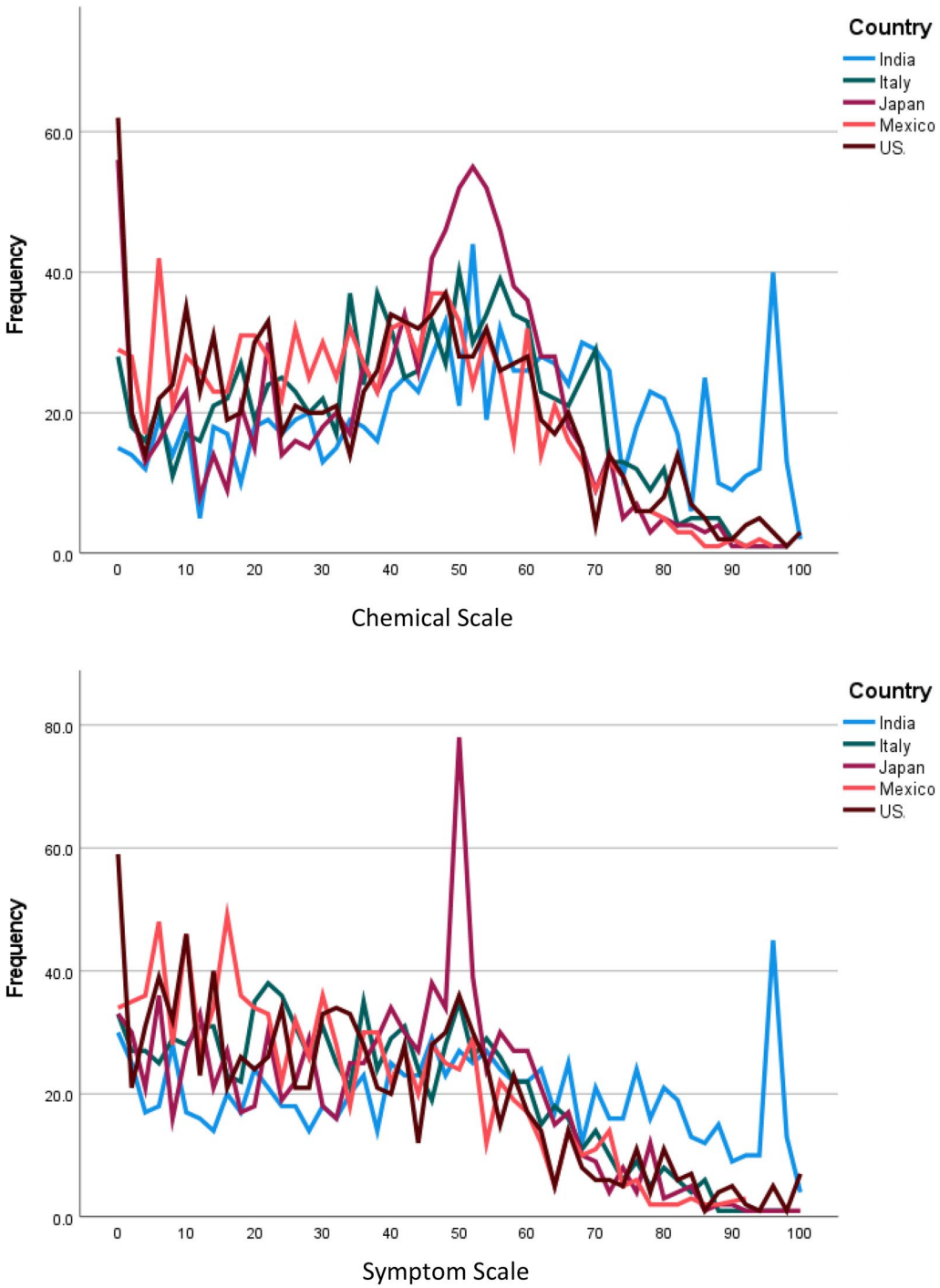

Fig. 3 Frequency of responses on the QEESI Chemical and Symptom Scales by Country. Japan's response tendency for central responses on Likert-type scales such as these is consistent with other research [37]

Limitations

There are several important limitations to this study. We conducted these studies without input from researchers in the countries we studied. Although the instruments were translated and back-translated in the language for each country, there was no cross-cultural validation by researchers in those countries. This may constitute a lack of cross-cultural validation of the BREESI or QEESI,

particularly in Japan. Notwithstanding, the QEESI has been translated into several languages and is used worldwide. It has emerged as the reference standard for assessing chemical intolerance [28].

As a result of the intentional sampling selection methods, the age ranges and gender distribution of the countries under study did not differ. However, the average age of the respondents across countries did differ (Table 1). This may be due to actual differing average ages of the populations. Nevertheless, age may remain a source of bias. We have attempted to mitigate this concern by including age as a covariate in the logistic models.

The CI prevalence estimates we obtained based on the QEESI (India 54.7%, Japan 40.3%, Italy 34.3%, U.S. 31.2%, Mexico 26.0%) are substantially higher than those of other population estimates [3, 8, 15, 17]. This calls into question how representative the sample is and thus these findings should be interpreted with caution. Without further extensive investigation, we cannot confirm that a representative sample from each country was obtained. For example, we lack basic information on important characteristics such as socioeconomic standing, lifestyle, general health, comorbidities, gender, and/or age. The participation rate among these paid volunteers does not allow a responders/non-responders comparison. These issues are a major contributor to selection bias and the prevalence estimates obtained in this study are most likely influenced by selection bias. However, these limitations do not affect our reported validation of the BREESI.

Although a clinical assessment of CI to confirm a diagnosis could have lessened concerns about inflated prevalence estimates, it was not feasible or practical to obtain physician-based diagnoses for this international study.

The present analysis confirms that the BREESI is a valid screener for CI, but it is not a substitute for the QEESI or clinical assessment. It is useful for clinicians to screen their patients for CI, for researchers conducting population health surveys, and for epidemiologists dealing with exposed populations (e.g., disasters, occupational exposures). We present the study as pilot work and recognize that future studies with larger samples are warranted.

Conclusion

There is growing international concern over intolerances to chemical inhalants, foods, and drugs. This study confirms two previous studies showing the BREESI's utility as a good screening tool for chemical intolerance. The BREESI is a practical tool for researchers, clinicians, and epidemiologists seeking to understand and address this important and prevalent condition in different populations.

Abbreviations

CI: Chemical intolerance; BREESI: The Brief Environmental Exposure and Sensitivity Inventory; QEESI: The Quick Environmental Exposure and Sensitivity Inventory; PPV: Positive predictive value; NPV: Negative predictive value; OR: Odds ratios.

Acknowledgements

We appreciate the generous support of the Marilyn Brachman Hoffman Foundation's, Fort Worth, Texas.

Authors' contributions

RFP, CRJ and CSM: conception and design of this work; RFP was responsible for the data analysis and interpretation as well as the first draft; RR and RBP were responsible for data acquisition and subsequent editing of the drafts; TTW, CSM and CRJ were responsible for substantial revisions of the work. All the authors read and approved the final manuscript.

Funding

This research was funded by the Marilyn Brachman Hoffman Foundation, Fort Worth, TX.

Availability of data and materials

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Institutional Review Board Statement: the study was conducted according to the guidelines of the Declaration of Helsinki and approved by the University of Texas Health Science Center San Antonio Institutional Review Board (Approval Number HSC20200718N). Written informed consent was waived due to completely anonymous volunteer participation.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests associated with this manuscript. The funders had no role in the design of the study, in the collection, analysis, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

Received: 12 September 2021 Accepted: 19 February 2022
Published online: 01 April 2022

References

1. Altman DG, Bland JM (1994) Diagnostic tests 2: predictive values. BMJ 309(6947):102. https://doi.org/10.1136/bmj.309.6947.102
2. Ashford N, Miller C (1998) Chemical exposures: low levels and high stakes. Van Nostrand Reinhold, New York
3. Azuma K et al (2015) Prevalence and characteristics of chemical intolerance: a Japanese population-based study. Arch Environ Occup Health 70:341–353
4. Bell IR, Schwartz GE, Peterson JM, Amend D (1993) Self-reported illness from chemical odors in young adults without clinical syndromes or occupational exposures. Arch Environ Health 48(1):6–13
5. BellSchwartz IRGE, Amend D, Peterson JM, Stini WA (1994) Sensitization to early life stress and response to chemical odors in older adults. Biol Psychiat 35(11):857–863
6. Bell IR, Hardin EE, Baldwin CM, Schwartz GE (1995) Increased limbic system symptomatology and sensitizability of young adults with chemical and noise sensitivities. Environ Res 70(2):84–97
7. Caress SM, Steinemann AC, Waddick C (2002) Symptomatology and etiology of multiple chemical sensitivities in the Southeastern United States. Arch Environ Health 57(5):429–436

8. Caress SM, Steinemann AC (2004) Prevalence of multiple chemical sensitivities: a population-based study in the southeastern United States. Am J Public Health 94(5):746–747
9. Cheung GW, Rensvold RB (2000) Assessing extreme and acquiescence response sets in cross-cultural research using structural equations modeling. J Cross Cult Psychol 31(2):187–212
10. Chun K-T, Campbell JB, Yoo JH (1974) Extreme response style in cross-cultural research: a reminder. J Cross-Cult Psychol 5(4):465–480. https://doi.org/10.1177/002202217400500407
11. Clarke I (2001) Extreme response style in cross-cultural research. Int Mark Rev 18(3):301–324
12. Genuis SJ (2010) Sensitivity-related illness: the escalating pandemic of allergy, food intolerance and chemical sensitivity. Sci Total Environ 408(24):6047–6061
13. Gupta RS, Warren CM, Smith BM et al (2019) Prevalence and severity of food allergies among US adults. JAMA Netw Open 2(1):e185630. https://doi.org/10.1001/jamanetworkopen.2018.5630
14. Heston TF (2011) Standardizing predictive values in diagnostic imaging research. J Magn Reson Imaging 33(2):505. https://doi.org/10.1002/jmri.22466
15. Hojo S, Kumano H, Yoshino H, Kakuta K, Ishikawa S (2003) Application of Quick Environment Exposure Sensitivity Inventory (QEESI©) for Japanese population: study of reliability and validity of the questionnaire. Toxicol Ind Health 19(2–6):41–49
16. Hojo S, Mizukoshi A, Azuma K, Okumura J, Ishikawa S, Miyata M, Mizuki M, Ogura H, Sakabe K (2018) Survey on changes in subjective symptoms, onset/trigger factors, allergic diseases, and chemical exposures in the past decade of Japanese patients with multiple chemical sensitivity. Int J Hyg Environ Health 221(8):1085–1096
17. Kreutzer R, Neutra RR, Lashuay N (1999) Prevalence of people reporting sensitivities to chemicals in a population-based survey. Am J Epidemiol 150(1):1–12
18. Hui CH, Triandis HC (1989) Effects of culture and response format on extreme response style. J Cross Cult Psychol 20(3):296–309
19. Macy E (2018) Chapter 16—Multiple drug intolerance syndrome. In: Khan DA, Banerji A (eds) Drug allergy testing. Elsevier, Amsterdam, pp 165–168. https://doi.org/10.1016/B978-0-323-48551-7.00016-X
20. Macy E, Ho NJ (2012) Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. Ann Allergy Asthma Immunol 108(2):88–93. https://doi.org/10.1016/j.anai.2011.11.006
21. Martini A, Iavicoli S, Corso L (2013) Multiple chemical sensitivity and the workplace: current position and need for an occupational health surveillance protocol. Oxidative Med Cell Longev 2013:13. https://doi.org/10.1155/2013/351457
22. McGee S (2002) Simplifying likelihood ratios. J Gen Intern Med 17(8):647–650
23. Miller CS (2001) The compelling anomaly of chemical intolerance. Ann NY Acad Sci 933:1–23
24. Miller CS, Prihoda TJ (1999) The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. Toxicol Ind Health 15(3–4):370–385
25. Miller CS, Prihoda TJ (1999) A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients and persons with multiple chemical sensitivity. Toxicol Ind Health 15(3–4):386–397
26. Omer HM, Hodson J, Thomas SK, Coleman JJ (2014) Multiple drug intolerance syndrome: a large-scale retrospective study. Drug Saf 37(12):1037–1045. https://doi.org/10.1007/s40264-014-0236-x
27. Palmer RF, Jaén CR, Perales RB, Rincon R, Forster JN, Miller CS (2020) Three questions for identifying chemically intolerant individuals in clinical and epidemiological populations: the Brief Environmental Exposure and Sensitivity Inventory (BREESI). PLoS ONE. https://doi.org/10.1371/journal.pone.0238296
28. Palmer RF, Walker T, Kattari D, Rincon R, Perales RB, Jaén CR, Grimes C, Sundblad DR, Miller CS (2021) Validation of a brief screening instrument for chemical intolerance in a large US national sample. Int J Environ Res Public Health 18:8714
29. Rael E, Sampath V, Nadeau KC (2020) Diagnosis and differential diagnosis of food allergy. In: Gupta R (ed) Pediatric food allergy. Springer, Cham. https://doi.org/10.1007/978-3-030-33292-1_320
30. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, Sigurdardottir ST, Lindner T, Goldhahn K, Dahlstrom J, McBride D, Madsen C (2007) The prevalence of food allergy: a meta-analysis. J Allergy Clin Immunol 120(3):638–646. https://doi.org/10.1016/j.jaci.2007.05.026
31. Roster CA, Rogers R, Albaum G (2003) A cross-cultural use of extreme categories for rating scales. Proceedings of Ninth Annual Cross Cultural Research Conference, Las Vegas
32. Sedighi I (2013) Interpretation of diagnostic tests: likelihood ratio vs. predictive value. Iran J Pediatr 23(6):717
33. SAS Institute Inc (2014) SAS® 9.4 statements: reference, 3rd edn. SAS Institute Inc., Cary
34. Steinemann A (2018) National prevalence and effects of multiple chemical sensitivities. J Occup Environ Med 60(3):e152–e156
35. Stening BW, Everett JE (1984) Response styles in a cross-cultural managerial study. J Soc Psychol 122(2):151–156
36. Szarek MJ, Bell IR, Schwartz GE (1997) Validation of a brief screening measure of environmental chemical sensitivity: the chemical odor intolerance index. J Environ Psychol 17(4):345–351
37. Wang R, Hempton B, Dugan JP, Komives SR (2008) Cultural differences: why do Asians avoid extreme responses? Surv Pract. https://doi.org/10.29115/SP-2008-0011
38. Young E, Stoneham MD, Petruckevitch A, Barton J, Rona R (1994) A population study of food intolerance. Lancet 343(8906):1127–1130. https://doi.org/10.1016/S0140-6736(94)90234-8
39. Zucco GM, Doty RL (2021) Multiple chemical sensitivity. Brain Sci 12(1):46. https://doi.org/10.3390/brainsci12010046

Publisher's Note