The Brief Environmental Exposure and Sensitivity Inventory (BREESI) An International Validation Study

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Research

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Abstract

Background

Chemical intolerance is a condition that may result in multisystem symptoms triggered by low levels of exposure to xenobiotics such as chemicals, foods, and drugs. The prevalence of chemical intolerance is estimated to be between 8% and 33% across several countries. Clinicians and researchers require a brief, practical tool for identifying chemical intolerance.

Objectives

This 5-country, population-based study investigates the validity of a three-item screening questionnaire, the Brief Environmental Exposure and Sensitivity Inventory (BREESI), against the 50-item Quick Environmental Exposure and Sensitivity Inventory (QEESI).

Methods

One thousand individuals (n = 1,000) in each of 5 countries, the U.S., Japan, Italy, Mexico, and India responded to both the QEESI and the BREESI on a Qualtrics platform by Dyanata, a survey company that provides recruitment services for researchers. We determined performance metrics for BREESI responses comparing the number of items chosen on the BREESI with QEESI scores for chemical intolerance. We used logistic regression to determine the likelihood of chemical intolerance based on scoring 0, 1, 2 or 3 items on the BREESI. We report BREESI 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 Japan. In Japan, the BREESI had poor sensitivity and a poor negative predictive value. Logistic regression shows that in all countries, with each increase in BREESI items endorsed, there is 4- to 5-fold increase in the odds of CI. Although the samples are relatively small for estimating population prevalence, our results suggest interesting differences and overall high prevalence of chemical intolerance. Applying QEESI criteria, India appears to have very high rates of chemical intolerance—over 50% of those sampled (54.7%, 95% CI = 52–58) followed by Japan (40.3%, 95% CI = 40–77), Italy (34.3%, 95% CI = 32–37), U.S. (31.2%, 95% CI = 28–34) and Mexico (26.0%, 95% CI = 23–29).

Discussion
This study confirms the results of a two recently published validation papers in the U.S. The BREESI performs well as a 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.

Introduction

There is growing international concern over intolerances to chemicals (Hojo et al., 2018; Steinemann, 2018), foods (Young et al., 1994; Rona et al., 2007), and drugs (Macy, 2018). Up to one-quarter of the U.S. population reports being either “especially” or “unusually” sensitive to certain chemicals, with about 5% reporting physician-diagnosed chemical intolerance (CI) (Caress and Steinemann, 2004; Palmer et al., 2020). Population-based surveys estimate that chemical intolerance prevalence is between 8% and 33% in several countries (Caress and Steinemann, 2004; Azuma et al., 2015; Kreutzer et al., 1999). Katerndahl et al. (2012) found that 20% of patients in our UT Health San Antonio family medicine clinic reported chemical intolerances. At least one in ten U.S. adults have well-documented food allergies, and one in five report food intolerances (Gupta et al., 2018; Rael et al., 2020). A large U.S. electronic medical records study showed that 2.1% of health plan patients reported three or more drug intolerances (Macy and Ho, 2012). Similarly, a U.K. 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, suggesting cross-intolerances (Omer et al., 2014). Despite its high prevalence, chemical intolerance often goes undiagnosed. Up to now, 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 16 countries with a collective N of ~32,000 (see Palmer et al., 2021 for a list of these studies using the QEESI). Although the 50-item QEESI can be completed in 15–20 minutes, 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.

Our first study reported the performance metrics for the BREESI in a U.S. sample of 293 individuals recruited from a primary care practice waiting room (Palmer et al., 2020). The BREESI showed excellent positive and negative predictive values (97% and 95% respectively) and good specificity and sensitivity (90% and 87% respectively). Further validation for the BREESI was obtained in a population-based U.S. sample of over 10,000 Americans (Palmer et al., 2021). That study was congruent with our initial study, demonstrating excellent positive and negative predictive values (83% and 97% respectively) and good specificity and sensitivity (93% and 91% respectively) with an overall accuracy statistic of 92%. These two studies validated the BREESI as a screening tool for CI in the U.S.
The BREESI’s three questions gauge an individual’s tendency to react adversely to diverse substances representing the three major exposure categories (chemicals, foods, and drugs) included in the Quick Environmental Exposure and Sensitivity Inventory (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_

Given the global relevance of the CI problem and international use of the QEESI, we wanted to investigate the BREESI’s performance in an international sample. We selected four countries other than the U.S. in which to re-validate the BREESI using random, population-based surveys. 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 U.S. in our previous study (Palmer et al., 2020), it is included here for comparison, using the same sampling methodology as the other four countries. This study provides the BREESI’s sensitivity and specificity, positive and negative predictive values, and positive and negative likelihood ratios.

**Materials And Methods**

Respondents were randomly recruited by email by Dynata, a panel (survey) company that provides recruitment services for researchers (www.dynata.com). Dynata adheres to the ESOMAR market research code of conduct. Dynata performed survey translation, including back-translation, for each country. Respondents were recruited from Dynata’s nationally representative research panel in each country. The sample was stratified with roughly 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. It was also stratified by gender for approximately equal numbers of males and females.

**QEESI and BREESI Scores:**
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: 0 = “not at all a problem” to 10 = “severe/disabling symptoms.” Scale totals range from 0-100. There is also a 10-item Masking Index which gauges ongoing exposures such as caffeine, alcohol, or tobacco use that can affect individuals’ awareness of their intolerances as well as the intensity of their responses to environmental exposures (Miller and Prihoda, 1999a).

There are three QEESI classifications for CI, based on responses to the Chemical Exposures and Symptom Severity Scales. Scores greater than or equal to 40 on CI intolerance indicate very suggestive of chemical intolerance. Scores less than 20 on both scales are not suggestive of CI (Miller and Prihoda, 1999a). Although the full QEESI is recommended for assessments in clinical practice or clinical research, for this epidemiological study we used only the Chemical Exposures and Symptom Severity Scales to assess CI.

**Statistical Analysis.**

We prepared prevalence estimates for each country. We calculated sensitivity and specificity, positive and negative predictive values, and likelihood ratios for the BREESI items. 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 (SAS 2014).

**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.
Table 1
Age and Gender by Country

| Country     | Age Range, years | Mean Ages, years (Std Dev) | Percent Female |
|-------------|------------------|-----------------------------|----------------|
| **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**  | 18–88      | 45.76 (16.87) c             | 51.00          |

*Values with different letters indicate statistical differences at p < .05

**No statistical difference by country Mantel Hanzel Chi-square p = .13

N = 1000 per country.

Figure 1 shows the average and the range of Chemical Exposures and Symptom Severity Scale scores for 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 U.S. averaged scores below 40 on both scales.

Figure 2 shows the prevalence of CI by country (“very suggestive” = scores ≥ 40 on both the Chemical Exposures and Symptom Severity Scales). India had the highest prevalence of CI (54.7%, 95% CI = 52–58) followed by Japan 40.3%, 95% CI = 40–77), Italy (34.3%, 95% CI = 32–37), U.S. (31.2%, 95% CI = 28–34), and Mexico (26.0%, 95% CI = 23–29), which had the lowest compared to other countries. On Fig. 2, letters indicate significant mean differences at < .05. Countries with the same letters are not significantly different from one another. Overall, all five countries’ average scores indicate a potentially high prevalence of CI.

The metrics in Table 2 indicate how well the BREESI correctly categorizes those with and without chemical intolerance as measured by the QEESI. We compared BREESI scores to the QEESI category of “very suggestive” as a positive case and to the QEESI category of “not suggestive” as a negative case. Sensitivity indicates how well a test predicts true positive cases. Specificity indicates how well a test predicts true negative cases. Sensitivity ranged from 79–93% 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

| 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 to 25.36               |
| Negative Likelihood Ratio | 0.09 | 0.07 to 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 to 81.39               |
| Negative Likelihood Ratio | 0.2 | 0.15 to 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 to 292.67              |
| Negative Likelihood Ratio | 0.83 | 0.78 to 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%                |
Positive predictive value (PPV) is the probability that subjects with a positive screening test truly have the disease. Negative predictive value (NPV) is the probability that subjects with a negative screening test truly do not have the disease. 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 USA, Mexico, India, and Italy ranged from 79–96%. 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%.

Specificity, sensitivity, PPV, and NPV are measures that depend upon the prevalence of the clinical event in the population under study (Altman and Bland, 1994). In contrast, positive likelihood ratios and negative likelihood ratios do not depend on disease prevalence and are therefore preferred and considered more accurate than NPV and PPV (Heston, 2011). Since prevalence estimates will vary in the sampling frame for these countries, we calculated likelihood ratios (see Table 2). The likelihood ratios are used to express the change in the odds that a person does or does not have a condition given a positive or negative result (Sedighi, 2013). For example, the positive likelihood ratio gives the change in the odds of having the condition among persons with a positive screen (Glenn, 2021).

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 (chemicals, foods, and drugs). In contrast, in Japan, only
5% endorsed all three.

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

| Number of BREESI Items chosen | India  | Italy  | Japan  | Mexico | USA  |
|------------------------------|--------|--------|--------|--------|------|
|                              | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (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 *

|                | %       | %       | %       | %       | %       |
|----------------|---------|---------|---------|---------|---------|
| None           | 19.6 a  | 33.3 b  | 59.4 c  | 23.4 a  | 32.3 b  |
|                | (17.2 – 22.2) | (30.3 – 36.3) | (56.2 – 62.5) | (20.8 – 26.1) | (29.4 – 35.3) |
| Chemicals      | 71.4 a  | 57.7 d  | 35.7 b  | 66.2 c  | 56.5 d  |
|                | (68.5 – 74.2) | (54.6 – 60.8) | (32.7 – 38.7) | (63.2 – 69.1) | (53.3 – 59.6) |
| Foods          | 55.3 a  | 34.2 d  | 9.2 b   | 39.5 c  | 32.9 d  |
|                | (52.2 – 58.4) | (31.3 – 37.2) | (7.5 – 11.2) | (36.4 – 42.6) | (29.2 – 35.9) |
| Drugs          | 60.0 a  | 36.1 c  | 13.8 b  | 38.9 c  | 35.6 c  |
|                | (49.7 – 69.6) | (33.1 – 39.1) | (11.7 – 19.1) | (35.8 – 42.0) | (32.6 – 38.6) |

Note: 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 < .05.
N and percentages exceed 1,000 or 100% due to respondents choosing multiple BREESI items. See Venn diagrams (Figs. 3b-7b) for overlap percentages.

Table 4 shows the odds of CI with each additional BREESI item chosen. The logistic regression probability graphs are shown in Fig. 3. 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 NPV for Japan, note that with 0 items on the BREESI, the predicted probability of CI is still 50%, yet increases with each additional BREESI item.

Table 4
Logistic regression of BREESI predicting chemical intolerance

| Estimate (SE) | Odds Ratio¹ | 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 |
| USA         | 1.45 (0.22) | 5.22       | 3.93–6.92 |

| Estimate (SE) | Odds Ratio² | 95% CI     |
|-------------|-------------|------------|
| India       | 0.86 (0.13) | 2.387      | 1.82–3.12 |
| Italy       | 0.84 (0.14) | 2.320      | 1.76–3.05 |
| Japan       | 0.84 (0.21) | 2.334      | 1.53–3.54 |
| Mexico      | 1.01 (0.11) | 2.736      | 2.23–3.36 |
| USA         | 1.10 (0.13) | 3.006      | 2.33–3.87 |

¹ Odds ratio for each one unit increase of BREESI comparing Very Suggestive of CI to Not Suggestive of CI

² Odds ratio for each one unit increase of BREESI comparing Suggestive of CI to Not Suggestive of CI

Discussion

We have shown that the BREESI is an efficient tool for determining potential CI in a range of health care settings and for epidemiological studies. Our initial pilot study of 293 primary care patients showed that the BREESI exhibited excellent positive and negative predictive values as well as sensitivity and specificity when evaluated against the QEESI reference standard (Palmer et al., 2020). In that paper, we recommended further evaluation of the BREESI's performance in other populations to confirm its validity.
Subsequently, the BREESI was found to have excellent predictive validity in a U.S. sample of over 10,000. (Palmer et al., 2021)

The results of the current population study of 4 non-U.S. countries with 1000 respondents each confirms the BREESI's utility as a screening tool for chemical intolerance. To address concerns about prevalence estimates affecting the Sensitivity, Specificity, Positive and Negative Predictive Values, we included the Positive and Negative Likelihood Ratios, which are not influenced by disease prevalence. Table 2 shows that all 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 were a significant number of false negatives on the BREESI, (e.g., 42% of those choosing no BREESI items had chemical intolerance) 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. 3, even in Japan, as the number of BREESI items increase, 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. We do not have an explanation for those results and can only speculate that language translation and/or interpretation of the BREESI items were a barrier for those endorsing no BREESI items but were still classified as very suggestive of CI on the QEESI.

Our prevalence estimates from this study (31.2%, 95% CI = 28–34) for the United States is somewhat higher than other recent estimates, yet within the range of other population-based samples (Caress and Steinemann, 2004; Azuma et al., 2015; Kreutzer et al., 1999). In our clinic-based study we found that 20.4% of primary care patients approached in a clinic had scores “very suggestive” of chemical intolerance (Palmer et al., 2020). Steinemann's 2018 U. S.-based survey found that 12.8% of participants said they had a diagnosis of multiple chemical sensitivity and 25.9% responded “yes” to the question, “Compared to other people, do you consider yourself allergic or unusually sensitive to everyday chemicals like those in household cleaning products, paints, perfumes, detergents, insect spray and things like that?” In Japan, Hojo et al., (2019) used the QEESI with modifications to the scoring criteria and the inclusion of the Life Impact Scale and Masking Index to estimate 6% prevalence of chemical intolerance that met the revised “very suggestive” criteria. Although Italy has several researchers working on CI or multiple chemical sensitivity, we did not find population-based prevalence estimates for Italy in the literature. Also, we found no publications describing chemical intolerance or multiple chemical sensitivity for India or Mexico.

According to the BREESI, intolerances to chemicals, foods, and drugs are highly prevalent across all populations, ranging from a low of 9.2% responding yes to food intolerances in Japan to a high of 71.4% responding yes to chemical intolerances in India. We hope these findings empower healthcare providers across the globe to consider how CI may drive a wide range of chronic and acute health problems. When patients have new-onset (or marked worsening) of chemical, food, and/or drug intolerances, health care providers can use the QEESI to help patients identify and avoid the exposures that trigger symptoms. This may improve a host of common health concerns across multiple organ systems, including problems with mood and concentration.
Two important limitations of this study are our sample size and that we conducted these studies without input from researchers in the countries we studied. We present these findings as pilot work and recognize that future studies with larger samples are warranted. We hope these estimates spark new research and collaborations in all of these countries. Our study adds to the evidence that CI is an important problem for both individuals and different populations. CI should be studied in recurrent national and regional surveys of population health as well as in timely investigations of exposed groups (e.g., disasters, occupational exposures). Epidemiologists may use the BREESI in population studies to minimize response burden and standardize CI measurement across countries, regions, cities, groups, clinical populations, or various exposure groups. We are looking forward to other researchers exploring this topic and these tools.

Conclusion

There is growing international concern over intolerances to chemicals, foods, and drugs. Current population estimates are on average 20%. This study confirms two previous studies showing the BREESI's utility as a screening tool for chemical intolerance, especially for specificity (e.g., identifying true positives). We have shown that the BREESI is an efficient tool for determining potential CI in a range of health care settings and for epidemiological studies in different populations. We encourage the use of this tool as a screener for CI, followed by a more thorough assessment using the QEESI.

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 Internal Review Board (approval number HSC20200718N). Written informed consent was waived due to a completely anonymous volunteer participation.

Consent for publication: N/A

Availability of data and materials: The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Competing interests: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Authors' contributions: RFP, CRJ and CSM in the 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, CMS and CRJ were responsible for substantial revisions of the work.

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**References**

1. Altman DG, Bland JM. (1994). “Diagnostic tests 2: Predictive values”. BMJ. 309 (6947): 102. Doi:10.1136/bmj.309.6947.102. PMC 2540558. PMID 8038641.

2. Azuma et al., (2015). Prevalence and Characteristics of Chemical Intolerance: A Japanese Population-Based Study. Arch Environ Occup Health; 70:341–353.

3. 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.

4. Glen S. “Likelihood Ratio (Medicine): Basic Definition, Interpretation” From StatisticsHowTo.com: Elementary Statistics for the Rest of Us! https://www.statisticshowto.com/likelihood-ratio/. Accessed 7/20/2020.

5. Gupta RS, Warren CM, Smith BM, et al. (2019) Prevalence and Severity of Food Allergies Among US Adults. JAMA Netw Open. 2(1):e185630. doi:10.1001/jamanetworkopen.2018.5630

6. Heston, Thomas F. (2011). Standardizing predictive values in diagnostic imaging research. Journal of Magnetic Resonance Imaging. 33 (2): 505, author reply 506–7. doi:10.1002/jmri.22466. PMID 21274995.

7. 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.

8. 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. International Journal of Hygiene and Environmental Health. 221:8: 1085-1096.

9. Katerndahl DA, Bell IR, Palmer RF, Miller CS. (2012) Chemical intolerance in primary care settings: prevalence, comorbidity, and outcomes. Ann Fam Med. 10(4): 357-365.

10. 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.

11. Jeon BH, Lee SH, & Kim HA. (2012) A validation of the Korean version of QEESI© (The Quick Environmental Exposure and Sensitivity Inventory). Korean J Occup Environ Med. 24(1):96-114.

12. Macy E. Chapter 16 – Multiple Drug Intolerance Syndrome, Editor(s): David A. Khan, Aleena Banerji. Drug Allergy Testing. Elsevier, 2018: 165-168, ISBN 9780323485517, https://doi.org/10.1016/B978-0-323-48551-7.00016-X.
13. Macy E, Ho NJ. (2012) Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. Ann Allergy Asthma Immunol. 108(2):88–93. Doi:10.1016/j.anai.2011.11.006.
14. McGee, S. (2002) Simplifying Likelihood Ratios. J Gen Intern Med. 17(8): 647–650.
15. Miller, CS. (2001) Toxicant-Induced Loss of Tolerance-The QESI®. Townsend Letter for Doctors and Patients. 85-89.
16. Miller CS, Prihoda TJ. (1999a) 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.
17. Miller CS, Prihoda TJ. (1999b) 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.
18. Nordin S and Andersson L. (2010) Evaluation of a Swedish version of the quick environmental exposure and sensitivity inventory. Int. Arch. Occup. Environ. 83(1):95-104.
19. Omer HM, Hodson J, Thomas SK, and Coleman, JJ. (2014). Multiple drug intolerance syndrome: a large-scale retrospective study. Drug Safety,37(12), 1037–1045. Doi:10.1007/s40264-014-0236-x
20. 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.
21. 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 U.S. National Sample. Int. J. Environ. Res. Public Health. 18, 8714.
22. Rael E., Sampath V., Nadeau K.C. (2020) Diagnosis and Differential Diagnosis of Food Allergy. In: Gupta R. (eds) Pediatric Food Allergy. Springer, Cham. https://doi.org/10.1007/978-3-030-33292-1_320.
23. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, Sigurdardottir ST, Lindner T, Goldhahn K, Dahlstrom J, McBride D, Madsen C. The prevalence of food allergy: A meta-analysis. Journal of Allergy and Clinical Immunology. Volume 120, Issue 3, 2007, Pages 638-646, https://doi.org/10.1016/j.jaci.2007.05.026.
24. Sedighi I. (2013) Interpretation of Diagnostic Tests: Likelihood Ratio vs. Predictive Value. Iran J Pediatr. Dec;23(6):717. PMID: 24910762; PMCID: PMC4025141.
25. Skovbjerg S, Berg ND, Elberling J and Christensen KB. (2012) Evaluation of the quick environmental exposure and sensitivity inventory in a Danish population. J Environ Public Health. 2012:304314. Doi: 10.1155/2012/304314. Epub 2012 Jan 12.
26. Steinemann A. (2018) National Prevalence and Effects of Multiple Chemical Sensitivities. Journal of Occupational and Environmental Medicine 60(3):e152-e156
27. SurveyMonkey Audience platform. (2020) SurveyMonkey Inc. San Mateo, California, USA. www.surveymonkey.com

28. SAS Institute Inc. (2014). SAS® 9.4 Statements: Reference, Third Edition. Cary, NC: SAS Institute Inc.

29. Young E, Stoneham MD, Petuckevitch A, Barton J, Rona R. (1994) A population study of food intolerance. The Lancet. 1994:343(8906):1127-1130, https://doi.org/10.1016/S0140-6736(94)90234-8.

30. Zhou XH, NA Obuchowski, DK McClish (2002) Statistical methods in diagnostic medicine. New York: Wiley.

**Figures**
Figure 1

Distribution of QEESI Chemical Intolerance and Symptom Scales by Country *Values with different letters indicate statistical differences at p < .05
Figure 2

Percent of respondents in each country with QEESI scores “very suggestive” of chemical intolerance.

Countries with different letters are significantly different from each other at $p < .05$.
Figure 3

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.