

Prevalence and Characteristics of Chemical Intolerance: A Japanese Population-Based Study

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Received 27 December 2013, Accepted 9 May 2014

Population-based cross-sectional study was performed to estimate the prevalence of chemical intolerance and to examine the characteristics of the sample. A Web-based survey was conducted that included 7,245 adults in Japan. The criteria for chemical intolerance proposed by Skovbjerg yielded a prevalence of 7.5% that was approximately consistent with that reported from a Danish population-based survey. Female gender, older age, and renovation in the house during the past 7 years were positively associated with chemical intolerance. Improvements in the condition were observed with daily ventilation habits. Medical history of atopic dermatitis, allergic rhinitis, food allergy, multiple chemical sensitivity, and depression were associated with chemical intolerance. Fatigue, depressed mood, and somatic symptoms were also positively correlated with chemical intolerance. Better elucidation of the causes, comorbidities, concomitants, and consequences of chemical intolerance has the potential to provide effective solutions for its prevention and treatment.

Keywords: adults, chemical intolerance, chemical sensitivity, characteristics, epidemiology, prevalence, psychosomatic state

Intolerance to odorous and pungent substances, known as chemical intolerance, is a frequently reported problem in industrialized countries. The prevalence of symptoms of chemical intolerance has been estimated to range from 8% to 33% in population-based surveys.^{1–10} Thus, chemical intolerance has become a strong public health concern during the past 2 decades, particularly in industrialized countries.

Chemical intolerance, also referred to as multiple chemical sensitivity (MCS), is a chronic acquired disorder characterized by nonspecific and recurrent symptoms in multiple organ systems associated with exposure to low levels of odorous chemicals (eg, organic solvents, pesticides, cleaning products, perfumes, environmental tobacco smoke, or combustion products).^{11–13} In general, the reported symptoms are reactions to previous chemical exposure that recur on subsequent exposure to the same or structurally unrelated chemicals at levels below those established as having harmful effects in the general population.¹² Phenomenologically, the development of MCS appears to be associated with the loss of toler-

ance following acute or chronic exposure to various environmental agents and the subsequent triggering of symptoms by extremely small quantities of previously tolerated chemicals. Thus, toxicant-induced loss of tolerance has been proposed as an alternative term for chemical sensitivity.¹⁴ Most definitions of MCS are almost entirely qualitative, relying on subjective reports from patients and clinicians of distressing symptoms and environmental exposure. Some authors prefer the term idiopathic environmental intolerance to avoid the confusion of diagnosis and etiology inherent in the term MCS.^{15,16} The symptoms of MCS may be related to specific psychiatric disorders rather than a toxicogenic or somatic source.^{12,17} However, in some cases, the symptoms cannot be explained solely on a psychogenic basis. The results of challenge tests following exposure to odorous chemicals indicated neurocognitive impairment in patients with MCS, and single-photon emission computed tomography brain dysfunction was observed particularly in odor-processing areas, thereby suggesting a neurogenic origin of MCS.¹⁸ Many of the symptoms involve the central nervous system (CNS), although respiratory, skin, and mucosal irritation and gastrointestinal, musculoskeletal, and cardiovascular problems have also been reported.^{12,19} CNS-related symptoms such as headache, fatigue, and cognitive deficit are particularly frequent.^{20,21} An association between asthma and chemical intolerance has been reported in

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several studies,^{1,7-10,22} and an association with hay fever has also been reported.⁸ An increasing body of evidence points to an association between chemical intolerance and symptoms of psychological distress such as depressive symptoms, somatization, negative affect, and anxiety.²³⁻²⁸ These symptoms are likely to add to the level of overall functional disability.

Chemical intolerance is associated with poor quality of life and functional impairment, leading to loss of employment and socioeconomic hardships.^{2,4,8,29} In a Swedish population-based study, 19% of the 1,387 participants were affected by odor intolerance in daily life to an extent that inflicted affective and behavioral consequences.⁷ In a Danish population-based study, 27% of the 4,242 participants reported symptoms related to inhalation of airborne chemicals, and 3.3% of the participants reported adjustments in social life or occupational conditions because of the symptoms.¹ These restraints in social life and occupational conditions are important to the affected individuals, and these individual consequences may also have socioeconomic implications. Thus, population-based studies focusing on the prevalence and characteristics of chemical intolerance are needed to determine the necessary social and individual interventions. To the best of our knowledge, no study has investigated the prevalence of chemical intolerance and the characteristics associated with chemical intolerance in a general population in Japan.

The aim of this study was to estimate the prevalence of chemical intolerance and to examine the demographic characteristics, housing environment, medical history, and impact with regard to psychosomatic states in the general Japanese adult population.

Methods

Study Population and Design

A population-based cross-sectional design was employed in this study. A Web-based survey was conducted targeting adult Japanese subjects randomly selected on the basis of demographic data obtained from a Web panel of a leading Internet-based research institute in Japan (Macromill Research Panel). An increasing number of population-based epidemiological surveys using a Web panel have been reported during the past 10 years, and their reliability has been demonstrated.³⁰⁻³⁴ A total of 1,066,953 members were registered for the Web panel as of 1 February 2012, of whom 980,327 were adults. The research institute developed a highly credible Web panel via thorough quality control and management and planned recruitment, carefully balancing the panel to represent all Internet users nationwide. At the end of 2011, the number of Internet users in Japan had reached 96.1 million. The Internet population penetration rate was 79.1%.³⁵ The research institute has periodically evaluated the demographic characteristics of the Web panel using a lifestyle survey. The institute surveyed members selected from the Web panel by stratified random sampling on the basis of gender, age, and region so that they matched the Japanese demographic data obtained from the Japanese Population Census. The previous survey was conducted in 2006.

According to the lifestyle survey conducted in 2011,³⁶ the results indicated that factors evaluated in that survey, such as marital status, family structure, annual income, property, alcohol intake, lifestyle, consumption habit, interests, distress, anxiety, life consciousness, and personality, excluding knowledge or use of a computer, corresponded fairly well to the results of population survey of the 2010 Population Census of Japan and other population-based surveys by the stratified random sampling, including the 2010 Public Survey on Living for Citizens, the Seikatsu Teiten 2010, and the 2011 White Paper on Life Design.

Data Collection

This Web-based survey was conducted between January 28 and 29, 2012. We prepared 80 clusters for this study, stratified by gender (female and male), age group (20-29, 30-39, 40-49, 50-59, and ≥ 60 years old), and region (Hokkaido, Tohoku, Kanto, Chubu, Kinki, Tyugoku, Shikoku, and Kyusyu), with the goal of allocating 7,000 samples to these clusters for analyses. The climate of Japan greatly varies from north to south. Thus, a stratified random sampling involving different regions was conducted. A total of 24,624 members were selected from the Web panel by stratified random sampling so that these clusters matched the Japanese demographic data obtained from the 2010 Population Census.³⁷

Members of the Web panel received an invitation by e-mail to complete the questionnaire on a Web site. To avoid selection bias, no information on the topic of the questionnaire was provided in the invitation. Identity verification was conducted by using registered e-mail addresses and passwords to avoid unauthorized access to the survey form by a third person. Security measures were implemented to restrict the frequency of video displays of the survey form. Inconsistent or incomplete responses to the questionnaire were controlled by a quality control system provided by the research institute. Responses made in a short time were liable to include irresponsible answers such as a cursory response without reading a question or an inconsistent response between similar questions. The research institute developed a system for removal of responses with an irrationally short response time (Japanese patent number JP4795496, registration date 2011-08-05). Thus, such responses were removed using the system. Members responding to the invitation were provided with a link to the questionnaire and were directed on the Web site to complete and transmit their responses.

Of the 24,624 members who received an invitation, 6,551 responded. Thus, invitations were sent to an additional 2,669 members that were also randomly sampled from the Web panel to ensure adequate numbers in several clusters. Of the 2,669 members, 694 responded. Finally, a total of 7,245 responses (response rate 26.8%, excluding the automatically removed 221 false responses due to the irrationally short response time) were obtained that were completely matched in terms of gender, age, and region for the Japanese demographic data.

Questionnaires

The Web-based self-reported questionnaire included items regarding gender, age, marital status, family structure, employment status, smoking status, drinking habits, environmental variables (type of housing, changes in the house during the past 7 years, ventilation habits, and indoor pets), medical history, chemical intolerance, and psychosomatic state during the past month as the acute stress index. Questions on medical history addressed asthma, hay fever, atopic dermatitis, psoriasis, allergic rhinitis, allergic conjunctivitis, food allergy, sick house syndrome (SHS) (ie, sick building syndrome in housing), MCS, and depression as the typical diseases or symptoms that are strongly associated with chemical intolerance. SHS has been registered in the International Classification of Diseases 10th revision (ICD-10)-based Japanese Standard Disease Code Master for electronic medical record and the disease name code for health insurance claims since 2002. MCS has also been registered since 2009. SHS and MCS were included in the medical history as questions based on medical diagnosis.

To identify the presence and degree of chemical intolerance, several self-reported questionnaires have been developed for research purposes.^{38–41} One questionnaire that appears to be the most widely applied is the Quick Environmental Exposure and Sensitivity Inventory (QEESI).^{10,39,42–45} QEESI is a reliable and valid self-administered questionnaire that was developed to gauge the multisystem symptoms and multiple intolerances often associated with chemical intolerance.^{39,40} Thus, we used QEESI for identifying the chemical intolerance status.

QEESI consists of 5 scales measuring different domains related to chemical intolerance: Symptom Severity (SS), Chemical (inhalant) Intolerances (CiI), Other Intolerances (OI) (eg, allergies, food or alcohol), Life Impact (LI) attributed to chemical intolerances, and ongoing exposure to routinely used products (Masking Index). Four of these scales include 10 items, with responses rated on an 11-point scale ranging from “not at all a problem” (0) to “disabling symptoms” (10). Total scores range from 0 to 100. The fifth scale, the Masking Index, also consists of 10 items, but the response format is dichotomous (0 or 1), resulting in a total score ranging from 0 to 10. The Japanese version of QEESI was used in this study. The Japanese version has been evaluated in terms of validity and reliability, and 3 of the QEESI subscales (SS, CiI, and LI) were determined to be valid.^{42,43}

To evaluate the association with the psychosomatic state, the stress response scale from the Brief Job Stress Questionnaire (BJSQ) was used. This questionnaire was developed and validated by a research group commissioned by the Japanese Ministry of Health, Labour and Welfare.⁴⁶ The stress response scale is composed of 18 general items related to psychological stress response and 11 items related to physical stress response for adults in the general population. Responses to the 29 items related to vigor, irritability, fatigue, anxiety, depressed mood, and somatic symptoms were rated on a 4-point Likert scale ranging from rarely (1) to very often (4). These responses were converted to vigor, irritability, fatigue, anxiety, depressed mood, and somatic symptoms using a score translation

table.⁴⁶ Thus, the stress response scale was used in this study for evaluating the psychosomatic state. Stress response as measured by the BJSQ indicates the risk for the onset of depression⁴⁷ and has been associated with a sense of contribution to society.⁴⁸

Estimation of the Prevalence of Chemical Intolerance

To evaluate the presence and degree of chemical intolerance, combined cutoff scores determined from the scales of some previous researchers were used. Miller and Prihoda reported a sensitivity of 83.2% and a specificity of 84.2% using a cutoff score of ≥ 40 for the CiI scale.³⁹ They analyzed data of 421 subjects with MCS, including 76 controls. Using the combined cutoff scores for the CiI scale (≥ 40), the SS scale (≥ 40), and the OI scale (≥ 25) provided a sensitivity of 67.2% and a specificity of 90.9%.³⁹ In an evaluation of 3 of the QEESI scales in a Japanese population, Hojo et al reported high discriminatory ability for the SS scale with a cutoff score of ≥ 20 , which provided a sensitivity of 84.8% and a specificity of 84.0%.⁴³ They analyzed data of 103 patients with MCS and 309 controls. Sensitivity and specificity for the LI scale were 84.8% and 85.7%, respectively, with a cutoff score of ≥ 10 . Contrary to the findings of Miller and Prihoda,³⁹ the results of Hojo et al⁴³ indicated that the CiI scale had a low sensitivity (73.4%) and specificity (69.6%) using a cutoff score of ≥ 40 . They recommended meeting any 2 of the 3 cutoff scales, although the sensitivity and specificity were not provided in that study.⁴³ Nordin and Andersson reported a good discriminatory power for the SS, CiI, and LI scales.⁴⁵ Skovbjerg et al recently reported that the discriminatory validity was the largest for the CiI and LI scales.¹⁰ They analyzed data of 315 patients with chemical intolerance and 2,000 controls representing the general population drawn from the Danish Civil Registration system. Using combined cutoff scores for the CiI scale (≥ 35) and LI scale (≥ 14) provided a sensitivity of 92.1% and a specificity of 91.8%.¹⁰ To the best of our knowledge, their results indicated the highest sensitivity and specificity in a population-based study using QEESI. These different findings may reflect cross-cultural differences in the responses to QEESI, but differences in study populations in terms of sample size or the selection and definition of cases may more likely be the reason.

The cutoff scores proposed by Miller and Prihoda³⁹ have been widely used in Japan and other countries. However, Hojo et al⁴³ recently proposed different cutoff scores based on a study of Japanese subjects. In addition, Skovbjerg et al¹⁰ recently reported the highest sensitivity and specificity in examination of chemical intolerance using different cutoff scores. For comparing the prevalence of chemical intolerance and to evaluate the validity of those criteria in this study with past studies, we used these 3 criteria (Miller and Prihoda,³⁹ Hojo et al,⁴³ and Skovbjerg et al¹⁰) to estimate the prevalence of chemical intolerance in the Web panel-based population selected for this study. Based on this comparison, the criteria that appeared most appropriate in a comprehensive manner to examine the characteristics of chemical intolerance were applied.

Statistical Analyses

For evaluating a more detailed geographical dispersal of the participants than the 8 regions, Spearman's rank correlation coefficient was calculated between the number of participants and the Japanese adult population³⁷ for each of the 47 prefectures in Japan. The internal consistency of the QEESI scales was evaluated using Cronbach's alpha. The prevalence of a medical history and chemical intolerance was estimated with 95% confidence interval (CI) assumed as a Poisson distribution. Differences between males and females in the prevalence of chemical intolerance and MCS medical history were evaluated using Fisher's exact test. Univariate associations between chemical intolerance status and all variables were examined. Potential variables for association with chemical intolerance with $p < .2$ were then selected for multivariate analysis. Demographic variables (gender, age, employment, and smoking status) and environmental variables were tested in multivariate logistic regression analyses to determine the possible environmental characteristics (Model 1). Further, both Model 1 and medical history were tested in multivariate logistic regression analyses to determine the potential background characteristics (Model 2). The final model was developed by adjusting for both Model 2 and the possible characteristics of the psychosomatic state (Model 3). We used $p < .05$ to indicate significance. Odds ratios (ORs) and 95% CIs were determined for the univariate and multivariate associations. All data analyses were performed using the SPSS statistics software, version 21 (IBM, Armonk, NY, USA).

Ethics

This study was approved by the ethical committee for human research at the Louis Pasteur Centre for Medical Research located in Kyoto (LPC.12). The study was completed in accordance with the Helsinki Declaration.

RESULTS

Participants

The characteristics of the participants are shown in Table 1. The mean age of the participants was 49.6 years (range: 20–88 years; 51.9% females, 48.1% males). The sex ratios completely corresponded with the Japanese adult population³⁷ (51.9% females, 48.1% males). The proportions of the population 20–29, 30–39, 40–49, 50–59, and ≥ 60 years old were 13.0%, 17.2%, 16.0%, 15.7%, and 38.0%, respectively. These proportions corresponded to the Japanese adult population³⁷ (13.2%, 17.4%, 16.1%, 15.6%, and 37.7%, respectively). Spearman's rank correlation coefficient between the number of participants and the Japanese adult population³⁷ for each of the 47 prefectures in Japan was .92 ($p < .001$). The proportion of participants to the Japanese adult population for each of the 47 prefectures averaged 0.0070% (range: 0.0028%–0.0096%). The percentage of unmarried females and males was 28.9% and 34.3%, respectively, in this study and 39.2% and 34.3%, respectively, in the Japanese adult population.³⁷ Loss of cog-

nitive or motor function or memory decline with aging makes it very difficult for elderly people to respond to questionnaires and to participate in a survey. Every questionnaire survey commonly has this limitation. This difference in the percentage of females occurred due to sampling limitations in elderly people over 70 years old. Rates of current smoking for females and males were 11.7% and 27.4% (19.2% in total), respectively, in this study and 9.7% and 32.4% (20.1% in total), respectively, in the National Health and Nutrition Survey, Japan, 2011.⁴⁹ In a cohort of participants aged 20–79 years, Fukutomi et al reported that the prevalence of “ever asthma” confirmed by a doctor and “asthma medication” were 7.4% (95% CI: 7.0%–7.7%) and 2.5% (95% CI: 2.3%–2.7%), respectively, through surveys in 10 municipalities from July 2006 to February 2007.⁵⁰ Our results in a cohort of the same age range indicated that the prevalence of “ever asthma” confirmed by a doctor and “asthma medication” were 10.0% (9.3%–10.7%) and 2.3% (1.9%–2.6%), respectively. This difference in “ever asthma” may likely be due to the survey years and areas in which the survey was conducted.

Prevalence of Chemical Intolerance

The score distributions of the 4 QEESI scales are shown in Figure 1. This figure indicated a good exponential family of distributions with no outliers. Thus, the population-based sampling of this study was appropriate. Cronbach's alpha coefficients on the 4 QEESI scales were .96 for CiI, .85 for OI, .90 for SS, and .86 for LI. Median scores on the 4 QEESI scales were 17 (interquartile range: 4–38) for CiI, 5 (0–13) for OI, 14 (5–29) for SS, and 2 (0–7) for LI. Cronbach's alpha coefficients were high (range: .85–.96) in all scales.

Table 2 shows the prevalence of chemical intolerance estimated from the 3 criteria recommended for evaluating chemical intolerance and prevalence of MCS in relation to gender. The prevalence of chemical intolerance as defined by Miller and Prihoda,³⁹ Hojo et al,⁴³ and Skovbjerg et al¹⁰ was 4.4%, 24.1%, and 7.5%, respectively. Compared with the prevalence according to the definitions of Miller and Prihoda³⁹ and Skovbjerg et al,¹⁰ the prevalence estimated according to Hojo et al⁴³ was several fold higher. Statistically significant differences in the prevalence of chemical intolerance were observed between males and females. The prevalence of “ever MCS” confirmed by a doctor and “under treatment for MCS” was 1.02% and 0.15%, respectively. The prevalence of “under treatment for MCS” was not statistically different between males and females.

The proportions of respondents indicating “ever MCS” confirmed by a doctor among the participants who met the criteria for chemical intolerance as defined by Miller and Prihoda,³⁹ Hojo et al,⁴³ and Skovbjerg et al¹⁰ were 21.6%, 62.2%, and 37.8%, respectively. The proportions of respondents indicating “under treatment for MCS” among the participants who met the criteria for chemical intolerance as defined by Miller and Prihoda,³⁹ Hojo et al,⁴³ and Skovbjerg et al¹⁰ were 18.2%, 81.8%, and 45.5%, respectively. Although the criteria for chemical intolerance as defined by Hojo et al⁴³ identified both patients with MCS and those under treatment for

Table 1. Characteristics of the Participants

Characteristic		Total		Females		Males	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
No. of participants		7,245		3,763		3,482	
Age group (%)							
20–29		939	13.0	462	12.3	477	13.7
30–39		1,249	17.2	616	16.4	633	18.2
40–49		1,162	16.0	576	15.3	586	16.8
50–59		1,139	15.7	572	15.2	567	16.3
≥60		2,756	38.0	1,537	40.8	1,219	35.0
Marital status (%)							
Married		4,963	68.5	2,675	71.1	2,288	65.7
Unmarried		2,282	31.5	1,088	28.9	1,194	34.3
Having a child (%)							
Yes		4,667	64.4	2,621	69.7	2,046	58.8
No		2,578	35.6	1,142	30.3	1,436	41.2
Employment (%)							
Employed		2,349	32.4	582	15.5	1,767	50.7
Self-employed		669	9.2	194	5.2	475	13.6
Housewife/househusband		1,828	25.2	1,822	48.4	6	0.2
Part-time employed		897	12.4	705	18.7	192	5.5
Student		249	3.4	90	2.4	159	4.6
Unemployed		595	8.2	174	4.6	421	12.1
Others		658	9.1	196	5.2	462	13.3
Smoking status (%)							
Never		4,662	64.3	2,477	65.8	2,185	62.8
Passive		1,190	16.4	847	22.5	343	9.9
Current		1,393	19.2	439	11.7	954	27.4
Drinking habits (%)							
Once or more a week		3,656	50.5	1,497	39.8	2,159	62.0
Less than once a week or never		3,589	49.5	2,266	60.2	1,323	38.0
Type of housing							
Owned detached house		4,086	56.4	2,126	56.5	1,960	56.3
Rented detached house		233	3.2	110	2.9	123	3.5
Condominium apartment		1,083	14.9	612	16.3	471	13.5
Rental apartment		1,711	23.6	854	22.7	857	24.6
Others		132	1.8	61	1.6	71	2.0
Changes in the house during the past 7 years							
Extension or reconstruction of the house		316	4.4	163	4.3	153	4.4
Conversion or renovation of a room		2,030	28.0	1,105	29.4	925	26.6
New furniture, bed or carpeting in a room		2,798	38.6	1,591	42.3	1,207	34.7
Ventilation, opening a window in a room							
Rarely		316	4.4	94	2.5	222	6.4
Sometimes, seasonal		927	12.8	433	11.5	494	14.2
Sometimes, not seasonal		1,525	21.0	731	19.4	794	22.8
Almost everyday		4,477	61.8	2,505	66.6	1,972	56.6
Indoor pets (with)		1,930	26.6	1,069	28.4	861	24.7
Psychosomatic state							
Vigor	Less	1,259	17.4	584	15.5	675	19.4
	Somewhat less	827	11.4	438(11.6)	11.6	389	11.2
	Medium	2,835	39.1	1,462	38.9	1,373	39.4
	Somewhat more	1,548	21.4	837	22.2	711	20.4
	More	776	10.7	442	11.7	334	9.6

(Continued on next page)

Table 1. Characteristics of the Participants (*Continued*)

Characteristic		Total		Females		Males	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Irritability	Low	1,066	14.7	546	14.5	520	14.9
	Somewhat low	1,398	19.3	740	19.7	658	18.9
	Medium	3,113	43.0	1,713	45.5	1,400	40.2
	Somewhat high	1,326	18.3	609	16.2	717	20.6
	High	342	4.7	155	4.1	187	5.4
Fatigue	Low	1,438	19.8	694	18.4	744	21.4
	Somewhat low	1,706	23.5	1,178	31.3	528	15.2
	Medium	2,752	38.0	1,279	34.0	1,473	42.3
	Somewhat high	1,063	14.7	486	12.9	577	16.6
	High	286	3.9	126	3.3	160	4.6
Anxiety	Low	1,642	22.7	897	23.8	745	21.4
	Somewhat low	1,242	17.1	658	17.5	584	16.8
	Medium	3,234	44.6	1,636	43.5	1,598	45.9
	Somewhat high	870	12.0	477	12.7	393	11.3
	High	257	3.5	95	2.5	162	4.7
Depressed mood	Low	1,769	24.4	882	23.4	887	25.5
	Somewhat low	1,304	18.0	712	18.9	592	17.0
	Medium	2,553	35.2	1,321	35.1	1,232	35.4
	Somewhat high	1,009	13.9	561	14.9	448	12.9
	High	610	8.4	287	7.6	323	9.3
Somatic symptoms	Low	832	11.5	572	15.2	260	7.5
	Somewhat low	2,319	32.0	1,173	31.2	1,146	32.9
	Medium	2,669	36.8	1,354	36.0	1,315	37.8
	Somewhat high	1,015	14.0	500	13.3	515	14.8
	High	410	5.7	164	4.4	246	7.1

MCS at the highest level, the prevalence estimated using the criteria of Hojo et al⁴³ was several fold higher than those estimated using the criteria of Miller and Prihoda³⁹ and Skovbjerg et al.¹⁰ Thus, the respondents who should not be identified with chemical intolerance were more likely to be identified by the criteria of Hojo et al.⁴³ In addition, compared with the findings based on the criteria for chemical intolerance defined by Skovbjerg et al.,¹⁰ the findings based on the crite-

ria defined by Miller and Prihoda³⁹ and Hojo et al⁴³ had a low sensitivity and specificity. Hojo et al tried to obtain higher sensitivity and specificity for Japanese subjects. However, their results were of low sensitivity and specificity especially in CiI scale, because the score distributions of the QEESI scales in MCS patients varied widely in their study.⁴³ Applying the criteria of Hojo et al⁴³ may result in the overestimation of the prevalence of chemical intolerance as mentioned above. The

Table 2. Prevalence of Chemical Intolerance and MCS in Relation to Gender Among All the Participants

Chemical intolerance/MCS	Total (<i>n</i> = 7,245)		Females (<i>n</i> = 3,763)		Males (<i>n</i> = 3,482)	
	Prevalence	95% CI	Prevalence	95% CI	Prevalence	95% CI
Chemical intolerance ^a						
Miller and Prihoda ^{b,***}	4.4	3.9–4.8	5.5	4.8–6.3	3.1	2.6–3.7
Hojo et al ^{c,***}	24.1	23.1–25.1	29.0	27.5–30.4	18.8	17.5–20.1
Skovbjerg et al ^{d,***}	7.5	6.8–8.1	9.6	8.7–10.6	5.1	4.4–5.8
MCS						
Ever confirmed by a doctor ^{***}	1.02	0.79–1.25	1.44	1.06–1.82	0.57	0.32–0.83
Under treatment	0.15	0.06–0.24	0.16	0.03–0.29	0.14	0.02–0.27

Note. MCS = multiple chemical sensitivity.

^aCriteria.

^bMeeting all cutoff scales of CiI (≥ 40), SS (≥ 40), and OI (≥ 25).

^cMeeting any 2 of the 3 cutoff scales of CiI (≥ 40), SS (≥ 20), and LI (≥ 10).

^dMeeting all cutoff scales of CiI (≥ 35) and LI (≥ 14).

***Significant difference between males and females at $p < .001$ by Fisher's exact test.

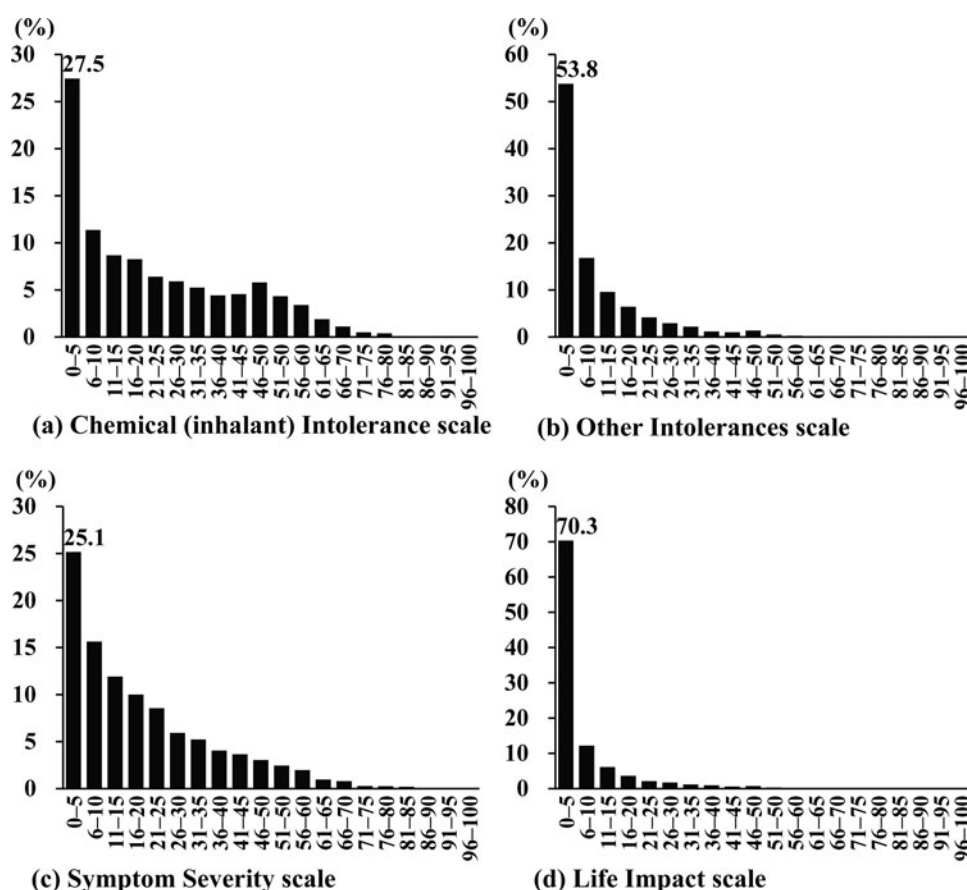


Fig. 1. Frequency distributions of the total points of 4 subscales in the QEESI.

definition of MCS patients using the criteria of Skovbjerg et al¹⁰ provided the highest sensitivity (92.1%) and specificity (91.8%) using combined cutoff scores for the CiI scale (≥ 35) and LI scale (≥ 14) through a population-based study. Based on these results, we used the criteria for chemical intolerance defined by Skovbjerg et al¹⁰ for examining the characteristics of chemical intolerance, as discussed in the following section.

Characteristics of Chemical Intolerance

Univariate associations between chemical intolerance using the criteria of Skovbjerg et al¹⁰ and all demographic variables and other categories of variable factors are listed in Table 3. The results of the multivariate regression analysis for the association with chemical intolerance using these criteria are shown in Table 4. Conversion or renovation of a room during the past 7 years was the only environmental variable significantly related to chemical intolerance in all models. Extension or reconstruction of the house during the past 7 years showed significant association with chemical intolerance only in Model 1. A significant association was found between increased frequency of ventilation and reduced chemical intolerance in Models 1 and 2 (Table 4). In univariate analyses, presence of indoor pets was a significant factor of chemi-

cal intolerance (Table 3), but after adjusting for demographic variables, the association with indoor pets was no longer significant.

The chemical intolerance was significantly increased in females compared with males in all models (Table 4). Older age significantly increased the possibility of reported chemical intolerance (Table 4, Models 2 and 3). A significant association was also found between current smoking and reduced chemical intolerance in the final model. In univariate analyses, all variables of medical history showed significant association with chemical intolerance. However, after adjusting for demographic and environmental variables, atopic dermatitis, allergic rhinitis, food allergy, and MCS remained significantly correlated with chemical intolerance in Models 2 and 3. A significant association was also found with depression in Model 2. However, no significant relationship was identified between chemical intolerance and asthma, hay fever, psoriasis, allergic conjunctivitis, or SHS (Table 4). In univariate analyses, irritability, fatigue, anxiety, depressed mood, and somatic symptoms were positively correlated with chemical intolerance status, and a negative correlation was found for vigor. After adjusting for other variables, vigor, fatigue, depressed mood, and somatic symptoms remained significantly correlated with chemical intolerance status. However, the relationships for irritability and anxiety did not persist after adjusting for other variables (Table 4, Model 3).

Table 3. Univariate Analysis for the Association With Chemical Intolerance Status

Variable	Crude OR	95% CI
<i>Demographic variables</i>		
Gender (female)	1.98***	1.64–2.38
Age		
20–29	Ref.	
30–39	1.43*	1.00–2.04
40–49	1.46*	1.02–2.09
50–59	1.69**	1.19–2.41
≥60	1.47*	1.07–2.02
<i>p</i> for trend	.068	
Marital status (married)	0.93	0.77–1.12
Having a child (yes)	0.96	0.80–1.15
Employment		
Employed	Ref.	
Self-employed	1.04	0.72–1.49
Housewife/househusband	1.68***	1.33–2.12
Part-time employed	1.57**	1.18–2.10
Student	0.47	0.22–1.02
Unemployed	1.56**	1.12–2.17
Others	1.48*	1.07–2.06
Smoking status		
Never	Ref.	
Passive	1.22	0.98–1.53
Current	0.75*	0.58–0.96
<i>p</i> for trend	.005	
Drinking habits (once or more a week)	0.92	0.77–1.10
<i>Medical history</i>		
Asthma	1.77***	1.39–2.27
Hay fever	1.65***	1.36–1.98
Atopic dermatitis	2.07***	1.62–2.64
Psoriasis	2.32***	1.55–3.48
Allergic rhinitis	1.99***	1.64–2.40
Allergic conjunctivitis	2.35***	1.82–3.02
Food allergy	3.20***	2.30–4.46
Sick house syndrome	5.50***	3.27–9.24
Multiple chemical sensitivity	7.92***	4.91–12.77
Depression	2.87***	2.17–3.78
<i>Environmental</i>		
Type of housing		
Owned detached house	Ref.	
Rented detached house	1.12	0.70–1.79
Condominium apartment	0.80	0.61–1.04
Rental apartment	0.91	0.74–1.13
Others	1.30	0.72–2.33
Changes in the house during the past 7 years		
Extension or reconstruction of the house	1.69**	1.19–2.42
Conversion or renovation of a room	1.37***	1.14–1.65
New furniture, bed or carpeting in a room	1.08	0.91–1.29
Ventilation, opening a window in a room		
Rarely	Ref.	
Sometimes, seasonal	1.00	0.64–1.56
Sometimes, not seasonal	0.86	0.56–1.33
Almost everyday	0.77	0.51–1.16
<i>p</i> for trend	.158	
Indoor pets (with)	1.26*	1.04–1.52

(Continued on next page)

Table 3. Univariate Analysis for the Association With Chemical Intolerance Status (*Continued*)

Variable	Crude OR	95% CI
<i>Psychosomatic state^a</i>		
Vigor ^b	0.74***	0.69–0.80
Irritability ^c	1.45***	1.33–1.58
Fatigue ^c	1.78***	1.63–1.93
Anxiety ^c	1.76***	1.62–1.92
Depressed mood ^c	1.74***	1.62–1.88
Somatic symptoms ^c	2.17***	1.99–2.37

Values are expressed as crude odds ratios and 95% CIs for 7,245 participants with complete data. Ref. = referent. Text in parentheses reflects case groups.

^aORs and 95% CIs for 5-level linear variables were calculated using 1 unit of change.

^bThe 5 levels were 1 = less, 2 = somewhat less, 3 = medium, 4 = somewhat more, and 5 = more.

^cThe 5 levels were 1 = low, 2 = somewhat low, 3 = medium, 4 = somewhat high, and 5 = high.

Significant at * $p < .05$, ** $p < .01$, and *** $p < .001$.

COMMENT

Symptoms of chemical intolerance have been prevalent, with estimates ranging from 8% to 33% in population-based surveys.^{1–10} However, population-based studies on chemical intolerance have yielded considerably different estimates of the prevalence of affected individuals depending on the applied definition. In this study, the prevalence of chemical intolerance as defined by Miller and Prihoda³⁹ Skovbjerg et al¹⁰ using QEESI was 4.4% and 7.5%, respectively. In addition, the prevalence of “ever MCS” confirmed by a doctor was 1.02%. Uchiyama and Murayama conducted a Japanese population-based cross-sectional survey on chemical intolerance using QEESI in July 2000.⁵¹ They interviewed 4,000 adults and estimated that the prevalence of chemical intolerance as defined by Miller and Prihoda³⁹ was 0.74% in a cohort of 2,582 responders, and the prevalence of “ever MCS” confirmed by a doctor was 0.81%.⁵¹ Although comparison of these results with those in this study is not appropriate because of differences in the investigative methods, the results of this study suggest that the prevalence of chemical intolerance is still high in the Japanese adult population after a gap of 11.5 years.

Skovbjerg et al estimated a prevalence of chemical intolerance of 8.2% in a random sample of 2,000 individuals (18–69 years old) representing the general population from the Danish Civil Registration System in January 2010.¹⁰ Compared with the prevalence estimated in that study, the prevalence of 7.5% in this study was slightly lower, but the difference in prevalence between the 2 studies was not significant. These results suggest that chemical intolerance is a widespread problem in society and a major threat to public health. These results also lend credence to chemical intolerance as a worldwide issue, at least in developed countries.

Over the past half-century, there have been major changes in building materials and consumer products used indoors. The personal habits of people, including the proportion of those who smoke indoors, have also changed. These changes have altered the types and concentrations of chemicals that people are exposed to in their homes, workplaces, and schools.⁵² People in some countries make great use of perfumes or fragrances, whereas in other countries these are not significant lifestyle factors. In addition, chemicals that are banned

in several countries, such as some pesticides or toxic chemicals, are still used in some other countries. The opportunities for exposure to hazardous chemicals that may induce chemical intolerance vary in different countries because of their different cultures, industries, or regulations, and also vary in accordance with the changes in each decade. Hence, the cross-sectional and longitudinal investigation of the prevalence of chemical intolerance in each country or at a community level and the development of social, technical, medical, or political interventions for improving chemical intolerance will be needed.

In the present study, the prevalence of chemical intolerance was significantly higher in females than in males. This effect of gender on chemical intolerance has been found repeatedly in population-based studies.^{1,2,4–9,26} Perfume, aftershave, deodorant, motor vehicle exhaust fumes, and cleaning agents have been reported as agents with a high prevalence of exposure that are related to the development of symptoms. In particular, females show more symptoms with respect to exposure to these agents.¹ In the present study, after adjusting for demographic and environmental variables, medical history, and the psychosomatic state in multivariate analyses, the chemical intolerance was significantly increased in females compared with males. This characteristic of gender on chemical intolerance was demonstrated in multivariate analyses adjusted for the related variables. Therefore, the characteristic appears to be a common trend.

Older age was significantly associated with reported chemical intolerance. Age is one of the most frequently studied demographic factors in relation to chemical intolerance; however, outcomes have been inconsistent. Similar findings to our results have been previously reported,⁴ but an increased chemical intolerance related to age has not been reported.^{7,8} In contrast to our findings, less chemical intolerance was identified in individuals over 60 years of age in other reports.^{1,5,9} This inconsistency is due, in part, to differences in definitions and scaling of chemical intolerance, study populations, and study designs. Standardized protocols must be developed for use in future studies to examine the characteristics of chemical intolerance, including age. A previous study reported no increased risk of chemical intolerance related to current smoking.⁷ A significant association between current smoking and decreased

Table 4. Multivariate Regression Analysis for the Association With Chemical Intolerance Status

Variable	Model 1		Model 2		Model 3	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
<i>Demographic variables</i>						
Gender (female)	2.08***	1.65–2.61	1.96***	1.62–2.37	2.00***	1.56–2.56
Age						
20–29	—		Ref.		Ref.	
30–39			1.65**	1.15–2.37	1.61*	1.09–2.39
40–49			1.66**	1.14–2.40	1.63*	1.09–2.44
50–59			1.95***	1.36–2.81	2.31***	1.55–3.45
≥60			1.74**	1.25–2.43	2.34***	1.60–3.43
<i>p</i> for trend			.008		<.001	
Employment						
Employed	Ref.		—		Ref.	
Self-employed	0.97	0.67–1.40			0.95	0.64–1.40
Housewife/househusband	1.04	0.79–1.37			1.29	0.95–1.76
Part-time employed	1.10	0.81–1.50			1.19	0.85–1.65
Student	0.43*	0.20–0.92			0.55	0.24–1.26
Unemployed	1.47*	1.05–2.05			1.59*	1.10–2.29
Others	1.38	0.99–1.92			1.42	0.98–2.04
Smoking status						
Never	—		—		Ref.	
Passive					1.06	0.83–1.34
Current					0.68**	0.52–0.90
<i>p</i> for trend					0.014	
<i>Medical history</i>						
Atopic dermatitis	—		1.43*	1.08–1.90	1.41*	1.05–1.88
Allergic rhinitis	—		1.63***	1.32–2.01	1.30*	1.05–1.62
Food allergy	—		1.70**	1.16–2.49	1.71**	1.15–2.53
Multiple chemical sensitivity	—		3.91***	2.29–6.67	3.94***	2.26–6.86
Depression	—		2.45***	1.81–3.30	1.37	0.99–1.90
<i>Environmental</i>						
Changes in the house during the past 7 years						
Extension or reconstruction of the house	1.48*	1.03–2.15	—		—	
Conversion or renovation of a room	1.26*	1.04–1.53	1.30	1.07–1.58**	1.34**	1.09–1.64
Ventilation, opening a window in a room						
Rarely	Ref.		Ref.		—	
Sometimes, seasonal	0.86	0.54–1.35	0.93	0.58–1.48		
Sometimes, not seasonal	0.75	0.48–1.16	0.79	0.50–1.23		
Almost everyday	0.63*	0.41–0.94	0.63*	0.41–0.96		
<i>p</i> for trend	.018		.005			
<i>Psychosomatic state^a</i>						
Vigor ^b	—		—		0.90*	0.82–0.98
Fatigue ^c	—		—		1.31***	1.16–1.47
Depressed mood ^c	—		—		1.23***	1.10–1.37
Somatic symptoms ^c	—		—		1.72***	1.54–1.93

Values are expressed as adjusted odds ratios and 95% CIs for 7,245 participants with complete data. Ref. = referent. Text in parentheses reflects case groups. Model 1: demographic variables (gender, age, employment, and smoking status) and environmental variables (changes in the house during the past 7 years, ventilation in a room, and indoor pets); Model 2: Model 1 + medical history; Model 3: Model 2 + psychosomatic state.

^aORs and 95% CIs for 5-level linear variables were calculated using 1 unit of change.

^bThe 5 levels were 1 = less, 2 = somewhat less, 3 = medium, 4 = somewhat more, and 5 = more.

^cThe 5 levels were 1 = low, 2 = somewhat low, 3 = medium, 4 = somewhat high, and 5 = high.

Significant at **p* < .05, ***p* < .01, ****p* < .001.

chemical intolerance was observed in the final model of multivariate analyses adjusted for the related variables in this study. The results only indicate the current status of the characteristics of chemical intolerance because this was a cross-sectional study, and the investigation of risk factors potentially linked to chemical intolerance was appreciably limited. This association indicates that people with chemical intolerance have lower smoking rates.

Conversion or renovation of a room during the past 7 years was positively and significantly associated with chemical intolerance in this study. Extension or reconstruction of the house during the past 7 years was also positively associated. In a population-based epidemiological study in the Atlanta, Georgia, metropolitan area, pesticides and solvents were reported as triggers of chemical intolerance.² Various chemicals present indoors were found to be significantly related to irritative and general symptoms in epidemiological studies conducted in 1998–2004 in Japan.⁵³ Despite the past administrative and voluntary actions in Japan,⁵⁴ prevention of health effects in residents after renovation or home improvement still remains a challenge. Further research and more effective actions are therefore needed. The results of the present study indicate that increasing the frequency of ventilation is one voluntary action that residents can take to reduce chemical intolerance. This ventilation effect was also observed in the above-mentioned study.⁵³

Depression was positively associated with chemical intolerance status in this study. Comorbid anxiety and depression have been identified as significant synergistic contributors to physical and cognitive symptoms in subjects with chemical intolerance.²³ An association between asthma and chemical intolerance has been reported in several studies.^{1,7–10,22} An association with hay fever has also been reported.⁸ In the present study, atopic dermatitis, allergic rhinitis, food allergy, and MCS were positively and significantly associated with chemical intolerance, but the association with asthma, hay fever, psoriasis, and allergic conjunctivitis was not significant after adjusting for demographic and environmental variables. This inconsistency is likely to be due to different definitions and scaling of chemical intolerance and different analytical models.

Previous studies focused on asthma or/and hay fever. When demographic variables, environmental variables, and asthma were included in a multivariate regression model (Model 1 and asthma), a positive and significant association was found between asthma and chemical intolerance (OR: 1.78, 95% CI: 1.39–2.28). Asthma and hay fever were positively associated with chemical intolerance when this relationship was tested with variables of the Model 1, asthma and hay fever (OR: 1.63, 95% CI: 1.26–2.09 and OR: 1.56, 95% CI: 1.28–1.89, respectively). However, when this relationship was tested with the variables of Model 1 and all variables of medical history (Model 2), the relationship with asthma or hay fever was no longer significant. Multicollinearity levels between asthma and other variables including past disorders were not a cause of concern (highest correlation coefficient: .23 for allergic rhinitis). Thus, the results indicated that the relationships of chemical intolerance with atopic dermatitis, allergic rhinitis, and food allergy were stronger than those with asthma or hay

fever. However, further evidence regarding these relationships will be needed.

Fatigue, depressed mood, and somatic symptoms were positively correlated with chemical intolerance status, and vigor showed a negative correlation. These symptoms are likely to add to the level of overall functional disability. Many clinicians regard chemical intolerance as having a psychiatric component. Several cross-sectional studies have demonstrated psychiatric comorbidities among patients with chemical intolerance, including somatization, anxiety, panic disorder, phobic disorder, and depression.^{19,23–25} It has been suggested that a current psychiatric illness may be a reaction to chemical intolerance rather than an explanation for the disorder.^{23,55,56} A 2-phase follow-up population-based study of chemical intolerance suggested that physical problems emerge first and emotional stress develops only afterward. Thus, chemical intolerance could be so disruptive that it induces substantial mental stress as individuals attempt to cope with the limitations it creates.² Hence, mental and psychosocial support for reducing and controlling comorbid psychological distress is also important for ensuring good quality of life in people with chemical intolerance.

Data collection using a Web-based survey methodology has several advantages. A Web-based research panel is an existing panel that readily provides a substantial amount of information on factors such as gender, age, residential area at the prefectural level, marital status, family status, and employment. Participants can be re-questioned if additional longitudinal follow-up is necessary. In this study, information was obtained from a diverse sample, representative of the Japanese population. The data collection occurred rapidly. In addition, access to this population also enabled evaluation of the prevalence of chemical intolerance within various demographic and socioeconomic groups. However, one limitation of this Web-enabled methodology, as with other survey techniques, is the potential bias that exists if some individuals do not participate in the Web panel because of concerns regarding the technology or other private reasons. However, the conclusions drawn from this study may be unaffected by this limitation because the demographic characteristics between the study participants and other population-based statistical data were evaluated using traditional measures. In addition, the demographic characteristics of the participants were confirmed to be similar to those of the Japanese population. However, the potential for bias may be increased in a population-based survey in a small area because the size of the Web panel is limited. Finally, because this was a cross-sectional study and the investigation of risk factors potentially linked to chemical intolerance was appreciably limited, the results only indicate the current status of the limited characteristics of chemical intolerance, and it is impossible to ascertain whether these characteristics are causes of chemical intolerance.

In conclusion, the results of our study are generally consistent with those of a Danish population-based survey on the prevalence of chemical intolerance and suggest several characteristics associated with chemical intolerance. Better elucidation of the causes, comorbidities, concomitants, and consequences of chemical intolerance at the national or

community level has the potential to improve our understanding of chemical intolerance and provide effective solutions for its treatment, thereby reducing concerns regarding its effect on public health.

Funding

This study was financially supported by a Grant-in-Aid for Health and Labour Sciences Research Grant (H23-health/crisis-010) provided by the Japanese Ministry of Health, Labour and Welfare.

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