BMJ Open

Methods for estimating causal relationships of adverse events with dietary supplements

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-009038
Article Type:	Research
Date Submitted by the Author:	10-Jun-2015
Complete List of Authors:	Ide, Kazuki; University of Shizuoka, Drug Evaluation & Informatics Yamada, Hiroshi; University of Shizuoka, Drug Evaluation & Informatics Kitagawa, Mamoru; University of Shizuoka, Drug Evaluation & Informatics Kawasaki, Yohei; University of Shizuoka, Drug Evaluation & Informatics Buno, Yuma; University of Shizuoka, Drug Evaluation & Informatics Matsushita, Kumi; Kikugawa General Hospital, Pharmacy Kaji, Masayuki; Shizuoka City Public Health Center, Fujimoto, Kazuko; Keio University, Pharmacy Waki, Masako; Shizuoka City Shizuoka Hospital, Nakashima, Mitusyoshi; Hamamatsu Institute of Clinical Pharmacology & Therapeutics, Umegaki, Keizo; National Institutes of Biomedical Innovation, Health and Nutrition,
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Evidence based practice, Public health, Pharmacology and therapeutics
Keywords:	CLINICAL PHARMACOLOGY, NUTRITION & DIETETICS, STATISTICS & RESEARCH METHODS

Article for BMJ Open

***Word counts**: 2065 **Number of Figures & Tables**: 5*

Title:

Methods for estimating causal relationships of adverse events with dietary supplements

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Key words: health food, adverse event, causal relationships, probability, reliability

ABSTRACT

Objective: Dietary supplement use has increased over past decades, resulting in reports of adverse events that could lead to severe disability or death. The aim of this study is to develop optimized methods for evaluating the causal relationships of adverse events with dietary supplements.

Design: Causal relationship assessment using prospectively collected data.

Setting & Participants: Four dietary supplement experts, 4 pharmacists, and 11 registered dietitians (5 men, and 14 women) examined 200 case reports of suspected adverse events.

Primary outcome measures: The distribution of evaluation results was analyzed and inter-rater (multi-rater) reliability among assessors ratings for the two modified methods were evaluated based on intraclass correlation coefficients and Fleiss' kappa.

Results: Most of the 200 case reports were categorized as "lack of information" or "possible" adverse effects based on these two methods. Inter-rater (multi-rater) reliability among entire assessors ratings for the two modified methods, based on intraclass correlation coefficients (ICC) and Fleiss' kappa, were classified as more than substantial (Modified Naranjo scale: ICC [95%CI], 0.873 [0.850, 0.895]; Fleiss' kappa [95%CI], 0.615 [0.615, 0.615]. Modified FDA algorithm: Fleiss' kappa [95%CI], 0.622

[0.622, 0.622]).

Conclusions: The methods we present may help assess the causal relationships between adverse events and dietary supplements. By conducting additional studies of these methods in different populations, researchers can expand the possibilities for the application of our methods.

STRENGHTS AND LIMITATIONS OF THIS STUDY

- There is no optimized method for evaluating these adverse events
- We developed two methods for assessing the causality of adverse events associated with dietary supplements and Inter-rater reliability among entire assessors were classified as more than substantial
- Our methods may be useful for assessing the adverse events with dietary supplements in clinical settings
- This simple and easy method for evaluating causal relationships can contribute to prompt issue evaluation, signal detection, and regulatory updating
- Additional studies with different populations are needed to expand the possibilities for application of our methods

INTRODUCTION

The entire functional food market is estimated to be worth over an $80 billion.[1] Its market reached $32.5 billion in the United States in 2012,[2] with more than half of adults reporting use of one or more dietary supplements. Sales of dietary supplements have also increased in Japan, with an estimated market size second only to the U.S.A.[1] In fact, one study indicated that over 50% of the Japanese population consumes dietary supplements.[3] With the increased use of dietary supplements, a number of adverse events have been reported.[4-8] Some of these adverse events can lead to severe disability or death, so managing risk and safety is essential for protecting consumers.

Evaluating the causality of adverse events is essential in determining the risk and safety of supplements. It can also help with issue evaluation, signal detection, and regulatory updating. Several methods exist for evaluating causality, including the Naranjo scale,[9, 10] the FDA algorithm,[11-13] the Kramer scale,[10, 14] the Liverpool scale,[15] and the WHO scale.[16] However, these methods are used primarily to assess adverse events associated with medications. They are not optimized for use on dietary supplements. The information available from consumers taking dietary supplements differs from information provided by patients taking medications.

Therefore, developing and optimizing methods for evaluating the causal relationship between adverse events and dietary supplements is essential for improving the quality of risk management.

In the present study, we easily modified the Naranjo scale and the FDA algorithm, then used them to assess 200 case reports of suspected adverse reactions to dietary supplements.

METHODS

Study design

The Naranjo[9, 10] scale and the FDA algorithm[11-13] were modified for use on dietary supplements. Two hundred case reports were randomly extracted from a database of adverse event reports associated with dietary supplements. Nineteen assessors (4 dietary supplement experts, 4 pharmacists, and 11 registered dietitians; 5 men and 14 women) evaluated the case reports by alternately using the modified Naranjo scale and the modified FDA algorithm. The characteristics of the 19 assessors are shown in **Table 1**. Three dietary supplement experts worked at a general hospital and one worked at a university as a full professor. All of four pharmacists worked at a general hospital. Among registered dietitians, four

assessors worked at a general hospital, and seven assessors worked at a city health care center.

Table 1. Assessor characteristics

	Dietary supplement expert	Pharmacist	Registered dietitian
Number, n	4	4	11
Age, mean ± SD	65.8 ± 11.5	37.8 ± 7.8	42.2 ± 12.4
Sex, n (%)			
Men	1 (25)	3 (75)	1 (9)
Women	3 (75)	1 (25)	10 (91)
Career length yrs, mean±SD	33.5 ± 2.4	8.6 ± 13.8	13.9 ± 17.4

SD, standard deviation; yrs, years

Assessment scale design

Modified Naranjo scale

The modified Naranjo scale is shown in **Figure 1**. The phrase "drug" in the Naranjo scale was changed to "dietary supplement." The section in question 3 of the Naranjo scale pertaining to a specific antagonist was deleted. Because these are dietary supplements, questions regarding placebo and blood (or other fluid) concentration were excluded. In addition to these changes, the scoring for questions pertaining to re-administration and confirmation by objective

evidence was changed by adding 1 point for positive answers to the original version of the Naranjo scale. The adverse event reports were assigned to a probability category from the total scores as follows: ≥ 9 highly probable, 5–8 probable, 3–4 highly possible, 1–2 possible, ≤ 0 unlikely. Case reports missing information about time relationships were excluded and categorized as "lack of information."

Modified FDA algorithm

Details of the FDA algorithm were previously described.[13] The modified FDA algorithm is shown in **Figure 2**. There was limited information included in case reports of dietary supplements, so the number of options for questions was changed from 2 to 3: "Yes," "No," and "Don't know." The scale was structured with 4 primary questions and 5 branch questions. Contents of main questions are as follows: (1) the temporal relationship, (2) changes in symptoms due to the adverse event being discontinued, (3) rechallenges, (4) objective evidence from laboratory tests such as a drug-induced lymphocyte stimulation test or patch test. Each of these questions has branch questions. Contents of branch questions are as follows: (1) existing clinical conditions, (2) objective evidence from laboratory tests such as a drug-induced lymphocyte

stimulation test or patch test, (3) previous adverse events experiences after taking the same or similar (e.g. including the same ingredients) dietary supplements. Adverse event reports were assigned to one of the following probability categories based on the answers to those questions: lack of information, unlikely, possible, highly possible, probable, and highly probable.

Statistical analysis

In order to quantify the level of agreement in the modified Naranjo scale, intraclass correlation coefficients with a 95% confidence interval were calculated using the methods described by Shrout and Fleiss.[17] Intraclass correlation coefficients were interpreted according to the following criteria: < 0.40, poor agreement; 0.40–0.75, moderate agreement; > 0.75, excellent agreement.[18]

Inter-rater (multi-rater) reliability for the modified Naranjo scale and the modified FDA algorithm was analyzed using Fleiss' kappa with a standard error.[19] Fleiss' kappa values for each question of the modified Naranjo scale were also calculated. The 95% confidence interval (CI) of Fleiss' kappa was calculated from its standard error. Fleiss' kappa values were interpreted according to the criteria defined by Landis and Koch:[20] -1.00, total disagreement; 0.00, no agreement; 0.01–.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60

moderate agreement; 0.61–0.80 substantial agreement; 0.81–0.99 almost perfect agreement; 1.00, perfect agreement. All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC).

RESULTS

The modified Naranjo scale and the modified FDA algorithm are shown in **Figures 1 and 2**. All assessors evaluated 200 case reports using the modified Naranjo scale and the modified FDA algorithm. No results were missing from the case report evaluations. The distribution of evaluation results is shown in **Figure 3** (3A for modified Naranjo scale, and 3B for modified FDA algorithm). Most of the 200 case reports were categorized as "lack of information" or "possible" adverse effects based on these two methods.

Modified Naranjo scale

The intraclass correlation coefficients (ICCs) and Fleiss' kappa coefficient (Fleiss' kappa) values for the modified Naranjo scale are shown in **Table 2**. The ICCs with a 95% confidence interval (95% CI) for each assessor group were as follows: dietary supplement experts, 0.865 [0.836, 0.891]; pharmacists, 0.890 [0.865, 0.911]; registered dietitians, 0.882 [0.859, 0.903]. For the entire group of assessors, the ICC

with a 95% CI was 0.873 [0.850, 0.895]. Fleiss' kappa values with a 95% CI for each assessor group were as follows: dietary supplement experts, 0.598 [0.596, 0.599]; pharmacists, 0.791 [0.790, 0.792]; registered dietitians, 0.610 [0.609, 0.610]. For the entire group of assessors, Fleiss' kappa value with a 95% CI was 0.615 [0.615, 0.615]. The levels of agreement based on the ICCs for each assessor group and all assessors combined were excellent. Inter-rater (multi-rater) reliability classifications based on Fleiss' kappa were as follows: fair agreement among dietary supplement experts; and substantial agreement among pharmacists, registered dietitians, and the entire group as a whole.

Fleiss' kappa values with a 95% CI for each question of the modified Naranjo scale were as follows: item 1 (product labeling), 0.048 [-0.169, 0.264]; item 2 (temporal relationship), 0.530 [0.530, 0.531]; item 3 (changes in adverse event after discontinuation), 0.944 [0.943, 0.945]; item 4 (rechallenges), 0.861 [0.857, 0.866]; item 5 (other factors related to the adverse event), 0.585 [0.584, 0.585]; item 6 (dose-dependency), 0.797 [0.754, 0.840]; item 7 (adverse event history), 0.057 [0.022, 0.093]; item 8 (objective evidence from laboratory tests), 0.561 [0.519, 0.603]. Items 1 and 7 presented with the two lowest levels of agreement.

Modified FDA algorithm

Fleiss' kappa values for the modified FDA algorithm are shown in **Table 2**. Fleiss' kappa values with a 95% CI for each assessor group were as follows: dietary supplement experts, 0.596 [0.594, 0.598]; pharmacists, 0.780 [0.779, 0.781]; registered dietitians, 0.624 [0.623, 0.624]. For all 19 assessors, Fleiss' kappa value with a 95% CI was 0.622 [0.622, 0.622]. Inter-rater (multi-rater) reliability based on Fleiss' kappa values were as follows: fair agreement among dietary supplement experts; substantial agreement among pharmacists, registered dietitians, and the entire group of assessors as a whole.

Table 2. Intraclass correlation coefficients and Fleiss' kappa coefficient values for modified Naranjo scale and modified FDA algorithm

	Modified Naranjo scale		Modified FDA algorithm
	Kappa coefficient [95%CI]	ICC [95%CI]	Kappa coefficient [95%CI]
Dietary supplement expert (n = 4)	0.598 [0.596-0.599]	0.865 [0.836-0.891]	0.596 [0.594-0.598]
Pharmacist (n = 4)	0.791 [0.790-0.792]	0.890 [0.865-0.911]	0.780 [0.779-0.781]
Registered dietitian (n = 11)	0.610 [0.609-0.610]	0.882 [0.859-0.903]	0.624 [0.623-0.624]
Total (n = 19)	0.615 [0.615-0.615]	0.873 [0.850-0.895]	0.622 [0.622-0.622]

ICC, intraclass correlation coefficients; CI, confidence interval

DISCUSSION

In this study, we modified the Naranjo scale and the FDA algorithm and used them to evaluated case reports of adverse reactions to dietary supplements. These reports were assessed by dietary supplement experts, pharmacists, and registered dietitians.

Agreement levels for the Naranjo scale based on ICCs for each individual group and the assessor group as a whole were classified as "excellent." Fleiss' kappa values for each assessor group and the group as a whole demonstrated more than fair agreement. These results indicate that the modified Naranjo scale would be useful for evaluating the causal relationships between adverse events and dietary supplements. It may also have broad utility among different professions. The only concerns were items 1 and 7 (product labeling and adverse event history, respectively), which produced the two lowest levels of agreement. To remedy this, assessors might easily obtain the information from consumers as they are reporting the adverse events. Revising these two items and also recording consumers' reports as they occur may improve inter-rater (multi-rater) reliability and usability of the modified Naranjo scale.

The modified FDA algorithm showed more than fair agreement for each assessor group and the entire group as a whole. Like the Naranjo scale, it has broad utility and would be useful for assessing the causality of adverse events.

For both methods, the inter-rater (multi-rater) reliability ratings based on ICCs and Fleiss' kappa analyses showed more than substantial agreement in the entire group of assessors as a whole. In fact, Fleiss' kappa values were nearly equal (0.615 for the modified Naranjo scale vs. 0.622 for the modified FDA algorithm). Between them, scientists could select the one that best suits their purpose. However, there are several limitations to this study.

The main limitation of this study is the distribution of evaluation results. For both evaluation methods, most of the 200 case reports were categorized as "lack of information" or "possible." This may due to the limited information included in the case reports used in this study. Case reports were recorded based on consumers' voluntary reports through telephone calls and were not structured for evaluating casual relationships. This might have affected the inter-rater (multi-rater) reliability ratings. Structured or semi-structured interviews of consumers can improve the quality of information in case reports. Validity of the methods may also be a limitation. In this study, we estimated inter-rater (multi-rater) reliability using ICCs and Fleiss' kappa. However, validation of the methods could not be performed. Other investigators may want to internally validate our methods in different populations to resolve this limitation and expand the possibilities for application of our methods in clinical and regulatory

settings. For example, medical institutions and regulatory agencies might use these modified methods to screen for adverse effects associated with dietary supplements, which may accelerate the detection of harmful events.

The FDA currently operates the Safety Reporting Portal,[21] intended for organizations, professionals, and consumers. The Safety Reporting Portal is the electronic version of MedWatch 3500, 3500A, and 3500B,[22] which are voluntary reporting forms for adverse events, tailored for dietary supplements. However, researchers point out that it suffers from incomplete reports. Other national departments or local health departments are often first to detect harm,[23] because these forms are detailed and possibly too complicated for people to use.[24] Combining a screening tool with detailed surveillance will make the reporting system more user-friendly. It may promote voluntary reporting and lead to rapid detection of harmful events.

In summary, we present the modified Naranjo scale and the modified FDA algorithm that may be used for assessing the causal relationships between adverse events and dietary supplements. They might also be used by regulatory agencies as screening tools to detect adverse effects from supplements, but additional studies are needed to expand the possibilities for application of our methods.

Acknowledgements

The authors gratefully acknowledge the assessors in this study.

Contributors

KI, HY, and MS designed the study. KI, HY, YB, MS, KM, MK, KU performed the research, and collected the data. YK, KI, and YB analyzed the data. KI, HY, and YK wrote the manuscript. All authors reviewed and approved the contents of the manuscript.

Funding

This work was supported in part by a grant from the Japanese Ministry of Health, Labor and Welfare (No. 24220501 to HY, and KU), and a grant from the Japan Society for the Promotion of Science (JSPS) through the Grant-in-Aid for JSPS Fellows (No.15J10190 to KI).

Competing interests

None declared.

Ethics approval

This study protocol was approved by the ethics committee of the University of Shizuoka (No. 26-6, 2014).

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FIGURE LEGENDS

Figure 1. Modified Naranjo scale

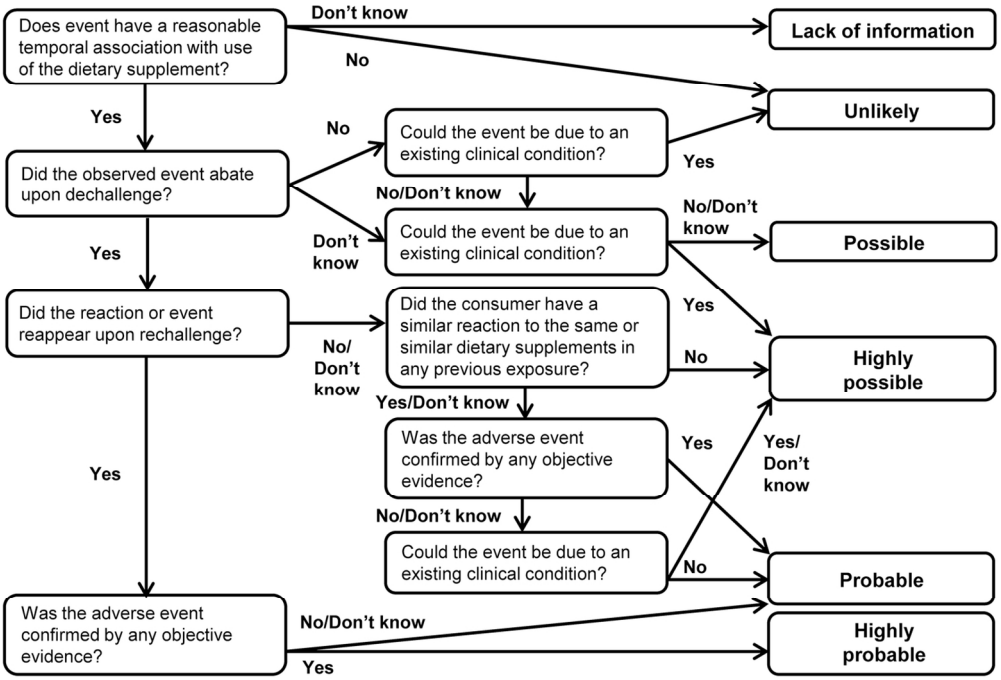
Figure 2. Modified FDA algorithm

Figure 3A. Distribution of results for the modified Naranjo scale

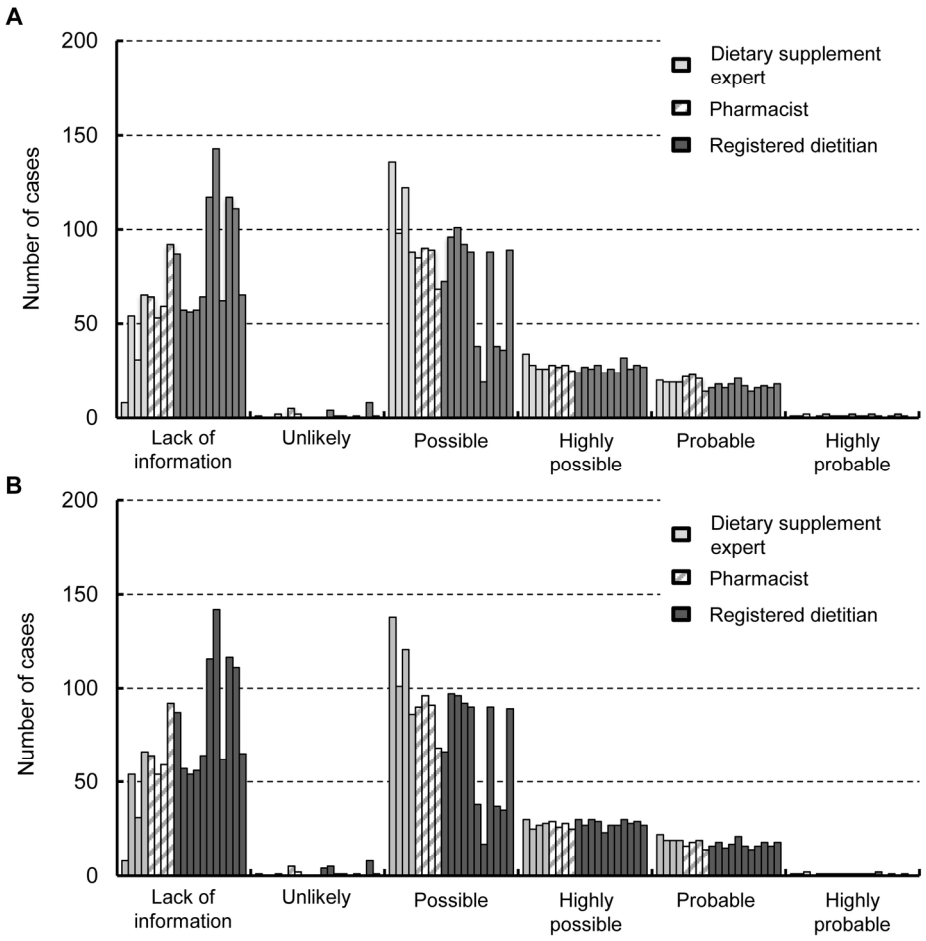
Figure 3B. Distribution of results for the modified FDA algorithm

No	Question	Yes	No	Do Not Know
1	Are there any notification about the reaction on the label or package insert of the dietary supplement?	+1	0	0
2	Did the adverse event appear after suspected dietary supplement intake?	+2	-1	0
3	Did the adverse reaction improve when the suspected dietary supplement was discontinued?	+2	0	0
4	Did the adverse event reappear when the dietary supplements re-intake?	+3	-1	0
5	Are there alternative causes (other than the dietary supplement) that could on their own have caused the reaction?	-1	+2	0
6	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
7	Did the consumer have a similar reaction to the same or similar dietary supplements in any previous exposure?	+1	0	0
8	Was the adverse event confirmed by any objective evidence?	+2	0	0

Modified Naranjo scale
100x56mm (300 x 300 DPI)



Modified FDA algorithm
128x92mm (300 x 300 DPI)



A. Distribution of results for the modified Naranjo scale
B. Distribution of results for the modified FDA algorithm
172x166mm (300 x 300 DPI)

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009038.R1
Article Type:	Research
Date Submitted by the Author:	13-Aug-2015
Complete List of Authors:	Ide, Kazuki; University of Shizuoka, Drug Evaluation & Informatics Yamada, Hiroshi; University of Shizuoka, Drug Evaluation & Informatics Kitagawa, Mamoru; University of Shizuoka, Drug Evaluation & Informatics Kawasaki, Yohei; University of Shizuoka, Drug Evaluation & Informatics Buno, Yuma; University of Shizuoka, Drug Evaluation & Informatics Matsushita, Kumi; Kikugawa General Hospital, Pharmacy Kaji, Masayuki; Shizuoka City Public Health Center, Fujimoto, Kazuko; Keio University, Pharmacy Waki, Masako; Shizuoka City Shizuoka Hospital, Nakashima, Mitusyoshi; Hamamatsu Institute of Clinical Pharmacology & Therapeutics, Umegaki, Keizo; National Institutes of Biomedical Innovation, Health and Nutrition,
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Evidence based practice, Public health, Pharmacology and therapeutics
Keywords:	CLINICAL PHARMACOLOGY, NUTRITION & DIETETICS, STATISTICS & RESEARCH METHODS

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Key words: health food, adverse event, causal relationships, probability, reliability

ABSTRACT

Objective: Dietary supplement use has increased over past decades, resulting in reports of potentially serious adverse events. The aim of this study was to develop optimized methods to evaluate the causal relationships between adverse events and dietary supplements, and to test these methods using case reports.

Design: Causal relationship assessment using prospectively collected data.

Setting & Participants: Four dietary supplement experts, 4 pharmacists, and 11 registered dietitians (5 men and 14 women) examined 200 case reports of suspected adverse events using the modified Naranjo scale and the modified FDA algorithm.

Primary outcome measures: The distribution of evaluation results was analyzed and inter-rater (multi-rater) reliability was evaluated for the two modified methods employed, using intraclass correlation coefficients (ICC) and Fleiss' kappa.

Results: Using these two methods, most of the 200 case reports were categorized as "lack of information" or "possible" adverse events. Inter-rater (multi-rater) reliability among entire assessors ratings for the two modified methods, based on intraclass correlation coefficients (ICC) and Fleiss' kappa, were classified as more than substantial (Modified Naranjo scale: ICC [95%CI], 0.873 [0.850, 0.895]; Fleiss' kappa [95%CI], 0.615 [0.615, 0.615]. Modified FDA algorithm: Fleiss' kappa [95%CI], 0.622 [0.622,

0.622]).

Conclusions: These methods may help to assess the causal relationships between adverse events and dietary supplements. By conducting additional studies of these methods in different populations, researchers can expand the possibilities for the application of our methods.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- There is no optimized method for evaluating these adverse events
- We developed two methods for assessing adverse events associated with dietary supplements and inter-rater reliability among entire assessors was classified as more than substantial
- Our methods may be useful for assessing adverse events caused by dietary supplements in clinical settings
- This simple and easy method for evaluating causal relationships can contribute to prompt issue evaluation, signal detection, and regulatory updating
- Additional studies with different populations are needed to expand the possibilities for application of our methods

INTRODUCTION

The entire functional food market is estimated to be worth over $80 billion.[1] This market reached $32.5 billion in the United States in 2012,[2] with more than half of adults reporting use of one or more dietary supplements. Sales of dietary supplements have also increased in Japan, with an estimated market size second only to that of the United States.[1] In fact, one study indicated that over 50% of the Japanese population consumes dietary supplements.[3] With the increased use of dietary supplements, a number of adverse events have been reported.[4-8] Some of these adverse events can lead to severe disability or death, so managing risk and safety is essential in order to protect consumers. Several legal systems have been developed to regulate labeling and manufacturing standards for dietary supplements, but there are no clear systems in place to detect and report adverse events.[9-11]

Evaluation of the causality of adverse events is essential in order to determine the risk and safety of supplements. It can also help with issue evaluation, signal detection, and regulatory updating. Several methods exist for evaluating causality, including the Naranjo scale,[12, 13] the FDA algorithm,[14-16] the Kramer scale,[13, 17] the Liverpool scale,[18] and the WHO scale.[19] However, these methods are primarily used to assess adverse events associated with medications. They are not optimized for

application to dietary supplements. The information available from consumers taking dietary supplements differs from information provided by patients taking medications. Therefore, the development and optimization of methods to evaluate the causal relationship between adverse events and dietary supplements is essential in order to improve the quality of risk management.

In the present study, we modified the Naranjo scale and the FDA algorithm and then used these to assess 200 case reports of suspected adverse reactions to dietary supplements. The main objective of this study was to test these modified methods using case reports.

METHODS

Study design

The Naranjo[12, 13] scale and the FDA algorithm[14-16] were modified for use with dietary supplements. Two hundred case reports were randomly sampled from a database of adverse event reports associated with dietary supplements. Case reports in the database were based on consumers' voluntary reports through telephone calls to the consumer information center in Japan and were not standardized for the evaluation of causal relationships. We recruited assessors from six institutions in

Japan (University of Shizuoka, Keio University, Kikugawa General Hospital, Shizuoka City Shizuoka Hospital, Shizuoka City Public Health Center, and Hamamatsu Institute of Clinical Pharmacology and Therapeutics) by announcement. Nineteen assessors (4 dietary supplement experts, 4 pharmacists, and 11 registered dietitians; 5 men and 14 women) enrolled and evaluated the case reports by alternately using the modified Naranjo scale and the modified FDA algorithm. The characteristics of the 19 assessors are shown in **Table 1**. Three dietary supplement experts worked at a general hospital and one worked at a university as a full professor. All four of the pharmacists worked at a general hospital. Four of the registered dietitians worked at a general hospital, and seven worked at a city health care center. None of the assessors received any training in the use of the two scales, and they did not familiar with causal assessment of adverse drug reactions since earlier.

Table 1. Assessor characteristics

	Dietary supplement expert	Pharmacist	Registered dietitian
Number, n	4	4	11
Age, mean ± SD	65.8 ± 11.5	37.8 ± 7.8	42.2 ± 12.4
Sex, n (%)			
Men	1 (25)	3 (75)	1 (9)
Women	3 (75)	1 (25)	10 (91)
Career length, mean yrs ± SD	33.5 ± 2.4	8.6 ± 13.8	13.9 ± 17.4

SD, standard deviation; yrs, years

Assessment scale design

Modified Naranjo scale

The modified Naranjo scale is shown in **Figure 1**. The phrase "drug" in the Naranjo scale was changed to "dietary supplement". The section in question 3 of the Naranjo scale pertaining to a specific antagonist was deleted. Questions regarding placebo and blood (or other fluid) concentrations were excluded. In addition to these changes, the scoring for questions pertaining to re-administration and confirmation by objective evidence was changed by adding 1 point for positive answers to the original version of the Naranjo scale. The adverse event reports were assigned to a probability category using the total scores, as follows: ≥ 9 highly probable, 5–8 probable, 3–4 highly possible, 1–2 possible, ≤ 0 unlikely. Case reports lacking information about time relationships were excluded and categorized as "lack of information".

Modified FDA algorithm

Details of the FDA algorithm have been described previously.[16] The modified FDA algorithm is shown in **Figure 2**. There was limited information

included in the dietary supplement case reports, so the number of options for questions was changed from 2 to 3: "Yes," "No," and "Don't know." The scale was structured, with 4 primary questions and 5 branch questions. The contents of the main questions were as follows: (1) the temporal relationship; (2) changes in symptoms due to the dietary supplement being discontinued; (3) rechallenges; (4) objective evidence from laboratory tests such as a drug-induced lymphocyte stimulation test or patch test. Each of these questions had branch questions relating to: (1) existing clinical conditions; (2) objective evidence from laboratory tests such as a drug-induced lymphocyte stimulation test or patch test; (3) previous experiences of adverse events after taking the same or similar (e.g. including the same ingredient) dietary supplement. Adverse event reports were assigned to one of the following probability categories based on the answers to these questions: lack of information, unlikely, possible, highly possible, probable, and highly probable.

Statistical analysis

In order to quantify the level of agreement in the modified Naranjo scale, intraclass correlation coefficients (ICCs) with a 95% confidence interval (CI) were calculated using the methods described by Shrout and Fleiss.[20] ICCs were interpreted

according to the following criteria: < 0.40, poor agreement; 0.40–0.75, moderate agreement; > 0.75, excellent agreement.[21]

Inter-rater (multi-rater) reliability for the modified Naranjo scale and the modified FDA algorithm was analyzed using Fleiss' kappa with a standard error.[22] Fleiss' kappa values were also calculated for each question of the modified Naranjo scale. The 95% CI of Fleiss' kappa was calculated from its standard error. Fleiss' kappa values were interpreted according to the criteria defined by Landis and Koch:[23] -1.00, total disagreement; 0.00, no agreement; 0.01–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60 moderate agreement; 0.61–0.80 substantial agreement; 0.81–0.99 almost perfect agreement; 1.00, perfect agreement. All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC).

RESULTS

The modified Naranjo scale and the modified FDA algorithm are shown in **Figures 1 and 2**. All assessors evaluated 200 case reports using the modified Naranjo scale and the modified FDA algorithm. No results were missing from the case report evaluations. The distribution of evaluation results is shown in **Figure 3** (3A for modified Naranjo

scale, and 3B for modified FDA algorithm). These case reports were based on voluntary consumer reports, included incomplete reporting, and were not standardized for the evaluation of causal relationships. Most of the 200 case reports were categorized as "lack of information" or "possible". The median (range) of cases in "lack of information" using the modified Naranjo Scale was 64 (8-143) and the corresponding values using the modified FDA scale were 64 (8-142) cases. The "possible" category included a median (range) of 88 (19-136) cases using the modified Naranjo Scale and 90 (17-138) cases using the modified FDA scale. The information on dosage, previous similar events, and objective evidence was particularly poorly reported in these case reports. A large proportion of the cases were mild. Skin symptoms such as pruritus (n = 56), and gastrointestinal symptoms such as abdominal discomfort (n = 62) were the most common. However, 2 serious adverse events related to hepatic dysfunction were reported.

Modified Naranjo scale

The ICCs and Fleiss' kappa coefficient (Fleiss' kappa) values for the modified Naranjo scale are shown in **Table 2**. The ICCs [95% CI] for each assessor group were as follows: dietary supplement experts, 0.865 [0.836, 0.891]; pharmacists, 0.890 [0.865, 0.911]; registered dietitians, 0.882 [0.859, 0.903]. For the entire group

of assessors, this value was 0.873 [0.850, 0.895]. Fleiss' kappa values [95% CI] for each assessor group were as follows: dietary supplement experts, 0.598 [0.596, 0.599]; pharmacists, 0.791 [0.790, 0.792]; registered dietitians, 0.610 [0.609, 0.610]. For the entire group of assessors, this value was 0.615 [0.615, 0.615]. The levels of agreement based on the ICCs for each assessor group and all assessors combined were excellent. Inter-rater (multi-rater) reliability classifications based on Fleiss' kappa were as follows: fair agreement among dietary supplement experts and substantial agreement among pharmacists, registered dietitians, and the entire group as a whole.

Fleiss' kappa values [95% CI] for each question of the modified Naranjo scale were as follows: item 1 (product labeling), 0.048 [-0.169, 0.264]; item 2 (temporal relationship), 0.530 [0.530, 0.531]; item 3 (changes in adverse event after discontinuation), 0.944 [0.943, 0.945]; item 4 (rechallenges), 0.861 [0.857, 0.866]; item 5 (other factors related to the adverse event), 0.585 [0.584, 0.585]; item 6 (dose-dependency), 0.797 [0.754, 0.840]; item 7 (adverse event history), 0.057 [0.022, 0.093]; item 8 (objective evidence from laboratory tests), 0.561 [0.519, 0.603]. Items 1 and 7 showed the two lowest levels of agreement.

Modified FDA algorithm

Fleiss' kappa values for the modified FDA algorithm are shown in **Table 2**. Fleiss' kappa values [95% CI] for each assessor group were as follows: dietary supplement experts, 0.596 [0.594, 0.598]; pharmacists, 0.780 [0.779, 0.781]; registered dietitians, 0.624 [0.623, 0.624]. For all 19 assessors, this value was 0.622 [0.622, 0.622]. Inter-rater (multi-rater) reliability based on Fleiss' kappa values were as follows: fair agreement among dietary supplement experts; substantial agreement among pharmacists, registered dietitians, and the entire group of assessors as a whole.

Table 2. Intraclass correlation coefficients and Fleiss' kappa coefficient values for the modified Naranjo scale and the modified FDA algorithm

	Modified Naranjo scale		Modified FDA algorithm
	Kappa coefficient [95% CI]	ICC [95% CI]	Kappa coefficient [95% CI]
Dietary supplement expert (n = 4)	0.598 [0.596-0.599]	0.865 [0.836-0.891]	0.596 [0.594-0.598]
Pharmacist (n = 4)	0.791 [0.790-0.792]	0.890 [0.865-0.911]	0.780 [0.779-0.781]
Registered dietitian (n = 11)	0.610 [0.609-0.610]	0.882 [0.859-0.903]	0.624 [0.623-0.624]
Total (n = 19)	0.615 [0.615-0.615]	0.873 [0.850-0.895]	0.622 [0.622-0.622]

ICC, intraclass correlation coefficient; CI, confidence interval

DISCUSSION

In this study, we modified the Naranjo scale and the FDA algorithm and used them to

evaluate case reports of adverse reactions to dietary supplements. These reports were assessed by dietary supplement experts, pharmacists, and registered dietitians.

Agreement levels for the Naranjo scale, based on ICCs for each individual group and the assessor group as a whole, were classified as "excellent". Fleiss' kappa values for each assessor group and for the group as a whole also demonstrated more than fair agreement. These results indicated that the modified Naranjo scale would be useful for evaluating the causal relationships between adverse events and dietary supplements. It may also have broad utility among different professions. The only concerns were items 1 and 7 (product labeling and adverse event history, respectively), which produced the two lowest levels of agreement. To remedy this, assessors might easily obtain the information from consumers as they are reporting the adverse events. Revising these two items and also recording consumers' reports as they occur may improve the inter-rater (multi-rater) reliability and usability of the modified Naranjo scale.

The modified FDA algorithm showed more than fair agreement between each assessor group and within the entire group. Like the Naranjo scale, it has broad utility and would be useful for assessing the causality of adverse events.

For both methods, the inter-rater (multi-rater) reliability ratings determined using ICCs and Fleiss' kappa analyses showed more than substantial agreement in the entire

group of assessors. In fact, the Fleiss' kappa values were very similar (0.615 for the modified Naranjo scale vs. 0.622 for the modified FDA algorithm). Between them, scientists could select the one that best suits their purpose.

A large proportion of the 200 cases assessed in this study reported mild symptoms, although 2 serious cases with hepatic dysfunction were included. Although mild symptoms are not life-threatening, they do affect quality of life. Therefore, analysis of causal relationships and the provision of information can improve the safety of dietary supplement usage. The number of serious adverse events was limited but these can lead to severe disability; the analysis of causality using this method can lead to prompt diagnosis and treatment, as well as regulatory actions.

There were several limitations to this study. The main limitation was the distribution of evaluation results. For both evaluation methods, most of the 200 case reports were categorized as "lack of information" or "possible." This may reflect the limited information included in the case reports used in this study. Case reports were based on voluntary consumer telephone calls and were not structured to facilitate evaluation of causal relationships. This might have affected the inter-rater (multi-rater) reliability ratings. In fact, most of the disagreements among assessors related to classification as either "lack of information" or "possible", while there was fairly good

agreement concerning “highly possible”, “probable”, and “highly probable” cases. This may be due to the evaluation based on speculation of each assessor in the cases categorized as “lack of information” or “possible”. Structured or semi-structured standardized interviews of consumers can improve the quality of information in case reports. When designing a structured or semi-structured interview form, information on dosage, previous similar events, and objective evidence should be requested, in addition to the essential information regarding temporal association and discontinuation. Even in the cases categorized as “probable”, some of these items of information were absent. For example, a man started to take a dietary supplement for health enhancement, and then developed oral inflammation. After discontinuation of the supplement, his oral inflammation resolved. When he started to take the dietary supplement again, oral inflammation recurred and he then stopped taking the supplement. This case included information on temporal association, discontinuation, and rechallenge, but lacked information on dosage, previous similar events, and objective evidence. Validity of the methods may also be a limitation. We estimated inter-rater (multi-rater) reliability using ICCs and Fleiss’ kappa. However, these methods were not validated. Future studies could validate these methods in different populations in order to address this limitation and expand the potential for application of our methods in other clinical and regulatory

settings. For example, medical institutions and regulatory agencies might use these modified methods to screen for adverse effects associated with dietary supplements, which may accelerate the detection of harmful events.

The FDA currently operates the Safety Reporting Portal[24] for organizations, professionals, and consumers. The Safety Reporting Portal is the electronic version of MedWatch 3500, 3500A, and 3500B,[25] which are voluntary reporting forms for adverse events, tailored to dietary supplements. However, researchers point out that these datasets contain many incomplete reports. Other national or local health departments are often the first to detect harm,[9] because these forms are detailed and possibly too complicated for people to use.[26] Combining a screening tool with detailed surveillance will make the reporting system more user-friendly. This may promote voluntary reporting and lead to more rapid detection of harmful events.

In summary, we present a modified Naranjo scale and a modified FDA algorithm that may be used to assess the causal relationships between adverse events and dietary supplements. These tools might also be used by regulatory agencies to screen for adverse supplement events, but additional studies are needed to expand the possibilities for application of our methods.

Acknowledgements

The authors gratefully acknowledge the assessors in this study.

Contributors

KI, HY, and MS designed the study. KI, HY, YB, MS, KM, MK, and KU performed the research and collected the data. YK, KI, and YB analyzed the data. KI, HY, and YK wrote the manuscript. All authors reviewed and approved the contents of the manuscript.

Funding

This work was supported in part by a grant from the Japanese Ministry of Health, Labor and Welfare (No. 24220501 to HY, and KU), and a grant from the Japan Society for the Promotion of Science (JSPS) through the Grant-in-Aid for JSPS Fellows (No.15J10190 to KI).

Competing interests

None declared.

Ethics approval

This study protocol was approved by the ethics committee of the University of Shizuoka (No. 26-6, 2014).

Data sharing statement

The dataset for this study is available on request from the corresponding author.

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FIGURE LEGENDS

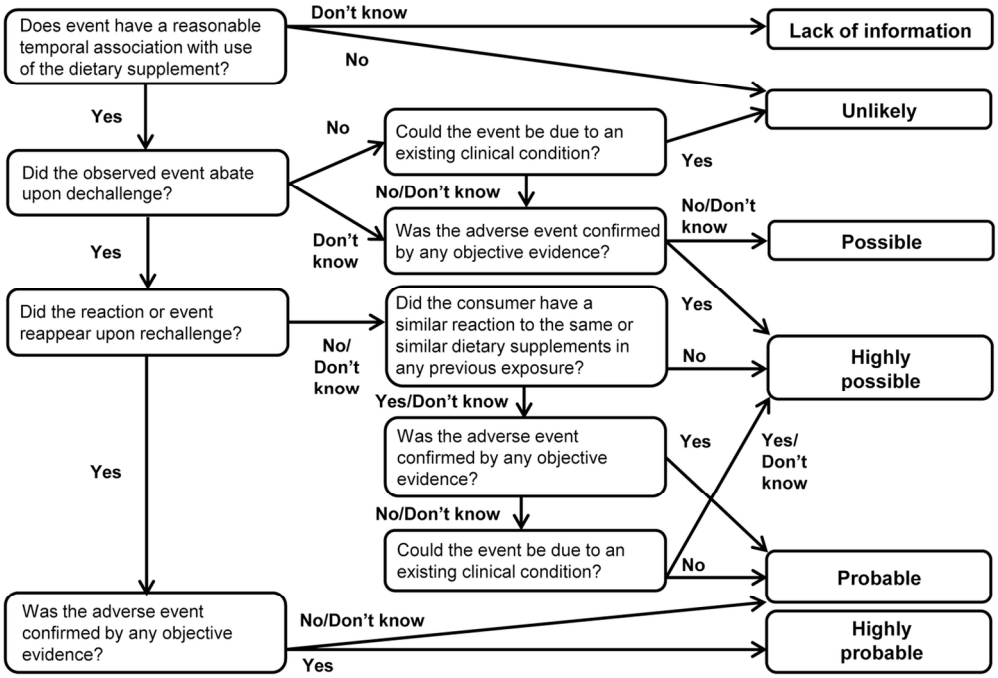
Figure 1. Modified Naranjo scale

Figure 2. Modified FDA algorithm

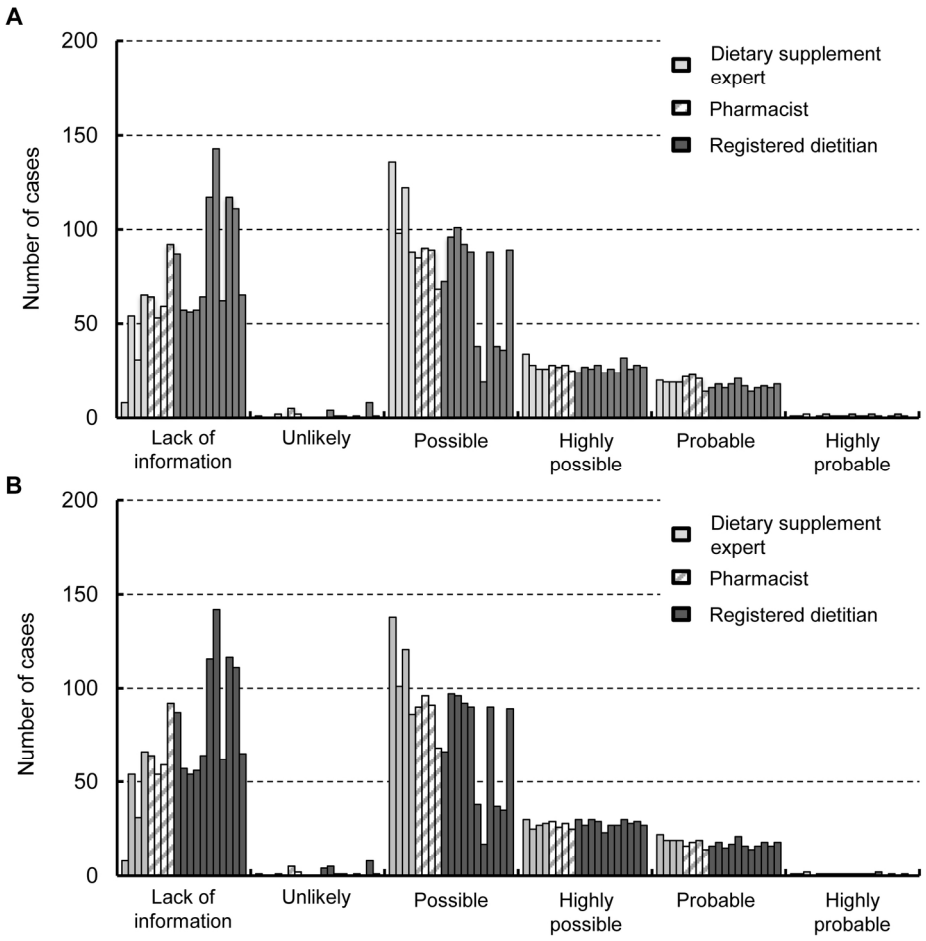
Figure 3. A. Distribution of results for the modified Naranjo scale. B. Distribution of results for the modified FDA algorithm

No	Question	Yes	No	Do Not Know
1	Are there any notification about the reaction on the label or package insert of the dietary supplement?	+1	0	0
2	Did the adverse event appear after suspected dietary supplement intake?	+2	-1	0
3	Did the adverse reaction improve when the suspected dietary supplement was discontinued?	+2	0	0
4	Did the adverse event reappear when the dietary supplements re-intake?	+3	-1	0
5	Are there alternative causes (other than the dietary supplement) that could on their own have caused the reaction?	-1	+2	0
6	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
7	Did the consumer have a similar reaction to the same or similar dietary supplements in any previous exposure?	+1	0	0
8	Was the adverse event confirmed by any objective evidence?	+2	0	0

Modified Naranjo scale
100x56mm (300 x 300 DPI)



Modified FDA algorithm
128x91mm (300 x 300 DPI)



A. Distribution of results for the modified Naranjo scale
B. Distribution of results for the modified FDA algorithm
172x166mm (300 x 300 DPI)

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009038.R2
Article Type:	Research
Date Submitted by the Author:	24-Sep-2015
Complete List of Authors:	Ide, Kazuki; University of Shizuoka, Drug Evaluation & Informatics Yamada, Hiroshi; University of Shizuoka, Drug Evaluation & Informatics Kitagawa, Mamoru; University of Shizuoka, Drug Evaluation & Informatics Kawasaki, Yohei; University of Shizuoka, Drug Evaluation & Informatics Buno, Yuma; University of Shizuoka, Drug Evaluation & Informatics Matsushita, Kumi; Kikugawa General Hospital, Pharmacy Kaji, Masayuki; Shizuoka City Public Health Center, Fujimoto, Kazuko; Keio University, Pharmacy Waki, Masako; Shizuoka City Shizuoka Hospital, Nakashima, Mitusyoshi; Hamamatsu Institute of Clinical Pharmacology & Therapeutics, Umegaki, Keizo; National Institutes of Biomedical Innovation, Health and Nutrition,
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Evidence based practice, Public health, Pharmacology and therapeutics
Keywords:	CLINICAL PHARMACOLOGY, NUTRITION & DIETETICS, STATISTICS & RESEARCH METHODS

Article for BMJ Open

***Word count**: 2700 **Number of Figures & Tables**: 5*

Title:

Methods for estimating causal relationships of adverse events with dietary supplements

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Key words: health food, adverse event, causal relationships, probability, reliability

ABSTRACT

Objective: Dietary supplement use has increased over past decades, resulting in reports of potentially serious adverse events. The aim of this study was to develop optimized methods to evaluate the causal relationships between adverse events and dietary supplements, and to test these methods using case reports.

Design: Causal relationship assessment using prospectively collected data.

Setting & Participants: Four dietary supplement experts, 4 pharmacists, and 11 registered dietitians (5 men and 14 women) examined 200 case reports of suspected adverse events using the modified Naranjo scale and the modified FDA algorithm.

Primary outcome measures: The distribution of evaluation results was analyzed and inter-rater (multi-rater) reliability was evaluated for the two modified methods employed, using intraclass correlation coefficients (ICC) and Fleiss' kappa.

Results: Using these two methods, most of the 200 case reports were categorized as "lack of information" or "possible" adverse events. Inter-rater (multi-rater) reliability among entire assessors ratings for the two modified methods, based on intraclass correlation coefficients (ICC) and Fleiss' kappa, were classified as more than substantial (Modified Naranjo scale: ICC [95%CI], 0.873 [0.850, 0.895]; Fleiss' kappa [95%CI], 0.615 [0.615, 0.615]. Modified FDA algorithm: Fleiss' kappa [95%CI], 0.622 [0.622,

0.622]).

Conclusions: These methods may help to assess the causal relationships between adverse events and dietary supplements. By conducting additional studies of these methods in different populations, researchers can expand the possibilities for the application of our methods.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- There is no optimized method for evaluating these adverse events
- We developed two methods for assessing adverse events associated with dietary supplements and inter-rater reliability among entire assessors was classified as more than substantial
- Our methods may be useful for assessing adverse events caused by dietary supplements in clinical settings
- This simple and easy method for evaluating causal relationships can contribute to prompt issue evaluation, signal detection, and regulatory updating
- Additional studies with different populations are needed to expand the possibilities for application of our methods

INTRODUCTION

The entire functional food market is estimated to be worth over $80 billion.[1] This market reached $32.5 billion in the United States in 2012,[2] with more than half of adults reporting use of one or more dietary supplements. Sales of dietary supplements have also increased in Japan, with an estimated market size second only to that of the United States.[1] In fact, one study indicated that over 50% of the Japanese population consumes dietary supplements.[3] With the increased use of dietary supplements, a number of adverse events have been reported.[4-8] Some of these adverse events can lead to severe disability or death, so managing risk and safety is essential in order to protect consumers. Several legal systems have been developed to regulate labeling and manufacturing standards for dietary supplements, but there are no clear systems in place to detect and report adverse events.[9-11]

Evaluation of the causality of adverse events is essential in order to determine the risk and safety of supplements. It can also help with issue evaluation, signal detection, and regulatory updating. Several methods exist for evaluating causality, including the Naranjo scale,[12, 13] the FDA algorithm,[14-16] the Kramer scale,[13, 17] the Liverpool scale,[18] and the WHO scale.[19] However, these methods are primarily used to assess adverse events associated with medications. They are not optimized for

application to dietary supplements. The information available from consumers taking dietary supplements differs from information provided by patients taking medications. Therefore, the development and optimization of methods to evaluate the causal relationship between adverse events and dietary supplements is essential in order to improve the quality of risk management.

In the present study, we modified the Naranjo scale and the FDA algorithm and then used these to assess 200 case reports of suspected adverse reactions to dietary supplements. The main objective of this study was to test these modified methods using case reports.

METHODS

Study design

The Naranjo[12, 13] scale and the FDA algorithm[14-16] were modified for use with dietary supplements. Two hundred case reports were randomly sampled from a database of adverse event reports associated with dietary supplements. Case reports in the database were based on consumers' voluntary reports through telephone calls to the consumer information center in Japan and were not standardized for the evaluation of causal relationships. We recruited assessors from six institutions in

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Table 1. Assessor characteristics

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Career length, mean yrs ± SD	33.5 ± 2.4	8.6 ± 13.8	13.9 ± 17.4

SD, standard deviation; yrs, years

Assessment scale design

Modified Naranjo scale

The modified Naranjo scale is shown in **Figure 1**. The phrase "drug" in the Naranjo scale was changed to "dietary supplement". The section in question 3 of the Naranjo scale pertaining to a specific antagonist was deleted. Questions regarding placebo and blood (or other fluid) concentrations were excluded. In addition to these changes, the scoring for questions pertaining to re-administration and confirmation by objective evidence was changed by adding 1 point for positive answers to the original version of the Naranjo scale. The adverse event reports were assigned to a probability category using the total scores, as follows: ≥ 9 highly probable, 5–8 probable, 3–4 highly possible, 1–2 possible, ≤ 0 unlikely. Case reports lacking information about time relationships were excluded and categorized as "lack of information".

Modified FDA algorithm

Details of the FDA algorithm have been described previously.[16] The modified FDA algorithm is shown in **Figure 2**. There was limited information

included in the dietary supplement case reports, so the number of options for questions was changed from 2 to 3: "Yes," "No," and "Don't know." The scale was structured, with 4 primary questions and 5 branch questions. The contents of the main questions were as follows: (1) the temporal relationship; (2) changes in symptoms due to the dietary supplement being discontinued; (3) rechallenges; (4) objective evidence from laboratory tests such as a drug-induced lymphocyte stimulation test or patch test. Each of these questions had branch questions relating to: (1) existing clinical conditions; (2) objective evidence from laboratory tests such as a drug-induced lymphocyte stimulation test or patch test; (3) previous experiences of adverse events after taking the same or similar (e.g. including the same ingredient) dietary supplement. Adverse event reports were assigned to one of the following probability categories based on the answers to these questions: lack of information, unlikely, possible, highly possible, probable, and highly probable.

Statistical analysis

In order to quantify the level of agreement in the modified Naranjo scale, intraclass correlation coefficients (ICCs) with a 95% confidence interval (CI) were calculated using the methods described by Shrout and Fleiss.[20] ICCs were interpreted

according to the following criteria: < 0.40, poor agreement; 0.40–0.75, moderate agreement; > 0.75, excellent agreement.[21]

Inter-rater (multi-rater) reliability for the modified Naranjo scale and the modified FDA algorithm was analyzed using Fleiss' kappa with a standard error.[22] Fleiss' kappa values were also calculated for each question of the modified Naranjo scale. The 95% CI of Fleiss' kappa was calculated from its standard error. Fleiss' kappa values were interpreted according to the criteria defined by Landis and Koch:[23] -1.00, total disagreement; 0.00, no agreement; 0.01–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60 moderate agreement; 0.61–0.80 substantial agreement; 0.81–0.99 almost perfect agreement; 1.00, perfect agreement. All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC).

RESULTS

The modified Naranjo scale and the modified FDA algorithm are shown in **Figures 1 and 2**. All assessors evaluated 200 case reports using the modified Naranjo scale and the modified FDA algorithm. No results were missing from the case report evaluations. The distribution of evaluation results is shown in **Figure 3** (3A for modified Naranjo

scale, and 3B for modified FDA algorithm). These case reports were based on voluntary consumer reports, included incomplete reporting, and were not standardized for the evaluation of causal relationships. Most of the 200 case reports were categorized as "lack of information" or "possible". The median (range) of cases in "lack of information" using the modified Naranjo Scale was 64 (8-143) and the corresponding values using the modified FDA scale were 64 (8-142) cases. The "possible" category included a median (range) of 88 (19-136) cases using the modified Naranjo Scale and 90 (17-138) cases using the modified FDA scale. The information on dosage, previous similar events, and objective evidence was particularly poorly reported in these case reports. A large proportion of the cases were mild. Skin symptoms such as pruritus (n = 56), and gastrointestinal symptoms such as abdominal discomfort (n = 62) were the most common. However, 2 serious adverse events related to hepatic dysfunction were reported. In one serious case, a woman started to take a dietary supplement for weight-loss. Two weeks after commencing this treatment, her health deteriorated and she presented at a general hospital. Laboratory analyses revealed abnormal hepatic enzyme results and she was diagnosed with liver dysfunction. This condition resolved after over two weeks of hospitalization. The attending doctor considered that the patient's dietary supplement had caused her liver dysfunction. In another case, a woman had been taking

a dietary supplement for weight control for several months and had experienced fatigue for several weeks. She presented at a general hospital, where laboratory analyses revealed abnormal hepatic enzyme results and she was diagnosed with hepatitis. Her attending doctor considered that this was due to the dietary supplement. The patient's hepatitis improved after around two weeks' hospitalization.

Modified Naranjo scale

The ICCs and Fleiss' kappa coefficient (Fleiss' kappa) values for the modified Naranjo scale are shown in **Table 2**. The ICCs [95% CI] for each assessor group were as follows: dietary supplement experts, 0.865 [0.836, 0.891]; pharmacists, 0.890 [0.865, 0.911]; registered dietitians, 0.882 [0.859, 0.903]. For the entire group of assessors, this value was 0.873 [0.850, 0.895]. Fleiss' kappa values [95% CI] for each assessor group were as follows: dietary supplement experts, 0.598 [0.596, 0.599]; pharmacists, 0.791 [0.790, 0.792]; registered dietitians, 0.610 [0.609, 0.610]. For the entire group of assessors, this value was 0.615 [0.615, 0.615]. The levels of agreement based on the ICCs for each assessor group and all assessors combined were excellent. Inter-rater (multi-rater) reliability classifications based on Fleiss' kappa were as follows: fair agreement among dietary supplement experts and substantial agreement among pharmacists, registered dietitians, and the entire group

as a whole.

Fleiss' kappa values [95% CI] for each question of the modified Naranjo scale were as follows: item 1 (product labeling), 0.048 [-0.169, 0.264]; item 2 (temporal relationship), 0.530 [0.530, 0.531]; item 3 (changes in adverse event after discontinuation), 0.944 [0.943, 0.945]; item 4 (rechallenges), 0.861 [0.857, 0.866]; item 5 (other factors related to the adverse event), 0.585 [0.584, 0.585]; item 6 (dose-dependency), 0.797 [0.754, 0.840]; item 7 (adverse event history), 0.057 [0.022, 0.093]; item 8 (objective evidence from laboratory tests), 0.561 [0.519, 0.603]. Items 1 and 7 showed the two lowest levels of agreement.

Modified FDA algorithm

Fleiss' kappa values for the modified FDA algorithm are shown in **Table 2**. Fleiss' kappa values [95% CI] for each assessor group were as follows: dietary supplement experts, 0.596 [0.594, 0.598]; pharmacists, 0.780 [0.779, 0.781]; registered dietitians, 0.624 [0.623, 0.624]. For all 19 assessors, this value was 0.622 [0.622, 0.622]. Inter-rater (multi-rater) reliability based on Fleiss' kappa values were as follows: fair agreement among dietary supplement experts; substantial agreement among pharmacists, registered dietitians, and the entire group of assessors as a whole.

Table 2. Intraclass correlation coefficients and Fleiss' kappa coefficient values for the modified Naranjo scale and the modified FDA algorithm

	Modified Naranjo scale	Modified FDA algorithm	
	Kappa coefficient [95% CI]	ICC [95% CI]	Kappa coefficient [95% CI]
Dietary supplement expert (n = 4)	0.598 [0.596-0.599]	0.865 [0.836-0.891]	0.596 [0.594-0.598]
Pharmacist (n = 4)	0.791 [0.790-0.792]	0.890 [0.865-0.911]	0.780 [0.779-0.781]
Registered dietitian (n = 11)	0.610 [0.609-0.610]	0.882 [0.859-0.903]	0.624 [0.623-0.624]
Total (n = 19)	0.615 [0.615-0.615]	0.873 [0.850-0.895]	0.622 [0.622-0.622]

ICC, intraclass correlation coefficient; CI, confidence interval

DISCUSSION

In this study, we modified the Naranjo scale and the FDA algorithm and used them to evaluate case reports of adverse reactions to dietary supplements. These reports were assessed by dietary supplement experts, pharmacists, and registered dietitians.

Agreement levels for the Naranjo scale, based on ICCs for each individual group and the assessor group as a whole, were classified as "excellent". Fleiss' kappa values for each assessor group and for the group as a whole also demonstrated more than fair agreement. These results indicated that the modified Naranjo scale would be useful for evaluating the causal relationships between adverse events and dietary supplements. It may also have broad utility among different professions. The only concerns were items 1 and 7 (product labeling and adverse event history, respectively), which produced the

two lowest levels of agreement. To remedy this, assessors might easily obtain the information from consumers as they are reporting the adverse events. Revising these two items and also recording consumers' reports as they occur may improve the inter-rater (multi-rater) reliability and usability of the modified Naranjo scale.

The modified FDA algorithm showed more than fair agreement between each assessor group and within the entire group. Like the Naranjo scale, it has broad utility and would be useful for assessing the causality of adverse events.

For both methods, the inter-rater (multi-rater) reliability ratings determined using ICCs and Fleiss' kappa analyses showed more than substantial agreement in the entire group of assessors. In fact, the Fleiss' kappa values were very similar (0.615 for the modified Naranjo scale vs. 0.622 for the modified FDA algorithm). Between them, scientists could select the one that best suits their purpose.

A large proportion of the 200 cases assessed in this study reported mild symptoms, although 2 serious cases with hepatic dysfunction were included. Although mild symptoms are not life-threatening, they do affect quality of life. Therefore, analysis of causal relationships and the provision of information can improve the safety of dietary supplement usage. The number of serious adverse events was limited but these can lead to severe disability; the analysis of causality using this method can lead to prompt

diagnosis and treatment, as well as regulatory actions.

There were several limitations to this study. The main limitation was the distribution of evaluation results. For both evaluation methods, most of the 200 case reports were categorized as “lack of information” or “possible.” This may reflect the limited information included in the case reports used in this study. Case reports were based on voluntary consumer telephone calls and were not structured to facilitate evaluation of causal relationships. This might have affected the inter-rater (multi-rater) reliability ratings. In fact, most of the disagreements among assessors related to classification as either “lack of information” or “possible”, while there was fairly good agreement concerning “highly possible”, “probable”, and “highly probable” cases. This may be due to the evaluation based on speculation of each assessor in the cases categorized as “lack of information” or “possible”. Structured or semi-structured standardized interviews of consumers can improve the quality of information in case reports. When designing a structured or semi-structured interview form, information on dosage, previous similar events, and objective evidence should be requested, in addition to the essential information regarding temporal association and discontinuation. Even in the cases categorized as “probable”, some of these items of information were absent. For example, a man started to take a dietary supplement for health enhancement, and

then developed oral inflammation. After discontinuation of the supplement, his oral inflammation resolved. When he started to take the dietary supplement again, oral inflammation recurred and he then stopped taking the supplement. This case included information on temporal association, discontinuation, and rechallenge, but lacked information on dosage, previous similar events, and objective evidence. Validity of the methods may also be a limitation. We estimated inter-rater (multi-rater) reliability using ICCs and Fleiss' kappa. However, these methods were not validated. Future studies could validate these methods in different populations in order to address this limitation and expand the potential for application of our methods in other clinical and regulatory settings. For example, medical institutions and regulatory agencies might use these modified methods to screen for adverse effects associated with dietary supplements, which may accelerate the detection of harmful events.

The FDA currently operates the Safety Reporting Portal[24] for organizations, professionals, and consumers. The Safety Reporting Portal is the electronic version of MedWatch 3500, 3500A, and 3500B,[25] which are voluntary reporting forms for adverse events, tailored to dietary supplements. However, researchers point out that these datasets contain many incomplete reports. Other national or local health departments are often the first to detect harm,[9] because these forms are detailed and

possibly too complicated for people to use.[26] Combining a screening tool with detailed surveillance will make the reporting system more user-friendly. This may promote voluntary reporting and lead to more rapid detection of harmful events.

In summary, we present a modified Naranjo scale and a modified FDA algorithm that may be used to assess the causal relationships between adverse events and dietary supplements. These tools might also be used by regulatory agencies to screen for adverse supplement events, but additional studies are needed to expand the possibilities for application of our methods.

Acknowledgements

The authors gratefully acknowledge the assessors in this study.

Contributors

KI, HY, and MS designed the study. KI, HY, YB, MS, KM, MK, and KU performed the research and collected the data. YK, KI, and YB analyzed the data. KI, HY, and YK wrote the manuscript. All authors reviewed and approved the contents of the manuscript.

Funding

This work was supported in part by a grant from the Japanese Ministry of Health, Labor and

Welfare (No. 24220501 to HY, and KU), and a grant from the Japan Society for the Promotion of Science (JSPS) through the Grant-in-Aid for JSPS Fellows (No.15J10190 to KI).

Competing interests

No, there are no competing interests.

Ethics approval

This study protocol was approved by the ethics committee of the University of Shizuoka (No. 26-6, 2014).

Data sharing statement

The dataset for this study is available on request from the corresponding author.

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FIGURE LEGENDS

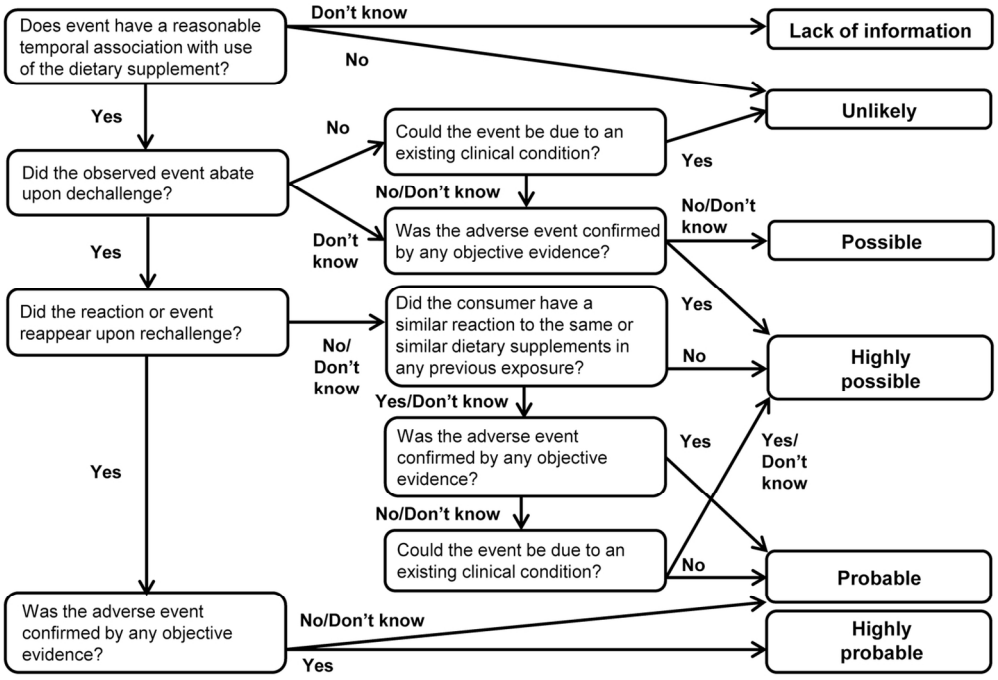
Figure 1. Modified Naranjo scale

Figure 2. Modified FDA algorithm

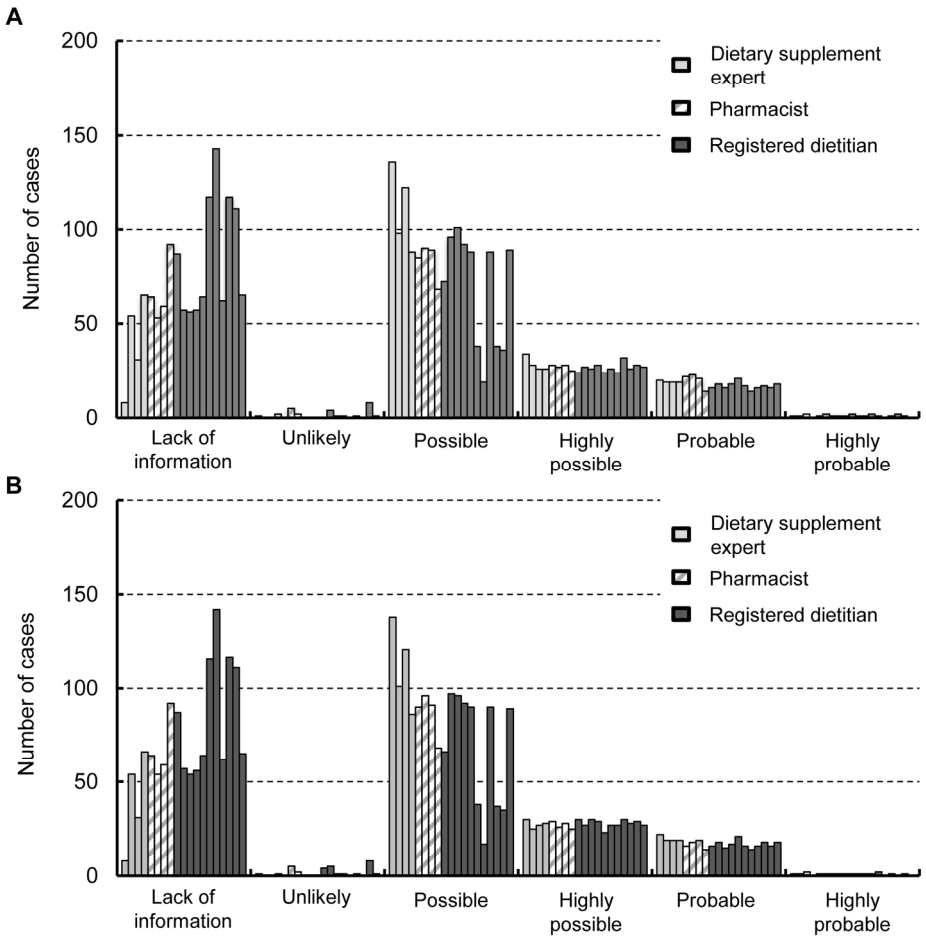
Figure 3. A. Distribution of results for the modified Naranjo scale. B. Distribution of results for the modified FDA algorithm

No	Question	Yes	No	Do Not Know
1	Are there any notification about the reaction on the label or package insert of the dietary supplement?	+1	0	0
2	Did the adverse event appear after suspected dietary supplement intake?	+2	-1	0
3	Did the adverse reaction improve when the suspected dietary supplement was discontinued?	+2	0	0
4	Did the adverse event reappear when the dietary supplements re-intake?	+3	-1	0
5	Are there alternative causes (other than the dietary supplement) that could on their own have caused the reaction?	-1	+2	0
6	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
7	Did the consumer have a similar reaction to the same or similar dietary supplements in any previous exposure?	+1	0	0
8	Was the adverse event confirmed by any objective evidence?	+2	0	0

Modified Naranjo scale
100x56mm (300 x 300 DPI)



Modified FDA algorithm
128x91mm (300 x 300 DPI)



A. Distribution of results for the modified Naranjo scale
B. Distribution of results for the modified FDA algorithm
172x166mm (300 x 300 DPI)