



# Current status of health-related clinical evaluation outcome: Overview of systematic literature reviews for improvement of intestinal environment health claim category

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## ABSTRACT

This study used systematic literature reviews conducted in Japan of a finished product or functional ingredient to identify foods with function claims. We used “stool frequency” as the benchmark for the health claim of “improvement of the intestinal environment.” We found 427 foods with function claims, 384 (89.9%) foods with function claims used “stool frequency.” We identified “supplement shape” (OR: 4.62; 95% CI [1.90, 11.20]) as a significant factor in the use of “stool frequency.” Our findings suggest that both supplements and using another shape as a food form could ensure real benefits for consumers by incorporating health-related outcomes.

## 1. Introduction

Food has three functions: 1) vital nutritional function, 2) sensory function, and 3) adjusting body conditions. The health effects of foods with health claims categorized in the third function have attracted the attention of the Japanese health food market (Tanemura et al., 2017) and foods marketed as improving the intestinal environment are especially popular (Yano Research Institute Ltd, 2021).

Foods classified under the third function are further subdivided into three categories in Japan: 1) food with nutrient function claims, 2) food for specified health uses, and 3) foods with function claims. The labeling of a health claim is based on scientific evidence and includes function ingredients. Business operators are permitted to describe health claims on the label under the regulatory policy of the Consumer Affairs Agency, Government of Japan. Foods with function claims require scientific evidence based on systematic literature reviews and/or randomized clinical trials. They do not require regulatory review or permission from the Government of Japan's Consumer Agency. Clinical evaluation criteria for foods with health claims must adhere to a single guideline published on the specified health uses of a food (Maeda-Yamamoto, 2017, 2021). Among the three food categories labeled under the third function, the number of foods with function claims submitted to the regulatory agency has increased in Japan (Yano Research Institute Ltd, 2021). This new food labeling system is useful because it has

significantly changed the domestic market environment and encouraged business operators to expand their business overseas. With free trade agreements such as the Trans-Pacific Partnership Agreement, the rules for functional foods must also meet international standards. The regulations of the export destination must also be investigated because these foods are not merely exported goods.

A 2011 report by the European Food Safety Authority in the EU reviewed functional substances submitted to both Japanese and European regulatory agencies. For instance, *Bifidobacterium longum* (BB536), with the third function of “improvement in bowel regularity,” is a food with a health claim in Japan. However, the European Food Safety Authority (EFSA) had not provided regulatory permission for this substance in this health claim category. Five papers submitted to the EFSA (Ogata et al., 1999; Ogata et al., 1997; Yaeshima T et al., 2001; Yaeshima T et al., 1998; Yaeshima et al., 1997) provide scientific evidence for this health claim in Japan. A 2011 European Food Safety Authority review of these papers however provided evidence that this third function is insufficient (European Food Safety Authority, 2011). We can attribute this to the clinical evaluation outcomes: the clinical trials used fecal flora, fecal spoilage products, enzyme activity, and fecal characteristics as outcomes without considering bowel movements. Clinical evaluation outcomes that allow benefit assessments are important for clinical research involving humans on food functions for health promotion. Other studies were considered insufficient due to inappropriate

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methodologies. For instance, their designs did not include randomization or blinding (Ogata et al., 1997; Yaeshima Tet al., 2001; Yaeshima Tet al., 1998; Yaeshima et al., 1997). Significantly, a regulatory gap exists between Japan and the EU, that is, the regulatory system for foods with health claims differs between countries and regions. Owing to this internationalization of the food trade has caused difficulties in completing food production processes within a single country (Tanemura et al., 2020).

This study aimed to identify foods with function claims with systematic literature reviews conducted in Japan. We chose reviews that used “stool frequency” as a clinical evaluation outcome to support scientific evidence for the health claim of “improvement of the intestinal environment.” Our review could provide evidence for the importance of standardized guidelines, thereby bridging the regulatory gap and promoting international harmonization regarding foods with health claims.

## 2. Materials and methods

### 2.1. Target health claims and material selection

Current guidelines stipulate that food with specified health uses can only be validated through clinical trials and not through systematic literature reviews. However, application dossiers for food with specified health uses are kept confidential. We therefore targeted foods with function claims with systematic literature reviews that offer the highest level of general scientific evidence.

Foods with function claims were selected based on scientific evidence of systematic literature reviews in the submitted dossiers for the health claim of “improvement of the intestinal environment.” Consumer Affairs Agency databases were accessed from April 1, 2016 to March 31, 2021 for this purpose. This regulatory system for foods with function claims was introduced on April 1, 2015. This was considered a suitable starting point for our review because it provided enough time from the point when sufficient notification records begin to be confirmed. In Japan, scientific evidence for foods with function claims, including their systematic literature reviews, are publicly available on the Consumer Affairs Agency’s website (<https://www.fld.caa.go.jp/caaks/cssc01/>). All study designs within systematic literature reviews for this review could therefore be identified.

### 2.2. Data collection

We extracted items based on data obtained from the submitted application dossiers, such as submission numbers, submission fiscal years, health claims, number of included articles, food forms, search criteria for literature reviews (i.e., target systematic reviews, number of search databases, target ages, and target populations), and the clinical evaluation outcomes in a systematic literature review.

### 2.3. Study outcomes

The main outcome of our study is the proportion of foods with function claims that used “stool frequency” as a clinical evaluation outcome in systematic literature reviews. A secondary outcome is the factors that led to the use of “stool frequency” in clinical evaluations.

### 2.4. Statistical analysis

We calculated the proportion of foods with function claims that used “stool frequency” as a clinical evaluation outcome in systematic literature reviews. We also calculated the frequencies and proportions for categorical variables and summary statistics for continuous variables. We stratified the differences between the two groups (i.e., stool frequency vs. no stool frequency as a clinical evaluation outcome in the systematic literature reviews), based on fiscal year of submission, number of articles included, food forms, and search criteria (i.e., target

of systematic literature reviews, number of search databases, target age, target population). We used chi-square tests or Fisher’s exact tests for categorical variables and Mann–Whitney *U* test for continuous variables. We used a two-sided alpha level of  $p < 0.05$  for statistical significance. To identify the factors that led to “stool frequency”, we performed multivariate logistic regression analysis (simultaneous forced entry) to calculate odds ratios (ORs) and 95% confidence interval (95% CI). We fixed three *a priori* criteria in the logistic model: lower age limit, target population, and supplement shape. We used the statistical application software EZR (Kanda, 2013), a modified version of R Commander that adds statistical functions frequently used in biostatistics, for analyses.

### 2.5. Ethics

As this was a retrospective study that used official materials available in the public domain (i.e., published on the websites of the Consumer Affairs Agency in Japan), none of the data included identifiable persons. An ethical review was therefore not required under local ethical guidelines.

## 3. Results

Among foods with function claims with systematic literature reviews, we identified 3,509 products between the fiscal years 2016 and 2020. Among these, 427 (12.2%) foods were evaluated for the health claim of “improvement of the intestinal environment,” and 3,019 foods with other target health claims were excluded. Of the 427 foods with function claims, 89.9% (384/427) used “stool frequency” as a clinical evaluation outcome (Fig. 1).

### 3.1. Characteristics of foods with function claims of stool frequency as clinical evaluation outcome

The proportion of foods with function claims submitted in the fiscal year 2020 was 31.5% for stool frequency and 27.9% for no stool frequency ( $p = 0.350$ ). The median number of articles included for “stool frequency” was higher than that of no stool frequency (7 and 3, respectively;  $p < 0.001$ ). The proportion of target populations, both healthy and with a tendency for constipation, was 55.2% for stool frequency and 9.3% for no stool frequency ( $p < 0.001$ ) (Table 1).

### 3.2. Factors leading to the use of stool frequency as clinical evaluation outcome

Correlation analysis among independent variables did not suggest any multicollinearity. Logistic regression analysis results for the identification of factors are shown in Table 2. The significant factors identified were as follows: target populations, both healthy and with a tendency for constipation (OR: 25.50; 95% confidence interval [8.38, 77.90]), and supplement shape (OR: 4.62; 95% confidence interval [1.90, 11.20]).

## 4. Discussion

This study examined the current status of health-related outcome assessments of improvement in the intestinal health claim category, which considers the regulatory gap between the EU and Japan. This health claim category has gained attention in recent years among consumers. According to a health food market survey (Yano Research Institute Ltd, 2021), “abdominal circumference” is the foremost concern for 40% and “bowel function” for 30% for consumers below 50 years. As the clear relationship between the intestinal environment and immunity has been recognized, the interest in the “bowel function” category among consumers has also increased. This may explain why the number of notifications in this category has been increasing, especially in the fiscal year 2020.

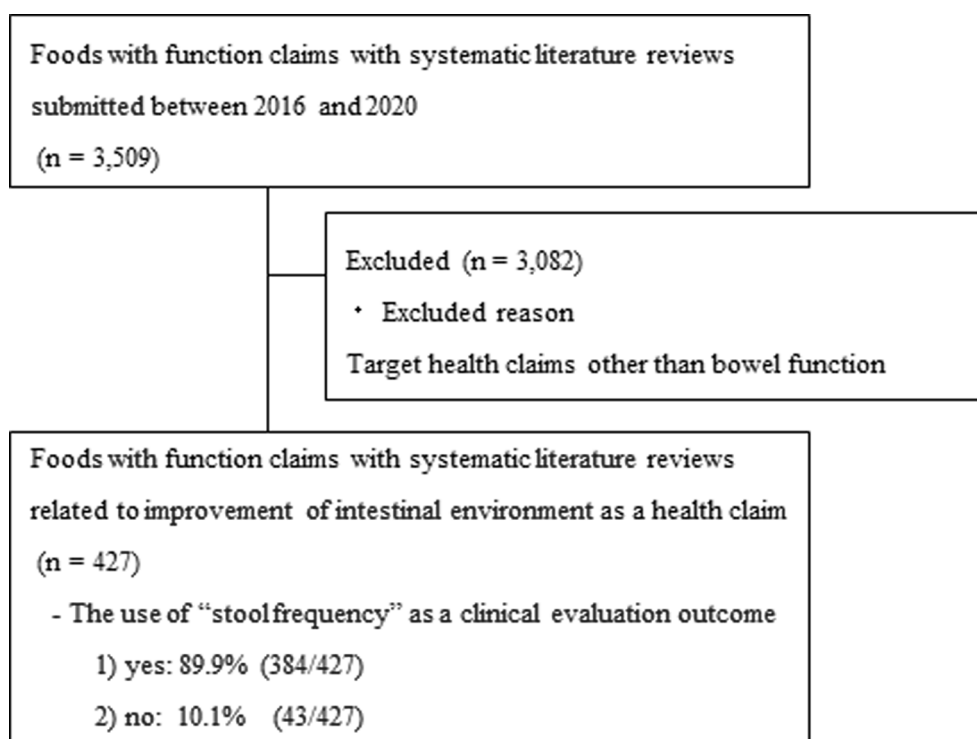


Fig. 1. Flow of the selection of foods of functional claims with systematic literature reviews for improvement of the intestinal health claim category.

#### 4.1. Status of stool frequency as a clinical evaluation outcome for improvement of the intestinal health claim category

Among the foods with function claims investigated in this study, 89.9% were evaluated on “stool frequency”. In Japan, the first clinical evaluation guideline was published in 2005, but the implementation method was not described or clarified for clinical trials in the improvement of the intestinal health claim category at that time. The updated guidance for scientific evidence in human subjects research in Japan suggests clinical evaluation outcomes (Consumer Affairs Agency, 2018) such as “stool frequency” for improvement of the intestinal health claim category (Table 3). The existence of internationally harmonized evaluation standard guidelines based on scientific evidence may have minimized the evaluation differences globally. However, it was revealed that the factor for the use of “stool frequency” was the supplement shape as food form. This suggests a tendency to avoid using the word “stool” in a health claim on food labeling for ordinary food forms such as yogurt. Our finding suggests that not only supplement but also another types of food shape could be useful for ensuring the real benefit for consumers by incorporating the health-related outcome.

#### 4.2. Perspectives on international harmonization of the evaluation guideline

Health-related outcomes as subjective items are important within clinical evaluation systems, as the final goals and clinical significance of evaluation outcomes in research should directly incorporate data from the affected individuals (Morishima, 2019). The daily experience of health effects is an important for efficacy evaluations considering the clinical benefit of functional foods promoting overall health (Lombardi et al., 2021; van Buul and Brouns, 2015; Wills et al., 2012). The balance between scientific evidence and meaningful experiential learning in information presented to consumers should be based on scientifically substantiated research (de Boer, 2021; Hung et al., 2019; Williams, 2005). Two outcomes described in EU guidelines, namely “sensation of complete/incomplete evacuation” and “transit time” were not included

in the Japanese guidelines (Table 3). This reflects policy differences between the two countries and raises the question of whether a final evaluation with direct benefit as a health-related outcome is required. Therefore, differences regarding the evaluation of health claims in the policies of the two countries can be minimized by continuing to examine the regulatory gap overseas. This perspective is important for stimulating international trade.

#### 5. Limitations

This was the first to identify the current status of clinical evaluation outcomes considering previous food regulatory gaps between Japan and the EU. Despite its substantial strengths, our investigation has one significant limitation. We only examined health claims using scientific evidence based on systematic literature reviews that evaluated improvement in the intestinal health claim category. Future research should also examine other health claims to elucidate the status of gaps in clinical evaluation and aim to improve harmonization by considering each regulatory system at the global level. They should also investigate other health claims from the perspective of international harmonization.

#### 6. Conclusion

We found that 89.9% of foods with function claim based on systematic literature reviews conducted in Japan evaluated “stool frequency” as a clinical evaluation outcome for improvement of the intestinal health claim category. We also clarified that the clinical evaluation outcomes used in the systematic literature reviews of foods with function claims conducted in Japan was consistent with those of studies conducted overseas.

##### Declaration of Competing Interest.

Dr. Hiroshi Yoshida received honoraria for speaking activities from Bayer Yakuhin, Ltd., Denka Company Limited, Kowa Company, Ltd., Mochida Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited., and an unrestricted research fund from Tosoh Corporation and Roche. The other two authors declare no conflicts of interest associated

**Table 1**

Characteristics of foods for systematic literature reviews supporting scientific evidence for improvement of the intestinal health claim category.

Items		Stool frequency as a clinical evaluation outcome				<i>p-value</i>
		Yes		No		
		n = 384		n = 43		
		n	%	n	%	
Submission fiscal year	2016	72	18.8	5	11.6	0.350
	2017	58	15.1	11	25.6	
	2018	64	16.7	9	20.9	
	2019	69	18.0	6	14.0	
	2020	121	31.5	12	27.9	
Number of included articles for systematic literature reviews						
	Median (min–max)	7	(1–34)	3	(1–18)	<0.01
<b>【Food form】</b>						
Supplement shape	Yes	118	30.7	8	18.6	0.114
	No	266	69.3	35	81.4	
<b>【Search criteria for systematic literature reviews】</b>						
Target systematic reviews	Final product	0	0	0	0	–
	Functional substance	384	100	43	100	
Number of search databases						
	Median (min–max)	4	(2–20)	4	(2–9)	0.715
Lower age limit						
	18 years	81	21.1	7	16.3	0.151
	20 years	285	74.2	31	72.1	
	Other	18	4.7	5	11.6	
Target population						
	Healthy people	172	44.8	39	90.7	<0.01
	Both healthy and tendency for constipation	212	55.2	4	9.3	

SD: standard deviation.

**Table 2**

Factors related to the use of stool frequency as a clinical evaluation outcome in the systematic literature reviews.

Items		Adjusted OR	95% CI
【Search criteria for systematic literature reviews】			
Lower age limit	18 years	(reference)	
	20 years	0.21	0.08–0.54
	Other	0.47	0.13–1.66
Target population			
	Healthy people	(reference)	
	Both healthy and tendency for constipation	25.50	8.38–77.90
【Food form】			
Supplement shape	No	(reference)	
	Yes	4.62	1.90–11.20

OR: odds ratio; CI: confidence interval.

**Table 3**

Outcomes in clinical evaluation as supporting scientific evidence for improvement of the intestinal health claim category specified in Japanese and EU guidelines.

Outcomes in clinical evaluation Policy	Japan*	EU**
	Pre-set appropriate evaluation outcomes	Outcomes that can provide information on bowel function and the mechanism of functional ingredient
(Example)		
Stool frequency	●	●
Fecal bulk	●	●
Fecal condition (stool consistency)	●	●
Fecal bacteria	●	
Sensation of complete/incomplete evacuation		●
Transit time		●

\* “Food for specified health uses guideline” (Consumer Affairs Agency, 2018).

\*\* “Guidance on the scientific requirements for health claims related to the immune system, the gastrointestinal tract and defense against pathogenic microorganisms” (EFSA Panel on Dietetic Products and Allergies, 2016).

with this manuscript.

#### Ethics statement.

As this was a retrospective study that used official materials available in the public domain (i.e., published on the websites of the Consumer Affairs Agency in Japan), none of the data included identifiable persons. Accordingly, an ethical review was not required under local ethical guidelines.

#### Author statement.

N.T., H.Y., and T.C. were involved in the study design and data interpretation. N.T. conducted the data analysis. All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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