Journal of Clinical Epidemiology 169 (2024) 111302

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Misleading presentations in functional food trials led by contract research organizations were frequently observed in Japan: meta-epidemiological study

Hidehiro Someko[a,b,*], Norio Yamamoto[b,c], Tatsuya Ito[d], Tomoharu Suzuki[e], Takahiro Tsuge[b,c,f], Hajime Yabuzaki[g], Eisuke Dohi[h], Yuki Kataoka[b,i,j,k]

[a]*Department of General Internal Medicine, Asahi General Hospital, I-1326, Asahi, Chiba, 289-2511, Japan*
[b]*Scientific Research WorkS Peer Support Group (SRWS-PSG), Osaka, Japan*
[c]*Department of Epidemiology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, 700-8558, Japan*
[d]*Department of Regulatory Science and Pharmaceutical Informatics, School of Pharmaceutical Sciences, Wakayama Medical University, Shichibancho 25-1, Wakayama, 640-8156, Japan*
[e]*Department of Hospital Medicine, Urasoe General Hospital, Maeda 1-56-1, Urasoe, Okinawa, 901-2102, Japan*
[f]*Department of Rehabilitation, Kurashiki Medical Center, 250 Bakuro, Kurashiki, Okayama, 710-8522, Japan*
[g]*Department of Neurological Surgery, Koga Community Hospital, Daikakuji 2-30-1, Yaizu, Shizuoka, 425-0088, Japan*
[h]*Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Ogawahigashi-cho 4-1-1, Kodaira, Tokyo, 187-8502, Japan*
[i]*Department of Internal Medicine, Kyoto Min-iren Asukai Hospital, Tanaka Asukai-cho 89, Kyoto, 606-8226, Japan*
[j]*Section of Clinical Epidemiology, Department of Community Medicine, Kyoto University Graduate School of Medicine, Shogoin Kawara-cho 54, Kyoto, 606-8507, Japan*
[k]*Department of Healthcare Epidemiology, Kyoto University Graduate School of Medicine/School of Public Health, Yoshida Konoe-cho, Kyoto, 606-8501, Japan*

Accepted 19 February 2024; Published online 28 February 2024

Abstract

Objectives: The functional food market has experienced significant growth, leading to an uptick in clinical trials conducted by contract research organizations (CROs). Research focusing on CRO-managed trials and the communication of trial outcomes to the consumer market remains underexplored. This metaepidemiological study aims to evaluate the quality of randomized controlled trials (RCTs) facilitated by prominent CROs in Japan and to examine the quality of the representations used to convey their results to consumers.

Study Design and Setting: This study focused on the food trials that were registered in the University Hospital Medical Information Network Clinical Trial Registry or the International Clinical Trials Registry Platform by the top 5 CROs. Press releases of study results or advertisements of food products based on the study results were identified by conducting a Google search. The risk of bias in the RCT publications was independently assessed by 2 reviewers, who also evaluated the presence of ''spin'' in the abstracts and full texts. An assessment of ''spin'' in press releases/advertisements was undertaken.

Results: A total of 76 RCT registrations, 32 RCT publications, and 11 press releases/advertisements were included. Approximately 72% of the RCT publications exhibited a high risk of bias due to selective outcome reporting. ''Spin'' was present in the results of the abstract (72%), abstract conclusion (81%), full-text results (44%), and full-text conclusion (84%). ''Spin'' appeared in 73% of press releases/advertisements due to the selective outcome reporting.

Conclusion: Functional food presentations in Japan frequently contained ''spin.'' The Japanese government should more rigorously check whether food manufacturers report outcomes selectively.

Keywords:: Nutritional research; Functional foods; Contract research organization; Selective outcome reporting; Misleading presentations; Meta-epidemiological study

Funding: There was no funding source for this study.

* Corresponding author. Department of General Internal Medicine, Asahi General Hospital, Scientific Research WorkS Peer Support Group (SRWS-PSG), I-1326 Asahi, Chiba, 289-2511, Osaka, Japan.

E-mail address: hidehirosomeko@gmail.com (H. Someko).

https://doi.org/10.1016/j.jclinepi.2024.111302

Plain language summary

This study looked into how well contract research organizations in Japan manage clinical trials for functional foods, which are foods that have health benefits beyond basic nutrition, and how the results of these trials are communicated to consumers. We focused on trials registered by the top five contract research organizations in two major clinical trial registries and analyzed the press releases and advertisements for the food products based on these trials. We found that many of the trial reports had a high risk of bias, mainly because they only reported selected outcomes that were favorable. Furthermore, our study found that both the scientific publications and the promotional materials often included "spin," meaning they were presented in a way that made the results look better than they actually were. Our study suggested that there should be stricter oversight in Japan to ensure that the results of functional food trials are reported more accurately and transparently to consumers.

1. Introduction

Functional foods are typically defined as foods that offer benefits that extend beyond their basic nutritional value [1]. Although the concept of functional foods may seem contemporary, ancient Hindu texts from India and traditional Chinese medicine have long recognized the idea of foods that promote health and wellbeing [2]. Despite historical references to the health benefits of certain foods, no country had established a formal regulatory system for functional foods until Japan instituted one in 1991, in response to the rising healthcare expenditures. Following Japan's lead, the concept of functional foods gained traction in Northern Europe, North America, and East Asia—regions populated by affluent consumers [3,4]. As of 2021, the functional food market was valued at USD 280 billion, with projections indicating a compound annual growth rate of 8.5% from 2022 to 2029 [5].

Japan's unique government system approves health claims for specific foods. The 1991 "Foods for Specified Health Use" (FOSHU) policy permits such claims for functional foods sanctioned by the Minister of Health and Welfare. In 2015, Japan launched the "foods with functional claims" (FFC) system to widen consumer choices and boost entrepreneurial involvement [6]. The model, mirroring the United States' approach to dietary supplements where health claims are not individually government-approved, places responsibility for health assertion accuracy and reliability on food manufacturers. This change aligns with Japan's broader economic regulatory reform. Since its start, FOSHU registrations with the Consumer Affairs Agency have gradually decreased to 1,054 as of October 2, 2023 [3,7]. By contrast, the number of products registered as FFC has surged, reaching 7565 items by October 13, 2023 [8].

To evaluate the effectiveness of functional foods like FOSHU and FFC, randomized controlled trials (RCTs) are common, yet in Japan, FFC's benefits are often confirmed through systematic reviews. These trials are frequently executed by contract research organizations (CROs) and private companies, especially for stakeholders in biotechnology and pharmaceutical sectors [9]. With the FFC system's introduction in Japan, the number of food RCTs by CROs has risen. The market value for such services was $73.38 billion in 2022, with a forecast to reach $163.48 billion by 2029, growing annually at 12.1% [10].

Despite the call for rigorous evidence, nutritional research has historically faced significant skepticism [11]. Previous metaepidemiological studies conducted outside Japan have indicated a potential bias owing to the use of sponsored products in nutritional trials, with the reported research quality being low [12,13]. A previous metaepidemiological study highlighted discrepancies between trial protocols and articles related to FFC [14]. Another study pointed to a high risk of bias (RoB) in FFC clinical trials [15]. These findings are as expected, considering that the oversight of the FFC system is considered as a form of deregulation. However, these studies have not specifically investigated the role of CROs. Moreover, the marketing strategies for these products have rarely been examined.

This metaepidemiological study aims to assess the overall quality of RCTs conducted by major CROs in Japan and how their results are communicated to consumers.

2. Methods

2.1. Study design and protocol

This is a metaepidemiological study. Our protocol was partially based on the guidelines for reporting metaepidemiological studies (Supplementary table 1) [16]. This protocol is publicly accessible on the OSF.iO website (https://osf.io/n3aqw). Our study targeted RCT registrations by the top 5 CROs in Japan, published RCTs, and press releases or advertisements of the products.

2.2. Top 5 CROs in Japan

CRO was defined as an organization that conducts intervention trials based on sponsor requests. We focused on the RCT registrations in the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) [17] and the International Clinical Trials Registry Platform (ICTRP) [18], which involved CROs in Japan. Considering

What is new?

Key finding

- Misleading presentations of functional food trials led by contract research organizations in Japan were common.

What this adds to what was known?

- While it is widely recognized that nutritional research led by industry often exhibits a high risk of bias and ''spin'' due to selective outcome reporting, the assessment of how these results are communicated to consumers has been limited.
- Our study revealed that this selective outcome reporting is directly transmitted to consumers.

What is the implication and what should change now?

- The Japanese government and Consumer Affairs Agency should verify if food manufacturers are selectively reporting outcomes.

that the Japanese Consumer Affairs Agency mandates the registration of dietary supplement trials in either the UMIN-CTR or the ICTRP [19], a search of these two databases should suffice to capture all relevant RCT registrations involving CROs in Japan, although 98% of the studies are registered in the UMIN-CTR [14].

As it was difficult to determine all CROs in Japan, we decided to focus on the top 5 CROs in Japan, defined in descending order of the number of RCTs on food interventions in Japan. We employed the following procedure to identify the top 5 CROs. On June 1, 2023, we used a comma-separated value (CSV) file downloaded from the UMIN-CTR that included all (50,787) registered trials in the database from June 2, 2005. We identified the top 5 CROs by counting the number of RCT registrations across all institutions (16,315) that registered trials in the UMIN-CTR and ranked them in descending order. The top 5 CROs were Orthomedico Inc (324), TTC Company Limited (217), CPCC Company Limited (158), KSO Corporation (154), and Japan Clinical Trial Association (152).

2.3. Identification of the RCT registrations

Our inclusion criteria for RCT registrations in the UMIN-CTR or ICTRP were as follows. We restricted the RCT completion date to at least 1 year before minimizing the likelihood of unpublished studies due to the completion of recent trials.

(i) RCTs on food interventions.
(ii) RCTs completed before May 31, 2022.
(iii) RCTs registered by the top 5 CROs in Japan (Orthomedico, Inc, TTC Company Limited, CPCC Company Limited, KSO Corporation, and Japan Clinical Trial Association).

We did not apply any exclusion criteria. Initially, we downloaded the complete list of RCT registrations for the UMIN-CTR as a CSV file. Next, we identified trials involving the top 5 CROs by searching the ''Institution'' column, which indicates the institution that performed the RCT, of the CSV file using each organization's name as keywords. Similarly, we performed keyword searches to find the names of these organizations in the ICTRP and downloaded the associated RCT registrations as a CSV file. By consolidating the CSV files from the UMIN-CTR and ICTRP and removing any duplicates, we compiled a comprehensive list of RCT registrations involving these organizations. We then refined the CSV file according to the study design (RCT) and completion date (before May 31, 2022). Through this process, we meticulously compiled a comprehensive list of RCT registrations associated with the target organizations. This CSV file contained all information detailed in the tabular view of the UMIN-CTR and ICTRP websites, including the trial title; study identifier; planned participant count; inclusion/exclusion criteria; primary and secondary outcomes; funding, registration, and institutional review board approval dates; and the start and end dates of the trial and participant follow-up.

2.4. Identification of publications of RCTs

We randomly selected 100 RCT registrations from the CSV file created using the aforementioned method and gathered the identifiers of these selected RCT registrations. Two authors (H.S. and N.Y.) independently excluded RCT registrations without food interventions. Subsequently, we obtained bibliographic information on published RCTs from the archives section (if available) of each organization's website. We also obtained bibliographic information on the published RCTs from the CSV file created using the method described above. If we were unable to find any bibliographic information about the publication in either way, one of the authors (H.S.) manually searched Google Scholar (https://scholar.google.com/) using trial identifiers and ascertained whether published articles corresponding to these RCT registrations existed in the first 10 search results. Another author confirmed the results of this search. If such articles were found, they were included as published RCTs. Disagreements were resolved by a third reviewer.

2.5. Identification of press releases or advertisements of merchandise

Additionally, H.S. manually searched Google (https://www.google.com/) using the titles of published RCTs to determine the existence of any merchandise-based press releases related to these studies in the first 10 search results.

Another author confirmed the results of this search. When a press release was found, it was included as such. In the absence of press releases, we searched for merchandise advertisements in the first 10 Google search results using the titles of published RCTs. Any disagreements (eg, whether the identified press releases or advertisements are truly related to the RCT publications) were addressed through discussions among the reviewers. If a consensus was not reached, a third reviewer was consulted to resolve the dispute.

2.6. Data extraction and assessment

Two independent reviewers extracted the following information on the RCT registrations from the CSV file.

1. Design (parallel-group, multiple-group, crossover, cluster RCT, or others): A multiple-group RCT was defined as a trial with three or more arms.
2. Number of primary outcomes: Outcomes that appeared in the primary outcome field of the CSV file were considered primary outcomes, and their total numbers were manually tallied.
3. Number of secondary outcomes: Outcomes that appeared in the secondary outcome field of the CSV file were considered secondary outcomes, and their total numbers were manually tallied.
4. Planned maximum timing of outcome measurement.
5. Funding source, classified as follows:
   - Industry: Funding is solely from the industry or from both the industry and nonindustry sources.
   - Nonindustry: Funding originates from governments and other academic or nonprofit organizations.
   - None: Eligible articles received no funding.

   Unclear: No information about funding is available.

We collected information on the title and the number of planned participants in the RCT from the CSV file. We examined the publication status, as outlined in the previous section. We extracted the following information from the RCT publications identified in the aforementioned manner:

1. The number of reported primary outcomes: Outcomes explicitly described as primary outcomes were regarded as such. If the article did not clearly define the primary outcome, it was considered primary.
2. The number of reported secondary outcomes: outcomes described as secondary were considered as such.
3. The funding source described in the full text.
4. Conflicts of interest described in the full text (present, nothing, or not reported).
5. The maximum duration of outcome measurement.
6. The number of participants.

Two authors independently assessed the RoB for the first registered primary outcome using the Cochrane Risk of Bias two tool [20]. If the results of the first registered primary outcome were not available, the first outcome described in the abstract was selected. Upon assessing the RoB, we did not directly reflect the presence of the conflicts of interests in the RCT; instead, we considered the presence of conflicts of interests. We quantified the effects of intention-to-treat analysis. These authors also independently evaluated the presence of ‘‘spin’’ in the results of the abstract, the abstract’s conclusion, the full-text results, and the conclusion of the full text. Furthermore, merchandise-based press releases and advertisements were investigated in the aforementioned manner.

‘‘Spin,’’ similarly defined as in previous studies for RCTs with no significant results in the primary outcome [21], refers to reporting practices that distort the interpretation of results, thus misleading conclusions that suggest a more favorable outcome than that substantiated by the data. If the results of the abstract omitted any primary outcomes detailed in the full text or exclusively reported statistically significant secondary outcomes or subgroup analyses, then the abstract’s results were considered to exhibit ‘‘spin’’ [21]. Similarly, if the conclusions drawn in the abstract relied solely on statistically significant findings or disregarded statistically nonsignificant primary outcomes, this was also deemed to represent ‘‘spin.’’ In the full text, if the results focused exclusively on statistically significant outcomes or visualized only these results, such presentation was categorized as ‘‘spin.’’ The assessment of ‘‘spin’’ in the full text’s conclusion was conducted in a manner analogous to that of the conclusion of the abstracts. Similarly, if the conclusions drawn in the abstract relied solely on statistically significant findings or disregarded statistically nonsignificant primary outcomes, this was also deemed to represent ‘‘spin.’’ In the full text, if the results focused exclusively on statistically significant outcomes or visualized only these results, such presentation was categorized as ‘‘spin.’’ The assessment of ‘‘spin’’ in the full text’s conclusion was conducted in a manner analogous to that of the conclusion of the abstracts.

Two independent authors determined whether the published RCT can be regarded as ‘‘specified clinical trials’’ as defined in paragraph (2) of Article 2 of the Clinical Trial Act. An RCT was judged to be a specified clinical trial if the intervention included unapproved pharmaceuticals. Functional foods can be regarded as unapproved pharmaceuticals if they are intended for use in the diagnosis, treatment, or prevention of disease in humans or animals, according to paragraph (2) of Article 2 of the Act on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals and Medical Devices [22]. Throughout the above procedure for RCT publications, any disagreements were addressed through discussions among the reviewers.

Two independent authors evaluated the presence of ‘‘spin’’ in the identified press releases or merchandise

advertisements. If these press releases or merchandise advertisements were based on statistically significant results only or failed to report the nonstatistically significant primary outcomes reported in the RCT publications, these press releases or merchandise advertisements were considered to have ''spin''. Additionally, the authors determined whether the claim of the merchandise was against Article 5 of the Unjustifiable Premiums and Misleading Representations Act [23]. Any disagreements were addressed through discussions among the reviewers.

2.7. Statistical analysis

Given the absence of an a priori hypothesis, we did not perform any sample size calculations. Continuous variables were reported as medians (interquartile ranges [IQRs]) and dichotomous variables as *n* (%), unless otherwise stated. All statistical analyses were performed using R 4.3.0, with the gtsummary package 1.7.2 [24]. The RoB summary and graphs were created using robvis package 0.3.0 [25].

2.8. Differences between the protocol and the actual study

To identify RCT publications, press releases, and advertisements, we initially intended to scrape Google/Google Scholar results, but we manually searched these platforms instead. We selected the robvis package to create RoB graphs and summaries. For the post hoc analysis, we calculated the ratio of the number of primary outcomes in the full text to the number of registered primary outcomes to highlight the differences in the number of outcomes in the actual RCTs and protocols. Additionally, similar to the method described in 2.6, we extracted additional RCT

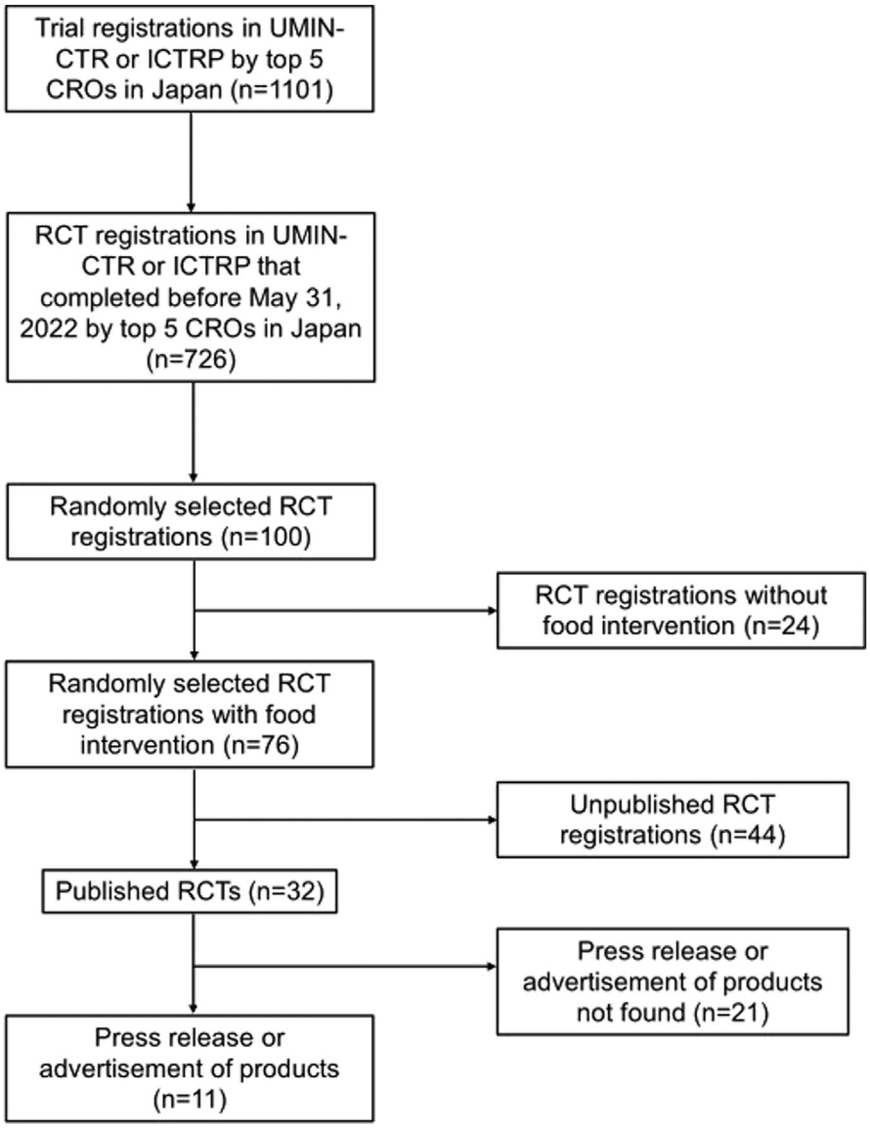

Figure 1. Flowchart of study selection. Abbreviations: UMIN-CTR, University Hospital Medical Network clinical trial registry; ICTRP, International Clinical Trials Registry Platform; CRO, Clinical Research Organization; RCT, randomized controlled trial.

Table 1. Characteristics of the included clinical trial registries

Characteristic	N = 76[a]
Number of primary outcomes	1 (1, 3)
Number of secondary outcomes	3 (1, 6)
Number of planned participants	40 (30, 60)
Maximum follow-up period (d)	56 (14, 84)
Not reported	51 (67%)
Funding Source	
Industry	73 (96%)
Nonindustry	2 (2.6%)
None	1 (1.3%)
Design	
Crossover	19 (25%)
Parallel	57 (75%)
Number of arms	
2	62 (82%)
3	11 (14%)
4	2 (2.6%)
6	1 (1.3%)

[a] Median (IQR); *n* (%).

Table 2. Characteristics of the included randomized control trials

Characteristic	N = 32[a]
Number of primary outcomes	4 (1, 12)
Number of secondary outcomes	6 (2, 14)
Number of participants	44 (36, 61)
Ratio of the number of primary outcomes in the full text to the number of registered primary outcomes	2 (1,3.3)
Maximum follow-up period (days)	56 (28, 84)
Not reported	1 (3.1%)
Funding Source	
Industry	31 (97%)
Unclear	1 (3.1%)
Conflicts of interests	
Present	29 (91%)
Nothing	2 (6.3%)
Not reported	1 (3.1%)
''Spin'' in the abstract results	
Yes	23 (72%)
No	7 (22%)
Not applicable	2 (6.3%)
''Spin'' in the abstract conclusion	
Yes	26 (81%)
No	4 (13%)
Not applicable	2 (6.3%)
''Spin'' in the full-text results	14 (44%)
''Spin'' in the full-text conclusion	27 (84%)
Specified clinical trials	28 (88%)

[a] Median (IQR); *n* (%).

registrations of the top 6−10 CROs (TES Holdings Co, Ltd,142; HUMA R&D CORP, 78; Soiken Inc,71; Healthcare Systems Co, Ltd, 69; imeQ RD Inc, 54). From among these 414 RCT registrations, we randomly selected 50 and assessed the RoB in the selection of the reported results and the presence of spin in RCT publications and press releases/advertisements.

3. Results

We identified 726 RCT registrations completed by the top 5 CROs until May 31, 2022. Of the 100 randomly selected RCT registrations by the top 5 CROs, 76 were related to food. Of them, 32 resulted in RCT publications [26−57], 11 of which were disseminated as press releases/advertisements [26,28,36,39,44−46,49,51,52,57] (Fig 1).

With respect to the RCT registration characteristics, the median number of primary outcomes was one (IQR: 1−3) (Table 1). The planned median number of participants was 40 (IQR: 30−60). The median maximum follow-up period was 56 days (IQR: 14−84 days), which was not specified in 67% of the trials. The industry provided funding for 96% of the RCTs.

For RCT publication characteristics, the median primary outcome count was 4 (IQR: 1−12) (Table 2). The median ratio of the primary outcomes in the full text to the registered outcomes was 2 (IQR: 1−3.3). The median planned participant count was 44 (IQR: 36−61). The median maximum follow-up period was 56 days (IQR: 14−84 days), and 3.1% of the publications did not specify this duration. Industry funded 97% of the RCTs. Approximately 72% of the overall RoB of the RCT publications was high owing to the high RoB in the selection of the reported results domains (Figs 2 and 3). We observed a ''spin'' in the results of the abstract (72%), abstract conclusion (81%), full-text results (44%), and full-text conclusion (84%). Approximately 88% of the studies were categorized as clinical trials in accordance with paragraph 2 of Article 2 of the Clinical Trial Act.

We identified three press releases and eight advertisements (Table 3, Supplementary table 2). ''Spin'' appeared in 8 (73%) of them. Nine (82%) displayed misleading presentations based on Article 5 of the Unjustifiable Premiums and Misleading Representations Act. One advertisement (https://www.dmjegao.com/contents/ingredients/150) was based on the statistically significant result of the primary outcome, which had been predetermined in the registry; however, it featured an illustration suggesting an improvement in gait function, a parameter not examined in the trial. Consequently, this advertisement was deemed a misleading representation, although it did not qualify as ''spin.''

Our post hoc analyses of the RCT registrations by the top 6−10 CROs identified 20 RCT publications [58−77]

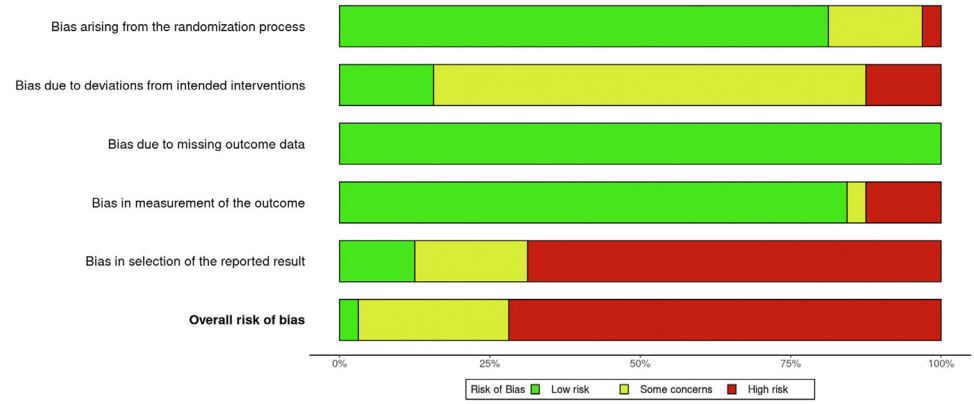

Figure 2. Risk of bias (RoB) graph of the included studies. The RoB for the first registered primary outcome was assessed using the Cochrane Risk of Bias two tool. As for bias due to deviation from intended interventions, assignment to intervention (''intention-to-treat effect'') was assessed. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

and 12 press releases/advertisements from 50 randomly selected RCT registrations, of which two were not food trials and thus excluded. RoB in the selection of the reported result was high in 14 (70%), with some concerns in 4 (20%), and low in 2 (10%). Spin in abstract results, conclusions, full-text results, and conclusions were 17 (85%), 19 (95%), 5 (25%), and 20 (100%), respectively. Spin was observed in all press releases/advertisements (Supplementary table 3), and thus, all were considered misleading representations.

4. Discussion

Our analysis included 76 RCT registries, 32 RCT publications, and 11 press releases/advertisements on functional foods. A high RoB from selective outcome reporting was evident in 72% of RCT publications, with the primary outcome ratio in full texts vs registered outcomes averaging 2. About 80% of RCT abstracts, full texts, and conclusions exhibited ''spin,'' similar to 73% in advertisements/press releases. This aligns with prior studies indicating widespread selective outcome reporting in Japanese FFC-related RCTs [14,15]. Metaepidemiological studies conducted in various countries have highlighted the problem of selective outcome reporting in nutritional research [13,78,79]. Hence, nutritional researchers should strive to enhance the quality of their studies and reporting.

However, relying solely on researcher autonomy might not adequately address the issue of selective outcome reporting. Indeed, no improvement was observed in study quality, even after the assessment of verification reports by the Consumer Affairs Agency [16]. Potential conflicts of interest between nutrition researchers and food manufacturers, as our study shows, may explain this. To prevent selective outcome reporting, it is crucial to prospectively register trials [80]. Nevertheless, all RCT publications included in our study were prospectively registered. Nutritional interventions usually pose fewer risks than pharmaceuticals do, yet 88% of studies were specified clinical trials. Although functional foods are not designed for diagnosing, treating, or preventing disease, these trials indicate potential disease benefits. Hence, tighter nutritional research regulations are necessary. For instance, mandating the complete specification of the primary outcome, including its domain, measurement, metric, method of aggregation, and timeframe [81], could decrease the prevalence of selective outcome reporting. UMIN-CTR, one of the registries required by the Japanese government for food trial registration, encourages researchers to include the timeframe of outcome measurements but does not enforce it, nor does it require details on other outcome elements [82]. Therefore, imposing a requirement for comprehensive outcome specification in UMIN-CTR could diminish selective outcome reporting. ClinicalTrials.gov, a more widely used registry for clinical trials, mandates the explicit declaration of outcome timeframes at the time of registration. Transitioning to ClinicalTrials.gov as the required registry may aid in reducing selective reporting; however, it should be noted that even this registry does not necessitate detailed specifications of outcome metrics and aggregation methods [83]. Thus, merely changing the registry will not afford a definitive solution. Considering that most food trials in Japan are registered with UMIN-CTR, which does not require detailed disclosure of the primary outcome, this remains an area for improvement. Additionally, it is essential to acknowledge the importance of comprehensively specifying outcomes among food researchers at the time of registration.

An additional strategy to reduce selective outcome reporting involves establishing an unbiased organization to conduct food studies. Indeed, the majority of studies included in our study were funded by food manufacturers, thereby presenting potential conflicts of interest. To maintain impartiality, unbiased organizations are necessary with neutral funding sources, such as governments or public

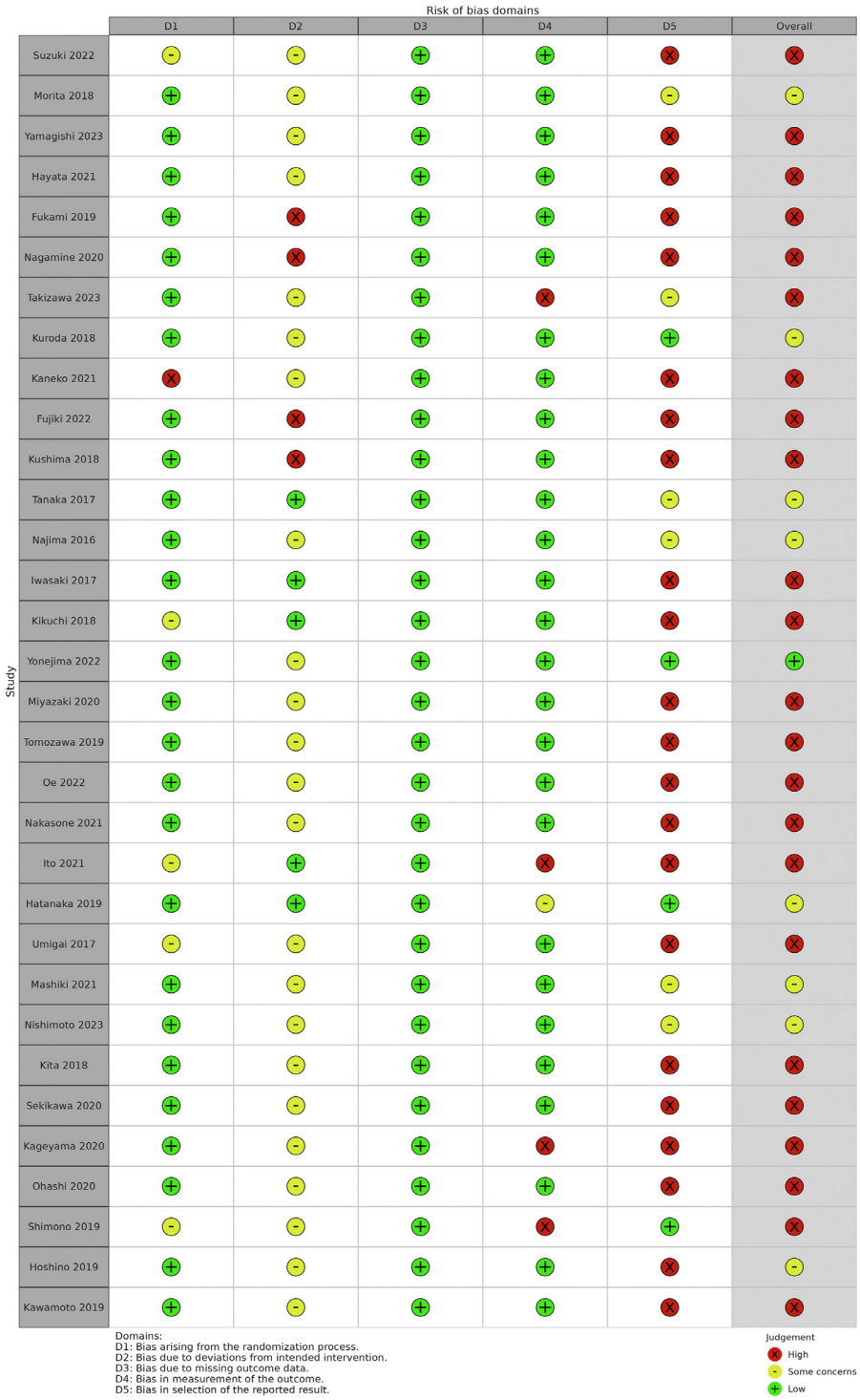

Figure 3. Risk of bias summary of the included studies. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

donations, involving various stakeholders like clinicians and consumer advocates and implementing external monitoring. Neutral funding may be insufficient to conduct food trials; however, conducting systematic reviews, which are currently accepted by the Japanese government for FFC registration, could present an alternative solution. Although certain FFCs are registered based on systematic reviews, their quality is generally low [84]. This issue, in part, arises because some reviews are conducted by the food manufacturers themselves. High-quality systematic reviews

Table 3. Characteristics of included press releases or advertisements of the products

Type	URLs	Cited article	"Spin"	Misleading representation
Advertisement	https://health.kirin.co.jp/kw/eyecare.html	Morita 2018 [57]	Present	Present
Advertisement	https://genryou.toyoshinyaku.co.jp/material/pueraria_flower_extract/#section08	Nagamine 2020 [26]	Present	Present
Advertisement	https://genryou.toyoshinyaku.co.jp/material/banasulin/	Fujiki 2022 [39]	Present	Present
Advertisement	https://www.toyoshinyaku.co.jp/gnc-rad/gnc-material/terminalia/	Tomozawa 2019 [36]	Present	Present
Advertisement	https://www.kirin.co.jp/softdrink/b-lactolin/	Kita 2018 [46]	Present	Present
Press release	https://www.bggjapan.com/wp/wp-content/uploads/2020/06/a82186564bdd0fc83642fb150bb15a5a.pdf	Sekikawa 2020 [45]	Present	Present
Press release	https://prtimes.jp/main/html/rd/p/000000009.000056517.html	Hoshino 2019 [44]	Present	Present
Advertisement	https://www2.kobayashi.co.jp/seihin/lt/cyb/kennou_01/	Kawamoto 2019 [28]	Present	Present
Advertisement	https://www.dmjegao.com/contents/ingredients/150	Najima 2016 [51]	Nothing	Present
Advertisement	https://www.morinagamilk.co.jp/learn_enjoy/research/story/aroesterol/	Tanaka 2016 [52]	Nothing	Nothing
Press release	https://kyodonewsprwire.jp/release/202210148173	Yonejima 2022 [49]	Nothing	Nothing

"Spin" is defined as reporting practices that distort the interpretation of results, leading to misleading conclusions that suggest a more favorable outcome than substantiated by the data. Misleading representation signifies "any representation where the quality, standard, or any other particular relating to the content of goods or services is portrayed to general consumers as being significantly superior to that of the actual goods or services" (article 5 of the Unjustifiable Premiums and Misleading Representations Act)

All URLs were accessed 1/9/2023.

URL, uniform resource locator.

conducted by unbiased organizations can identify biases and problems in the published food trials, thus improving the overall quality of food trials.

Our study suggests that the Japanese government and Consumer Affairs Agency rigorously assess "spin" in functional food advertisements and representations. Despite not needing Consumer Affairs Agency approval, these advertisements and representations are subject to whistleblower reports and occasional reviews by the agency. Upon identifying misleading content, the agency mandates corrective measures. For instance, it has ordered action on food products advertised for high−blood pressure patients [85]. This action was undertaken due to the manufacturer's persistent presentation of the product as FOSHU despite the retraction of approval owing to the insufficient content of the active ingredient. Recently, the agency's order for action stemmed not from advertising claims but from inadequate scientific evidence. The agency targeted products purporting to lower blood triglyceride levels in healthy individuals, as the active ingredient quantity was lower than reported in the relevant literature. These studies, part of a systematic review submitted by the manufacturer, provided scientific evidence for the active ingredient [85].

No actions have been taken on selective outcome reporting in functional food advertisements and representations. The Consumer Affairs Agency banned such reporting. August 2020's postcheck guidelines for FFC presentations and advertisements [86] state that advertising multiple primary outcomes with only some showing significant results, without a valid explanation, is inappropriate.

The significant 2-fold discrepancy between primary outcomes in full texts and registered primary outcomes suggests possible misinterpretation or oversight of these guidelines by food manufacturers and the Consumer Affairs Agency. For example, a study evaluating whole-grain wheat bread's effect on visceral fat obesity identified visceral fat area and serum lipids as primary outcomes [50]. After a 12-week intervention, the intervention group exhibited a significant reduction in visceral fat area without altering serum lipid levels, body weight, or waist circumference. These unchanged outcomes, conflicting with visceral fat area results, were overlooked. Focusing product advertisements exclusively on reducing visceral fat area might seem accurate, as other outcomes like serum lipid levels are not pertinent to this function. However, this represents selective outcome reporting and constitutes "spin" [87]. We observed such selective outcome reporting frequently in our examined studies. As stated in the announcement provided by the Consumer Affairs Agency, all results based on scientific evidence should be published properly.

We suggest removing "for the functionality to be presented" from the guideline. Reporting only selected significant differences among multiple primary outcomes constitutes selective outcome reporting regardless of functionality. The Consumer Affairs Agency, when reviewing clinical trial publications cited in food manufacturer's presentations or advertisements, should examine full texts, not just abstracts, which often contain "spin" in results and conclusions. Proactive Consumer Affairs Agency action would likely prompt greater vigilance against selective

outcome reporting among food manufacturers and nutritional researchers.

Our study has limitations. First, not all RCT registries and publications on functional foods in Japan were examined. While there might be a higher proportion of studies with ''spin'' in our selection, the existence of such misrepresentations under current regulations is concerning. Second, we only included CRO-conducted studies. Studies conducted by neutral entities, such as government organizations or academic faculties, may exhibit a lower prevalence of ''spin'' than those undertaken by CROs or food manufacturers. Third, our main analysis was limited to trial registries by the top 5 CROs. A more comprehensive approach, such as selection based on quality metrics or including a wider range of CROs (eg, top 20), could have yielded a more representative sample of functional food trials in Japan. However, our post hoc analysis demonstrated that including smaller CROs rather than the top 5 CROs would lead to a greater prevalence of selective outcome reporting and spin. Fourth, the impact of ''spin'' presentations on consumer decisions was not assessed, suggesting a need for future research in this area. Finally, our results, specific to Japan, might not apply elsewhere.

Despite these limitations, our findings highlight the necessity for stricter functional food advertising regulations given the selective reporting of outcomes.

5. Conclusions

In Japan, functional food presentations often contain misleading information. Therefore, nutritional researchers should be cautious about selective outcome reporting. More importantly, the Japanese government and Consumer Affairs Agency should check whether food manufacturers report outcomes selectively.

Ethics approval

Not required.

CRediT authorship contribution statement

Hidehiro Someko: Writing − original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Norio Yamamoto:** Writing − review & editing, Investigation, Conceptualization. **Tatsuya Ito:** Writing − review & editing, Methodology, Conceptualization. **Tomoharu Suzuki:** Writing − review & editing, Investigation. **Takahiro Tsuge:** Writing − review & editing, Investigation. **Hajime Yabuzaki:** Writing − review & editing, Investigation. **Eisuke Dohi:** Writing − review & editing, Investigation. **Yuki Kataoka:** Writing − review & editing, Supervision, Methodology, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT4.0 to improve the language quality. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Data availability

Data were extracted from open-source trial databases, RCT, and press releases/advertisements of functional foods, all of which are available and accessible.

Declaration of competing interest

T.I. reports a relationship with Nomura Research Institute, Ltd that includes consulting or advisory. There are no competing interests for any other author.

Acknowledgments

We thank Editage for language editing.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2024.111302.

References

[1] Farr DR. Functional foods. Cancer Lett 1997;114:59−63.
[2] Henry CJ. Functional foods. Eur J Clin Nutr 2010;64:657−9.
[3] Farid M, Kodama K, Arato T, Okazaki T, Oda T, Ikeda H, et al. Comparative study of functional food regulations in Japan and globally. Glob J Health Sci 2019;11:132.
[4] Lang T. Functional foods. BMJ 2007;334:1015−6.
[5] Functional foods market size, share & trends analysis report by ingredient (carotenoids, prebiotics & probiotics, fatty acids, dietary fibers), by product, by application, by region, and segment forecasts, 2022 - 2030 n.d. Available at: https://www.grandviewresearch.com/industry-analysis/functional-food-market. Accessed May 29, 2023.
[6] Sato K, Kodama K, Sengoku S. Optimizing the relationship between regulation and innovation in dietary supplements: a case study of food with function claims in Japan. Nutrients 2023;15:476.
[7] About foods for specific health use n.d. Available at: https://www.caa.go.jp/policies/policy/food_labeling/foods_for_specified_health_uses/. Accessed October 13, 2023.
[8] Search for notification information of Foods with Functional Claims n.d. Available at: https://www.fld.caa.go.jp/caaks/cssc01/. Accessed October 13, 2023.
[9] Roberts DA, Kantarjian HM, Steensma DP. Contract research organizations in oncology clinical research: Challenges and opportunities. Cancer 2016;122:1476−82.
[10] Fortune Business Insights. Contract research organization (CRO) services market size [2022-2028] worth USD 163.48 billion. Fortune business insights. 2022. Available at: https://www.globenewswire.

com/en/news-release/2022/04/04/2415723/0/en/Contract-Research-Organization-CRO-Services-Market-Size-2022-2028-worth-USD-163-48-Billion-exhibiting-a-CAGR-of-12-1.html. Accessed May 29, 2023.
[11] Ioannidis JPA. The challenge of reforming nutritional epidemiologic research. JAMA 2018;320:969−70.
[12] Lesser LI, Ebbeling CB, Goozner M, Wypij D, Ludwig DS. Relationship between funding source and conclusion among nutrition-related scientific articles. PLoS Med 2007;4:e5.
[13] Gkiouras K, Choleva M-E, Verrou A, Goulis DG, Bogdanos DP, Grammatikopoulou MG. A meta-epidemiological study of positive results in clinical nutrition research: the good, the bad and the ugly of statistically significant findings. Nutrients 2022;14:5164.
[14] Kamioka H, Origasa H, Kitayuguchi J, Tsutani K. Compliance of clinical trial protocols for foods with function claims (FFC) in Japan: consistency between clinical trial registrations and published reports. Nutrients 2021;14:81.
[15] Kamioka H, Origasa H, Kitayuguchi J, Yoshizaki T, Shimada M, Wada Y, et al. Risk of bias in clinical trials reported for foods with functional claims in Japan: a cross-sectional study on research quality. J Clin Trials 2022;12:100503.
[16] Murad MH, Wang Z. Guidelines for reporting meta-epidemiological methodology research. Evid Based Med 2017;22:139−42.
[17] UMIN clinical trials registry(UMIN-CTR) n.d. Available at: https://www.umin.ac.jp/ctr/index-j.htm. Accessed May 29, 2023.
[18] International clinical trials registry platform (ICTRP) n.d. Available at: https://www.who.int/clinical-trials-registry-platform. Accessed May 29, 2023.
[19] Natural T. A guide to functional foods. TastesNatural. 2020. Available at: https://tastesnatural.com/guide_to_functional_foods/. Accessed May 29, 2023.
[20] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
[21] Boutron I, Dutton S, Ravaud P, Altman DG. Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. JAMA 2010;303:2058−64.
[22] Clinical trial act n.d. Available at: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000163417.html. Accessed May 29, 2023.
[23] Act against unjustifiable premiums and misleading representations n.d. Available at: https://www.japaneselawtranslation.go.jp/ja/laws/view/2888/en. Accessed May 29, 2023.
[24] Daniel S, Whiting K, Curry M, Lavery JA, Larmarange J. Reproducible summary tables with the gtsummary package. R J 2021;13:570−80.
[25] McGuinness L.A. Robvis: an R package and web application for visualising risk-of-bias assessments. Available at: https://Github.com/Mcguinlu/Robvis. Accessed August 29, 2023.
[26] Nagamine R, Takano A, Kamiya T, Takagaki K, Suzuki S, Kurokawa S. The effect of food containing Pueraria flower extract on energy metabolism—A randomized, double—blind, placebo—controlled, parallel—group study. Jpn Pharmacol Ther 2020;48:835−41.
[27] Mashiki S, Fujiki K, Takano A, Kamiya T, Takagaki K, Iwama Y. Antiglycation effect of Garcinia mangostana extract —A randomized, double−blinded, placebo−controlled, parallel−group study. Jpn Pharmacol Ther 2021;49:991−7.
[28] Kawamoto K, Hirata T, Hosoo S, Yamaguchi Y, Yamasaki H, Konno H, et al. Effects of composite supplement containing curcumin, ferulic acid, and soybeanderived phosphatidylserine on cognitive function in healthy middleaged and senior adults. Jpn Pharmacol Ther 2019;47:1253−68.
[29] Shimono T, Hoshino T, Takara T. Effects of an oral nutritional supplement drink containing Lactobacillus paracasei MCC1849 on improving the immune system of elderly people. Jpn Pharmacol Ther 2019;47:97−113.
[30] Oohashi K, Tomoguchi K, Taishi M, Nomura T, Abe T, Izumi T. Effects of consumption of a tablet containing dry powder of rice shochu distilled residue, skipjack tuna elastin, and tomato seed extract on the skin of healthy Japanese adults. Jpn Pharmacol Ther 2020;48:2219−43.
[31] Kageyama M, Tomobe H, Kobashi R, Nakashima N, Akiyoshi K, Omori R, et al. The effects of consuming a tablet supplement containing Terminalia bellirica and Banaba leaf extracts on postprandial blood triglycerides and glucose in healthy Japanese subjects. Jpn Pharmacol Ther 2020;48:1999−2009.
[32] Umigai N, Saito T, Kahara T, Yamashita S, Naoko S, Takara T. Effects of cryptoxanthincontaining Paprika Oleoresin on the quality of Life of healthy adult Volunteers with Mild knee pain. Jpn Pharmacol Ther 2017;45:223−33.
[33] Ito Y, Ishibashi R, Tajima S, Ueda T, Kageyama S, Yamada S, et al. Suppressive effects of a supplement containing pomegranate fruit extract on urinary stress in women—A randomized, single—blind, placebo—controlled, parallel—group, three—arm study : A pilot study. Jpn Pharmacol Ther 2021;49:143−53.
[34] Tou T, Nakasone T, Kameyama K, Saito J. Effects of consumption of blackvinegarmashgarlic containing food on feelings of fatigue, decreased vitality and sleep quality in daily Life. Jpn Pharmacol Ther 2021;49:1665−79.
[35] Oe M, Yamashita S, Tanaka T, Kimura M, Seino S, Kajiyama D, et al. Effect of gluconacetobacter hansenii GK-1 on physical condition maintenance by regulating IFN-α: an eight-week double-blinded, placebo-controlled study. Jpn Pharmacol Ther 2022;50:2249−56.
[36] Tomozawa H, Nagamine R, Takano A, Kamiya T, Takagaki K, Iwama Y. Confirmation study on the effect of food containing Terminalia bellirica extract on postprandial blood glucose levels. Jpn Pharmacol Ther 2019;47:1245−51.
[37] Miyazaki H, Kato N, Nakamura F, Sakano K, Uchida M, Namba T, et al. Effect of beverage containing ethyl caproate on lipid metabolism in healthy adult males. Jpn Pharmacol Ther 2020;48:1401−7.
[38] Iwasak S, Yokoi K, Suzuki N, Yamashita S, Iio S, Takara T. Effects of a drink containing Lactobacillus casei on improving the intestinal environment in people with constipation. Jpn Pharmacol Ther 2017;45:1947−62.
[39] Fujiki K, Inatomi T, Ogami T, Takano A, Kamiya T, Takagaki K, et al. Effect of lagerstroemia speciosa leaf extract and exercise on gait function, posture, and QOL. Jpn Pharmacol Ther 2022;50:711−20.
[40] Fukami K, Suehiro D, Takara T. Safety evaluation of long—term intake and effects on Bone mineral density of Corn Syrup Solids containing maltobionic acid (maltobionic acid Calcium Salt) in healthy Japanese women —A randomized double—blind placebo—controlled study. Jpn Pharmacol Ther 2019;47:229−45.
[41] Yamagishi Y, Shirakura Y, Oda Y, Seki S, Kobuna Y. Effects of composite supplements on knee joint function and movement function. Jpn Pharmacol Ther 2023;51:675−84.
[42] Suzuki M, Atsuko O, Okumura K, Suzuki M, Ebihara S, Yada N. Effects of oral ingestion of hotrienol on autonomic nervous system activity and central nervous function. Jpn Pharmacol Ther 2022;50:247−56.
[43] Kaneko T, Miyata A, Nakamura A. Slimming effect by ingesting processed coffee powder foods. Med Cons New-Remed 2021;58:479−83.
[44] Hoshino T, Yamashita S-I, Suzuki N, Baba A, Ogawa S, Izumi T. Impact of Acacia bark extract tablets on the skin of healthy humans: a randomized, double-blind, placebo-controlled study. Biosci Biotechnol Biochem 2019;83:538−50.
[45] Sekikawa T, Kizawa Y, Li Y, Takara T. Cognitive function improvement with astaxanthin and tocotrienol intake: a randomized, double-blind, placebo-controlled study. J Clin Biochem Nutr 2020;67:307−16.
[46] Kita M, Obara K, Kondo S, Umeda S, Ano Y. Effect of supplementation of a whey peptide rich in tryptophan-tyrosine-related peptides

on cognitive performance in healthy adults: a randomized, double-blind, placebo-controlled study. Nutrients 2018;10:899.
[47] Nishimoto Y, Fujisawa K, Ukawa Y, Kudoh M, Funahashi K, Kishimoto Y, et al. Effect of urolithin A on the improvement of vascular endothelial function depends on the gut microbiota. Front Nutr 2022;9:1077534.
[48] Hatanaka M, Kanzato H, Tsuda R, Nadaoka I, Yasue M, Hoshino T, et al. Safety evaluation of the excessive intake of Bacillus subtilis C-3102 in healthy Japanese adults: a randomized, placebo-controlled, double-blind, parallel-group, comparison trial. Toxicol Rep 2020;7:46−58.
[49] Yonejima Y, Yamada K, Takara T. Effects of consumption of HYA - contalnlng food on the visceral fat area in healthy subjects. Prog Med 2022;42:887−93.
[50] Kikuchi Y, Nozaki S, Makita M, Yokozuka S, Fukudome S-I, Yanagisawa T, et al. Effects of whole grain wheat bread on visceral fat obesity in Japanese subjects: a randomized double-blind study. Plant Foods Hum Nutr 2018;73:161−5.
[51] Najima M, Munekata M, Soeda Y. Usefulness of the supplement containing proteoglycan for Japanese healthy people feeling Knee's discomfort. Med Cons New-Remed 2016;53:228−36.
[52] Tanaka M, Yamamoto Y, Misawa E, Nabeshima K, Saito M, Yamauchi K, et al. Effects of aloe sterol supplementation on skin elasticity, hydration, and collagen score: a 12-week double-blind, randomized, controlled trial. Skin Pharmacol Physiol 2016;29:309−17.
[53] Kushima M, Okamoto K, Kizawa Y, Sekikawa T, Li Y, Takara T. A verification study on the improvement of urination issues with ingestion of saw palmetto fruit extract : a randomized, double-blind, parallel-group, placebo-controlled study. Pharmacometrics 2018;95:101−11.
[54] Kuroda R, Higuchi H, Yoshida K, Yonejima Y, Hisa K, Utsuyama M, et al. Effects of chocolate containing Leuconostoc mesenteroides strain NTM048 on immune function: a randomized, double-blind, placebo-controlled trial. Immun Ageing 2018;15:29.
[55] Takizawa J, Baba A, Takara T. A ''PAKU-PAKU KOUBO-KUN'' containing yeast and mulberry extract postprandial glycemic control in healthy Japanese men and women: a randomized, placebo-controlled, crossover study. Funct Foods Health Dis 2023;13:167−78.
[56] Soda K, Mikami Y, Fujio M, Yoshida M, Ito K. Effects of a rice bran-containing diet to improve stratum corneum hydration and epidermal barrier function in adult women who feel uneasy about their skin dryness. Jpn Pharmacol Ther 2021;49:105−16.
[57] Morita Y, Jounai K, Miyake M, Inaba M, Kanauchi O. Effect of heat-killed Lactobacillus paracasei KW3110 ingestion on ocular disorders caused by visual display terminal (VDT) loads: a randomized, double-blind, placebo-controlled parallel-group study. Nutrients 2018;10:1058.
[58] Ohara K, Misaizu A, Kaneko Y, Fukuda T, Miyake M, Miura Y, et al. β-Eudesmol, an oxygenized sesquiterpene, reduces the increase in saliva 3-methoxy-4-hydroxyphenylglycol after the ''trier social stress test'' in healthy humans: a randomized, double-blind, placebo-controlled cross-over study. Nutrients 2018;11:9.
[59] Machida N, Hirota J, Kubo N. Effects of dietary supplementation with devils claw extract on discomfort in knee joints —A randomized, double−blind, placebo−controlled, parallel−group study. Jpn Pharmacol Ther 2020;48:979−88.
[60] Akagi R, Maruo T, Mori N, Fukuda M, Suzuki T. Effects of black soybean seed coat extract on attenuating fatigue sensation in healthy Volunteers —A randomized, double—blind, placebo—controlled, crossover comparison trial. Jpn Pharmacol Ther 2021;49:953−64.
[61] Kim K, Sun J, Lee H, Ono T, Yonei Y. Effect of a dietary supplement containing porcine placenta extract on skin hydration —a Placebo—controlled, randomized, double—blind, clinical study. Jpn Pharamocol Ther 2018;46:1023−34.
[62] Xiao J, Katsumata N, Bernier F, Ohno K, Yamauchi Y, Odamaki T, et al. Probiotic bifidobacterium breve in improving cognitive functions of older adults with suspected Mild cognitive impairment: a randomized, double-blind, placebo-controlled trial. J Alzheimers Dis 2020;77:139−47.
[63] Watanabe S, Ohno A, Inamasu S, Watanabe K, Sugino T, Fukuda M. Arctigenin in forsythia leaf extract attenuates fatigue sensation and improves sleep quality —A randomized, double−blind, placebo−controlled, parallel−group trial. Jpn Pharmacol Ther 2022;50:61−77.
[64] Oya H, Masuda T, Ishikawa H, Takimoto Y, Seki S, Hotta T, et al. A randomized, single-blind, parallel-group comparative study on the effects of long-term pineapple intake for improvement of skin function and intestinal environment in healthy subjects. FSTR 2023;70:73−83.
[65] Yoshizumi K, Oikawa Y, Miyahara K, Takaki Y, Shimura M, Kobayashi Y, et al. Effect of regular intake of Mekabu (Undaria pinnatifida sporophylls) on blood pressure lowering and swelling improvement —A randomized, single−blind, parallel comparison study. Jpn Pharmacol Ther 2022;50:1613−22.
[66] Yoshinaga K, Mitamura R. Effects of undaria pinnatifida (wakame) on postprandial glycemia and insulin levels in humans: a randomized crossover trial. Plant Foods Hum Nutr 2019;74:461−7.
[67] Asahina Y, Masuda T, Nakada M, Seki S, Hotta T, Otaki H, et al. Effects of banana powder on fasting glucose levels and postprandial blood glucose levels. Jpn Pharmacol Ther 2023;51:1195−205.
[68] Yamaguchi Y, Kitagawa M, Iida T, Kishimoto Y, Kashiwagi S, Sugino T, et al. Effects of a single intake of Psicose (Allulose) on fat oxidation during exercise —A randomized, double−blind, placebo−controlled, cross−over trial. Jpn Pharmacol Ther 2019;47:517−25.
[69] Okunishi I, Miura Y, Nakamura Y, Hira Y, Hou D-X. Assessment of mutagenicity, acute and sub-acute toxicity and human trial safety of wasabi leaf extract powder. Food Sci Technol Res 2021;27:131−49.
[70] Shimamoto Y, Ono T, Sawabe A. Examination of the effects of a food containing NMN (nicotinamide Mononucleotide) on skin function and safety —A double−blind randomized controlled trial of 8−week treatment. Jpn Pharmacol Ther 2023;51:75−87.
[71] Kawano T, Naito J, Nishioka M, Nishida N, Takahashi M, Kashiwagi S, et al. Effect of food containing paramylon derived from euglena gracilis EOD-1 on fatigue in healthy adults: a randomized, double-blind, placebo-controlled, parallel-group trial. Nutrients 2020;12:3098.
[72] Hemmi J, Makino S, Yokoo T, Kano H, Asami Y, Takeda K, et al. Consumption of yogurt fermented with Lactobacillus delbrueckii ssp. bulgaricus OLL1073R-1 augments serum antibody titers against seasonal influenza vaccine in healthy adults. Biosci Microbiota Food Health 2023;42:73−80.
[73] Masuda T, Matsubara A, Ishikawa H, Takimoto Y, Seki S, Hotta T, et al. Effect of pineapple intake on intestinal environment and skin improvement in Japanese women -randomized, single-blind, parallel-group comparative study. New Diet Theapy 2021;37:3−11.
[74] Sato A, Fukawa-Nagira A, Sashihara T. Lactobacillus paragasseri OLL2809 improves premenstrual psychological symptoms in healthy women: a randomized, double-blind, placebo-controlled study. Nutrients 2023;15:4985.
[75] Yoshizumi K, Izumida H, Misumi S, Kobayashi Y, Shimura M, Masuda T, et al. Evaluation of the effects of long−term ingestion of dried powdered Brown alga ecklonia stolonifera from nishinoshima town, oki islands, on the reduction of eye and nasal discomfort and its safety profile —A randomized, double−blind, placebo−controlled parallel−group comparison study. Jpn Pharmacol Ther 2021;49:2111−25.
[76] Inagaki S, Baba Y, Ochi T, Sakurai Y, Takihara T, Sagesaka YM. Effects of black vinegar beverage intake on exercise-induced fatigue in untrained healthy adults: a randomized, double-blind, placebo-controlled trial. J Phys Fitness Sports Med 2020;9:115−25.

[77] Yamashita M, Miyoshi M, Iwai M, Takeda R, Ono T, Kabuki T. Lactobacillus helveticus SBT2171 alleviates perennial allergic rhinitis in Japanese adults by suppressing eosinophils: a randomized, double-blind, placebo-controlled study. Nutrients 2020;12:3620.

[78] Kaiser KA, Cofield SS, Fontaine KR, Glasser SP, Thabane L, Chu R, et al. Is funding source related to study reporting quality in obesity or nutrition randomized control trials in top-tier medical journals? Int J Obes 2012;36:977−81.

[79] Myers EF, Parrott JS, Cummins DS, Splett P. Funding source and research report quality in nutrition practice-related research. PLoS One 2011;6:e28437.

[80] Azar M, Riehm KE, Saadat N, Sanchez T, Chiovitti M, Qi L, et al. Evaluation of journal registration policies and prospective registration of randomized clinical trials of nonregulated health care interventions. JAMA Intern Med 2019;179:624−32.

[81] Zarin DA, Tse T, Williams RJ, Rajakannan T. Update on trial registration 11 Years after the ICMJE policy was established. N Engl J Med 2017;376:383−91.

[82] UMIN-CTR. Explanation of terms. Available at: https://www.umin.ac.jp/ctr/UMIN-CTR_Yougo.htm. Accessed February 2, 2024.

[83] Gov C. Clinicaltrials.gov protocol registration data element definitions for interventional and observational studies. Available at: https://prsinfo.clinicaltrials.gov/definitions.html. Accessed February 2, 2024.

[84] Kamioka H, Tsutani K, Origasa H, Yoshizaki T, Kitayuguchi J, Shimada M, et al. Quality of systematic reviews of the foods with function claims in Japan: comparative before- and after-evaluation of verification reports by the consumer Affairs agency. Nutrients 2019;11:1583.

[85] [Consumer Affairs Agency orders mail-order company to pay surcharge and cancels FOSHU] in Japanese. The Nikkei. Available at: https://www.nikkei.com/article/DGXLASDG07H59_X00C17A6CR8000/. Accessed October 5, 2023.

[86] [Guidelines for ensuring transparency of ex post facto regulations (ex post facto check) based on laws and regulations relating to food labeling, etc., for food with functional claims] in Japanese. Available at: https://www.caa.go.jp/policies/policy/food_labeling/about_foods_with_function_claims/pdf/about_foods_with_function_claims_200324_0003.pdf. Accessed October 5, 2023.

[87] Wasserstein RL, Lazar NA. The ASA statement on p-values: context, process, and purpose. Am Stat 2016;70:129−33.