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ORIGINAL RESEARCH

Assessing conflict of interest reporting and quality of clinical trials on infant formula: a systematic review

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Abstract

Objectives: This study aims to assess the quality, risk of bias, and conflicts of interest (COIs) of clinical trials conducted on the effects of fortified infant formula.

Study Design and Settting: Systematic review including all randomized clinical trials targeting healthy children and using three arms: fortified infant formula; standard formula; and breastfeeding. We performed a descriptive analysis of the studies reviewed, assessed their quality using the ''Risk of Bias 2- RoB 2'' tool, and identified COIs.

Results: A total of 40 studies were included. All showed a high overall risk of bias, with this being especially noteworthy in the ''deviations from intention to treat'' and ''missing outcome data'' domains. Of the total included studies, 29 reported conclusions in favor of the fortified formula; 15 studies reported multiple conclusions that were either contradictory or not in line with the results. COIs with industry were identified in 33 studies, and in 17 studies, these conflicts were not declared in the appropriate section.

Conclusion: From a methodological perspective, studies on fortified infant formula display low quality, made evident by the high risk of bias. Additionally, there are frequent COIs. These aspects must be considered by health professionals and the population when drawing up recommendations for the use of this product.

Keywords: Conflict of interest; Infant formula; Industry; Quality; Breast feeding; Funding

1. Introduction

Breastfeeding improves and protects the health and development of infants in that it provides the appropriate energy, nutrients, water, and antibodies required for this stage of babies' lives and adapts to their needs [1]. The World Health Organization (WHO) recommends that breastfeeding be initiated in the first hour after birth and be exclusively used for the first 6 months of life (''exclusive breastfeeding'') [2]. Despite this recommendation and the various international initiatives that have been in force for many years, the prevalence of exclusive breastfeeding is still far removed from the WHO's original goal of 70% of all infants being fed exclusive breastfeeding by 2030 [3]. It should be mentioned that there are some situations where breastfeeding is not possible, so infant formula becomes the only alternative. Nevertheless, infant formula is not exempt from different factors, such as the presence of pollutants in the formula powder or polluted water [4,5].

In 1981, the WHO issued the ''International Code of Marketing of Breastmilk Substitutes'' (hereinafter referred to as ''the Code''). This is the largest single international policy within the public health framework designed to protect women, families, children, and the health system from marketing strategies to promote infant formula and other products targeted at this population [6]. Even though the Code properly governs the marketing of infant formula, the legislation, control, and application depends, exclusively on the political will of each nation [7]. In 2020, only 32 countries had applied measures totally in accordance with the Code, and only 19 countries had barred scientific

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What is new?

Key findings

- We have observed that almost all the studies included received funding from the industry and that most of the conclusions are in favour of the infant formula.
- Conflicts of interest (COIs) are frequent. Moreover, all the studies have high risk of bias (RoB) revealing methodological biases.

What this adds to what was known?

- Previous studies have warned about the lack of veracity of claims about infant formulas, as an interference of the industry.
- This study highlights how private industry is related to clinical trials specifically about fortified infant formula, which distinguishes it from other systematic reviews.

What is the implication and what should change now?

- It is crucial to foster and encourage independent clinical research that would confirm or refute the results that the industry attributes to fortified infant formula.

and health associations from accepting industry sponsorship of infant formula [8−10]. A further 41 countries applied only some of the Code's articles, whereas 50 countries did not adhere to any type of measure [9].

In the last 20 years, the infant formula industry has doubled its sales, frequently making use of strategies that are not in line with the Code [11]. One of these is expanding the portfolio of products wherein the novelty in the formula is the addition of an ingredient, and then marketing these using messages such as ''supports digestive health'', or ''fosters cognitive development''. These messages are known as ''marketing claims'', and when they specifically refer to health aspects are called ''health claims" [12,13]. The public consumer tends to think that these phrases have a scientific foundation, though in most cases, this is no guaranteed. Indeed, for the formula in which these claims are said to be based on the results of research studies, recent papers report that the evidence in question is not of sufficient robust to support such messages [14−16].

An interesting definition of the presence of conflicts of interest (COIs) is that a COI exists when a past, current, or expected interest creates a significant risk of inappropriately influencing an individual's judgment, decision, or action when carrying out a specific duty [17]. The COI and the interference of the industry can bias the results and conclusions of the studies. This interference has been identified in several scientific studies related to the tobacco and food industries [18−20]. With a different approach, some authors have already reported that the infant formula industry is not exempt from this situation [14,16].

The aim of this study was therefore to assess the quality, risk of bias, and conflicts of interest in clinical trials on fortified infant formula.

2. Methods

We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [21]. The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) no. CRD42023399640.

We carried out a literature search in MEDLINE (PubMed), EMBASE, and CINAHL in October 2022, that was updated in February 2023, combining the following free terms and MesH terms: ''enriched infant formula''; ''supplemented infant formula''; ''fortified infant formula''; ''artificial feeding''; ''formula feeding''; ''bottle feeding''; ''clinical trial''; and ''humans.'' No language or date restrictions were applied. The search strategy is set out in the supplementary material (Table S1).

The selection criteria were defined in accordance with the patient, intervention, comparator, outcome and study (PICOS) model [22]. This systematic review included articles in which: a) subjects were healthy infants; b) the use of fortified, enriched, or supplemented infant formula (hereinafter jointly referred to as ''fortified'') was evaluated as the intervention; c) the control group consisted of infants fed with standard formula; d) changes in health-related parameters were assessed; and e) the study design was a randomized clinical trial. Furthermore, trials had to contain at least 3 study groups: infants fed with fortified formula, compared with infants fed with standard formula, and a third group of infants who were breastfed, as this is considered a good practice among clinical trials of infant formula [23].

Opinion articles, communications to congresses, and editorials were excluded, as were studies with a qualitative approach and those in which the study subject and outcome variables were focused on the mother rather than the child.

The selection of potentially eligible studies based on their titles and abstracts was carried out manually by three researchers working separately (GG, MPR, and CCP). Papers flagged as potentially relevant by at least one of the three researchers were preselected for a reading of the full text, with any differences of opinion being settled by consensus. The same method was used to select studies based on reading of the full text.

Papers were grouped by reference to their main outcome variables: microbiota, growth, vitamins and minerals,

neurodevelopment, bone function, fatty acids, immune function, and miscellaneous.

Information of interest was manually extracted using a predesigned data-extraction sheet, adapted in accordance with the CONSORT guidelines [24]. Working separately, two researchers (GG, MPR) extracted data on: age of inclusion of children in the study; follow-up time; sample size, overall and in each study arm; component/s with which formula had been supplemented; presence of COI; funding; acknowledgments; author affiliations; and study conclusions. Regarding COI, funding, and acknowledgments, we considered whether the presence of a specific section declaring them and whether COI and funding by industry could be identified in the specific section or within a different section of the article. In 1993, the definition of COI was introduced to the International Committee of Medical Journal Editors (ICMJE) rules, and at this point, the declaration was required in the acknowledgments section. After 2003 it became required to state COI in a specific section of the article. We registered how many articles complied with such recommendations. Conclusions were assessed by whether they were in favor, not clear or neutral or against fortified infant formula.

Additionally, we have analyzed the potential association between the direction of the conclusion of the included studies and different variables, namely COI, funding, financial ties, and donation of the infant formula, using Fisher's exact test.

We assessed the risk of bias in clinical trials using the Cochrane RoB tool version 2 [25], considering the five types of biases or domains included. The risk of bias was taken into account, both overall and broken down by domain. Assessment was carried out by peers (GG, CCP), with any differences of opinion being settled by consensus.

We drew up a descriptive synthesis of the evidence and the quality of the studies included.

3. Results

The search identified 888 papers, 260 of which were discarded for being duplicates (Fig 1). Once the titles had been screened, 154 papers were included; after their abstracts had been screened, 79 were selected for a full-text review. Of these, 45 papers were excluded for not meeting the inclusion criteria. We included a further seven papers identified on the basis of references cited by other papers. Finally, a total of 41 papers fulfilled the eligibility criteria.

Of the nine papers that had microbiota as their main outcome variable, two reported the same results of the same

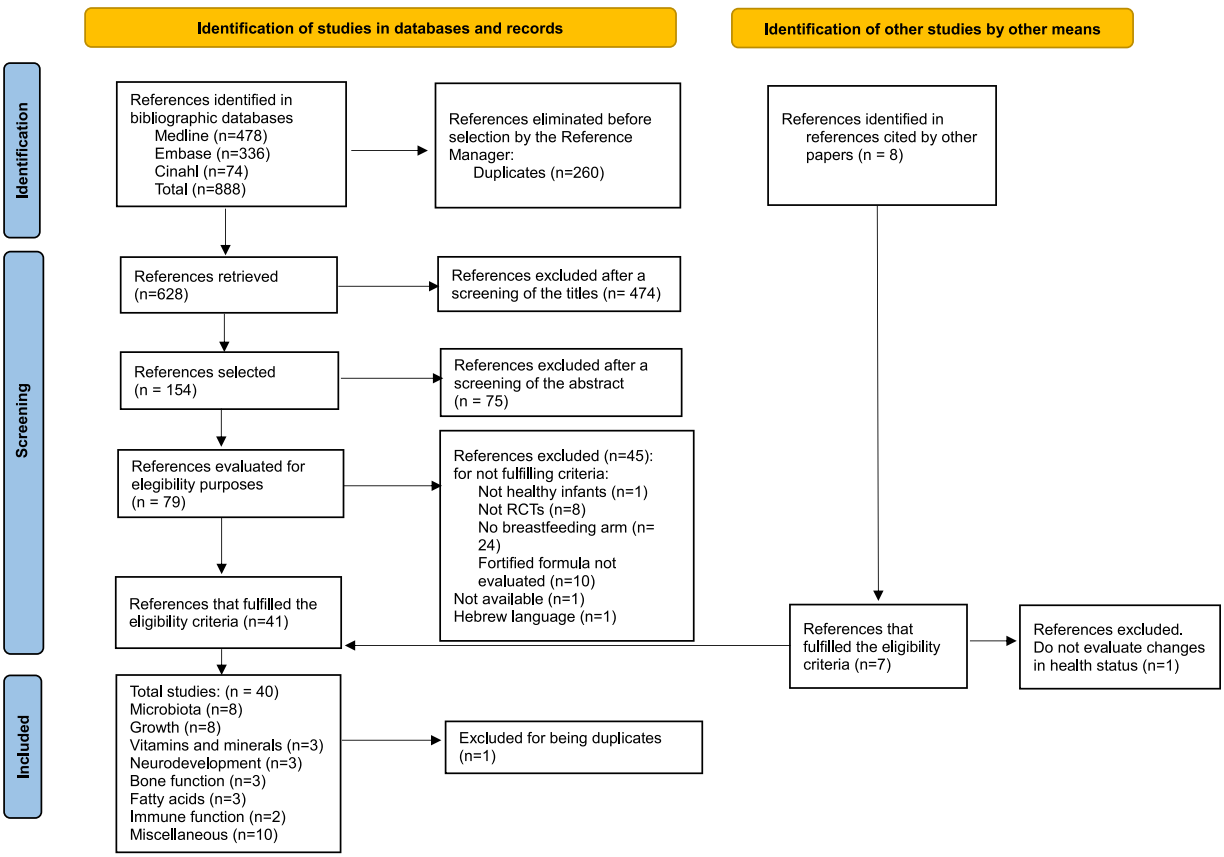

Figure 1. PRISMA flowchart of studies included. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

clinical trial, published in different journals and in a different language. For this reason, one was excluded for being considered a duplicate publication [26,27], including a total of 40 articles in the review.

Based on the main outcome variable, papers were classified into eight groups: microbiota ($n = 8$); growth ($n = 8$); vitamins and minerals ($n = 3$); neurodevelopment ($n = 3$); bone function ($n = 3$); fatty acids ($n = 3$); immune function ($n = 2$); and a miscellaneous group ($n = 10$) (Fig 1).

The main characteristics of the studies included are shown in the supplementary material (Table S2). References to the studies are listed in the supplementary material (Table S3).

The papers included were published between 1987 and 2023, and reported studies conducted from 1981 through 2020. Total initial sample sizes ranged from 60 to 1678 participants. In 11 studies, neither the total sizes of the samples nor those of the study arms were clearly shown [27−37].

With respect to the fortified formula used as intervention, 15 studies reported its nutritional composition [27,28,30,38−49]. When it came to the formula of comparison, namely, the standard formula, 12 studies reported its nutritional composition [28,30,38,40,42−49].

3.1. Conflicts of interest and acknowledgments

Only one study was published prior to 1993 and there was no mention of COI. Among the 12 studies published between 1993 and 2003, which should have declared their COI in the acknowledgments section, two studies complied. However, COI with industry were identified in 10 of them in other sections. In 27 studies published after 2003, a total of 18 studies were identified in which a section was reserved for declaration of COI: in this section, 16 of these studies acknowledged having COI with industry.

Regardless of the presence of a specific section, 33 studies had potential COI with industry: in 17, COI were identified via the acknowledgments, funding, and/or author affiliations sections (Table 1).

An acknowledgments section was identified in 32 studies, with industry being thanked in 15 of these.

3.2. Funding

Sixteen studies with a funding section were identified: 14 declared having received funding from industry, and one identified industry funding in the acknowledgments section. In 20 studies, no funding section was shown, but industry funding was identified in another section of the paper. Regardless of whether or not a specific section was identified, 35 studies were associated with industry through funding (Table 1).

With respect to the role of industry in the studies, there were 14 studies in which people involved in the analysis of samples and/or data had a declared relationship with industry.

Six studies did not clearly identify their authors' individual affiliations. Regardless of whether an affiliation was clearly declared, there were 28 studies with at least one author who had an affiliation with industry.

3.3. Conclusions of the included studies

The conclusions of 29 studies were favorable to the fortified formula. Only one study was identified with a conclusion opposed to the fortified formula; the remaining conclusions were not clear or were neutral with respect to fortified formula. There were 15 studies that reported a series of conclusions that were mutually contradictory or not fully in accordance with the results (Table 1).

No association was found between the direction of the conclusion and COI, funding, financial ties, and donation of the infant formula (data not shown).

Detailed results on COIs, acknowledgments, funding and financial ties are shown in the supplementary material (Tables S5 and S6).

Table 1. COI, funding, and conclusions in favor of fortified formula

Studies	COI declaration section (section exists/Total)	Potential COI with industry (identified/Total)	Industry funding (identified/Total)	Conclusion (in favor of fortified formula/Total)
Microbiota	5/8	5/8	7/8	8/8
Growth	4/8	8/8	7/8	6/8
Vitamins and minerals	1/3	2/3	2/3	0/3
Neurodevelopment	2/3	3/3	2/3	3/3
Bone function	0/3	1/3	3/3	2/3
Fatty acids	1/3	3/3	3/3	3/3
Immune function	0/2	2/2	2/2	1/2
Miscellaneous	5/10	9/10	9/10	6/10
Total	18/40	33/40	35/40	28/40

COI, conflicts of interest.

3.4. Assessment of risk of bias

The overall risk of bias was high in all the studies identified. The ''randomization process'' domain was pinpointed as being the one that most frequently displayed biases in all groups, except ''immune function''. There were frequent differences, both in group characteristics and in the lack of information about whether allocation of the intervention to the participants had been concealed. The ''deviations from ITT (intention to treat)'' domain was noteworthy across all groups, in that most of the studies showed a high risk of bias, due to the lack of information about the type of analysis conducted. In the ''missing outcome data'' domain, more than half the studies displayed a high risk of bias in all groups, except ''growth'' and ''vitamins and minerals''. The main reason was not having data available for all participants, with this conceivably having affected the result. In the case of the ''measurement of the outcome'' domain, a high risk of bias was more frequently to be seen in the ''microbiota'', ''growth'', ''neurodevelopment'' and ''miscellaneous'' groups; this was essentially due to the fact that measurement of the outcome may have been inappropriate, and that there was no information as to whether the person tasked with outcome measurement was blind to the intervention (Table 2).

Detailed results of the Risk-of-Bias 2.0 tool are shown in the supplementary material (Table S4).

4. Discussion

This study clearly highlights two aspects: first, the high and frequent COIs in published studies that evaluate fortified infant formula; and second, the low methodologic quality of these studies, as shown by the application of a commonly used scale for evaluation of clinical trials. The combination of these two aspects suggests that the available evidence on fortified infant formula is, at the very least, weak and might even be dubious.

4.1. Relationship between industry and fortified infant formula

The results yielded by this systematic review suggest a relationship between industries and fortified infant formula studies. This association is not only directly evident through funding but can also be observed in the authors' affiliations and acknowledgments and in the participation of people directly related to the industry in the analysis of study data. In other cases, COIs are not clearly declared, being placed in unrelated areas of the paper, such as the acknowledgments section or, for instance, in Zhu et al. [39] and Nieto-Ruiz et al. studies [50], after the Reference section, thereby making it difficult to check. This may be due to the positioning of journals and professional organizations, such as the British Medical Journal and its subsidiary publications, the UK Royal College of Pediatrics and Child Health, and the International Society for Social Pediatrics and Child Health, which have announced that they will stop carrying advertising and/or receiving funding and sponsorship from the infant formula industry, with the aim of standing by the Code and promoting independent quality scientific evidence in the analysis of the utility of infant formula [51–53].

A previous study that analyzed the association of COI in studies on electronic cigarettes and the direction of conclusions found that studies with COI were more likely to have positive conclusions toward the use of electronic cigarettes [20]. However, we did not find an association between the direction of the conclusion and the COI, or with funding, financial ties, or the donation of the infant formula (data not shown). The lack of association found in this analysis may be due to the small sample size.

4.2. Quality and risk of bias

Low methodologic quality is observed in practically all the clinical trials analyzed due to problems in various domains, such as randomization, blinding, or losses to follow-up. In clinical trials, the method of randomization

Table 2. High risk of bias – Cochrane RoB 2.0

Studies	Domain 1. Randomization process	Domain 2. Deviations from ITT	Domain 3. Missing outcome data	Domain 4. Measurement of the outcome	Domain 5. Selection of the reported result	Overall risk of bias
Microbiota	1/8	8/8	7/8	3/8	3/8	8/8
Growth	2/8	7/8	3/8	3/8	1/8	8/8
Vitamins and minerals	1/3	2/3	0/3	0/3	0/3	3/3
Neurodevelopment	2/3	2/3	3/3	2/3	0/3	3/3
Bone function	0/3	2/3	2/3	0/3	0/3	3/3
Fatty acids	2/3	3/3	3/3	1/3	0/3	3/3
Immune function	0/2	2/2	2/2	0/2	0/2	2/2
Miscellaneous	4/10	8/10	7/10	6/10	0/10	10/10

ITT, intention to treat.

should be uniform [54]. Studies such as Estorninos et al. [38], in which the method is dynamic, allow changes in distribution to be made once randomization has been performed and the clinical trial has begun. The fact that randomization is performed by the same industry as that which provides the formula for the study, as in the case of Birch et al. [55], may also be a potential source of bias. Other cases, such as Salas-Lorenzo et al. study, exclude participants after randomization [43]. Furthermore, other studies fail to specify which randomization method was used and/or whether allocation was concealed from the participants [27,29,31,33,43,48,50,56−59].

One of the requirements for clinical trials is that interventions should be mutually distinguishable [54]. Approximately only half of the studies report the nutritional composition of the formula used. It is thus difficult to establish what the true difference is between a fortified formula and a standard formula in terms of nutritional composition. Previous studies indicate how a single food additive is related to many ''health claims'' and vice versa, giving rise to a problem about claiming benefits associated with a novel ingredient [14].

Sample sizes are not clearly shown in some cases, thereby limiting comprehension of the study in question. Additionally, part of the studies includes ''mixed feeding'' arms in which the children are simultaneously breastfed and fed with infant formula [27,28,36,37,39,43,56,59−64]. For instance, in the case of Bazanella et al. study [28], all the study arms are made up of ''mixed feeding''; in this case, differentiating between the effect of formula and that of breastmilk is practically impossible. Additionally, in these studies, the amount of each type of milk offered is exclusively the decision and responsibility of the parents, ruling out any possible control by the researchers. This type of feeding, albeit possible, is questionable in the context of clinical trials: presenting a group in which the benefits of the composition of breastmilk and fortified formula are combined may bias the outcome, with these results being exclusively attributed to fortified formula. Hence, any comparisons with this arm and the ensuing conclusions should be approached with caution.

Another key aspect of clinical trials should be to keep the participants and their parents, persons tasked with administering the intervention, and those tasked with data analysis blind to the intervention [54]. The studies by Ben et al., Oropeza-Ceja et al., Marriage et al., Sepúlveda-Valbuena et al., and Lasekan et al. [27,46,47,57,62], which assess growth, only keep the participants blind or do not specify this information, leaving the reader to interpret how this has been done. This assumes special relevance in studies in which those tasked with data analysis are employees of the industry that funds the clinical trial [29,33,43,46,47,60,61].

In the studies reviewed, there were a high number of losses to follow-up. This is worrying because, in theory, losses should be lower than in studies on adults, and more so still, bearing in mind that the participants are infants [65]. The high number of missing participants could suggest ''selective losses'' that may affect the result. Moreover, any loss of participants in the studies should be well documented and specified. The reality of the studies included is far from this ideal, however, not only due to the lack of specifications but also because no study provides some objective measure of the intervention's achievement [66]. This reflects one of the greatest problems displayed by these studies, that is, the type of analysis performed. Once subjects are allocated to a group, they must be included in the analysis, regardless of the degree to which the intervention is fulfilled, thus ensuring that randomization is maintained; in other words, despite the intervention having been discontinued or varied, subjects should be analyzed in their randomization source group. Where the aim of the study is, as in this case, to observe how a given type of feeding affects an outcome variable, all subjects must be included in the analysis. This type of analysis is ''intention to treat'' and should be the analysis of choice [66]. Yet, many of the studies report their results on the basis of a main analysis performed using the ''pharmacologic efficacy'' or ''per protocol'' method (the term used in the RoB-2 tool, hereinafter referred to as ''per protocol'') or do not provide sufficient information to indicate the type of analysis performed. Per protocol analysis, only those who complete the intervention are included, without taking into account whether they changed from one study arm to another during the study period. In this way, randomization loses its effect. Only four studies did not use this type of analysis [42,48,63,64].

4.3. Strengths and limitations

By way of strengths, this study carried out an exhaustive search in various databases to ensure inclusion of all the studies conducted. Despite the existence of guidelines for clinical trials on infant formulas [23], we highlight the use of the RoB-2 tool, specifically to assess the risk of bias. It is a well-known, validated tool that makes it possible to ascertain the risk of bias both in detail and with a breakdown by domain. Moreover, along with the identification of COIs with industry, this review assessed acknowledgments, funding, and author affiliations as possible sources of COIs, thereby providing a broad overview.

This study also has limitations, such as failing to carry out an in-depth review of the protocols registered and/or note their absence. Despite the fact that RoB-2 includes a question in which consulting the protocols is suggested, when it comes to future research, it would be important to assess whether the information reported in a given paper does in fact coincide with the protocols.

Another limitation of this study is that we did not analyze COIs based on whether the endpoints were surrogate or patient-relevant. Due to the heterogeneity of the outcomes in the included studies, we were not able to analyze the outcomes in detail.

5. Conclusions

The results of this review indicate that clinical trials of fortified infant formula show a high risk of bias which may substantially affect the validity of their outcomes and conclusions. This should lead one to question the true validity of such studies. A further relevant result is that the presence of COIs is highly prevalent in these studies, where there is scarcely any independent research. Funding by industry was also highly prevalent. In line with the position adopted by a number of journals and professional organizations [51−53], it is essential to foster and encourage independent clinical research that would confirm or refute the results that the industry attributes to such fortified infant formula.

CRediT authorship contribution statement

Guadalupe García: Writing − original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Mónica Pérez-Ríos:** Writing − review & editing, Supervision, Methodology, Data curation, Conceptualization. **Alberto Ruano-Ravina:** Writing − review & editing, Supervision. **Cristina Candal-Pedreira:** Writing − review & editing, Supervision, Methodology, Data curation, Conceptualization.

Data availability

The data that support the findings of this study are publicly available.

Declaration of competing interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare no competing interests. This article is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2024.111313.

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