YHEC

York Health Economics Consortium

Providing consultancy and research in health economics for the NHS, pharmaceutical and health care industries since 1986

Danone Institute International

Scoping Review of Yoghurt

Final Protocol (with amendments)

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THE UNIVERSITY of York

INVESTORS IN PEOPLE

Contents

Abbreviations

EFSA	European Food Safety Authority
HRQoL	Health-related quality of life
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Section 1: Introduction

York Health Economics Consortium (YHEC) has been commissioned by Danone Institute International (DII) to conduct a scoping review of the evidence of the health benefits conferred by the consumption of yoghurt. The purpose of this review is to assess the volume of research evidence for the health benefits of yoghurt and inform potential future systematic reviews. This document is the protocol for this work, and sets out how YHEC will approach this task and its constituent tasks.

1.1 DEFINING YOGHURT

The Codex Alimentarius international food standards define yoghurt as a form of fermented milk that contains symbiotic cultures of Streptococcus thermophiles and Lactobacillus delbrueckii subsp. Bulgaricus. To be called a yoghurt a fermented milk product must contain milk protein, milk fat, lactic acid, ethanol, microorganisms and yeasts in the proper proportions (Table 1)(1). Probiotic yogurt is differentiated from conventional yoghurt through the addition of further strains of probiotic bacteria (2).

Table 1 The composition of fermented milk products (1)

	Fermented Milk	Yoghurt, Alternate Culture Yoghurt and Acidophilus milk	Kefir	Kumys
Milk protein	Min 2.7%	Min 2.7%	Min 2.7%	
Milk fat	Less than 10%	Less than 15%	Less than 10%	Less than 10%
Titrable acidity, expressed as % lactic acid (%m/m)	Min 0.3%	Min 0.6%	Min 0.6%	Min 0.7%
Ethanol(% vol/w)				Min 0.5%
Sum of microorganisms constituting the starter culture (cfu/g, In total)	min. 10^7	min. 10^7	min. 10^7	min. 10^7
Labelled microorganisms (cfu.g, total)	min. 10^6	min. 10^6		
Yeasts (cfu/g)			min. 10^4	min. 10^4

The beneficial health effects of yoghurt have been the subject of investigation for over a century. The health improvements attributed to it include improvements in lactose digestion and reductions in body weight (3). In recent years a lot of attention has been paid to

conducting systematic reviews of the of the health effects of probiotic yoghurts and DII is interested if a similar case can be made for yoghurt.

Section 2: Objectives

The objective of this project is to conduct a scoping review of the evidence of the health benefits of yoghurt consumption limiting the review to yogurt as defined by the Codex standard for fermented milks (CODEX STAN 243-2003) and presented in Table 1 (section 1).

The scoping review will be used to inform discussion of the feasibility of systematic reviews.

Section 3: Methods

This scoping review will be conducted using as many of the methods of a systematic review as possible. A systematic review involves the systematic and transparent identification, selection, extraction and synthesis of studies relevant to the research question (4). The first stage of this scoping review is to define the research question and the inclusion and exclusion criteria (Table 3.1).

3.1 RESEARCH QUESTION

To be included in the scoping review, studies must meet all of the following inclusion criteria.

3.1.1 Study types

Relevant studies will be those which report (or might potentially report, since we may not be able to obtain full text for all studies in the scoping review) research findings on the human health benefits of yoghurt. These are likely to include:

- Epidemiological studies;
- Cohort studies;
- Open label studies;
- RCTs.

Studies with relevant designs published as abstracts, conference presentations or unpublished reports will be included in the review if they report all items from Section 3.1.

Trial protocols, where the study results have not yet been reported, will be noted in a table of forthcoming studies.

We will also retrieve systematic reviews of evidence on the human health benefits of yoghurt to identify any additional studies that might be eligible to be included in the review.

The following study designs will not be eligible for inclusion:

- Case reports

Letters, comments and editorials will be excluded from the search.

3.1.2 Participants

To be included in the review eligible studies will examine the human health benefits of yoghurt in the following populations:

- The general human population

Studies will be categorised by the age groups they investigate, as follows:

- Infants (aged under 1 year)
- Toddlers (aged between 1 and 5 years)
- Older children (aged between 6 and 18 years)
- Adults (18-65 years)
- Older adults (aged over 65)

Studies only examining the health benefits of yoghurt in the following situations will be excluded:

- Human populations with specific diseases;
- Any animal population;
- In vitro studies;
- Studies using technologies that mimic stomachs.

3.1.3 Interventions

Studies eligible for inclusion in this scoping review will include the following interventions:

- Yoghurt, or any of its synonyms (Yogurt; Yoghourt; Yaourt; Joghurt; Yogourt; Yaghourt; Yahourth; Yoghurd; Joghourt; Jogourt; Maas (Amasi); Dahi; Doi; Perugu; Thayir; Mosaru; Curd; Matsun; Matsoon; Matsoun; Matxoun; Madzoon; Madzoun; Mancun; Matson; Matsoni; Dadiah; Dadih; Stragisto).

Studies will also be eligible for inclusion where yoghurt is featured as an intervention in combination with:

- Any other non-probiotic substance.

Studies only reporting the following interventions will not be eligible for inclusion:

- Probiotic yoghurt;
- Fermented milk, kefir and kumys;
- Fermented baby formula;
- Milk.

For the purposes of this scoping review, we will consider yoghurt which is reported to contain any bacteria other than *Streptococcus thermophilius* and *Lactobacillus delbrueckii* subsp. *Bulgaricus* not eligible for inclusion.

Only studies reporting oral consumption of yoghurt are relevant. Topical application of yoghurt as an intervention is not relevant.

3.1.4 Comparators

Studies do not have to feature a comparator to be eligible for inclusion in the scoping review. Where studies do have a comparator, those that compare yoghurt with one or more of the following will be eligible for inclusion:

- Any non-probiotic yoghurt (e.g. low fat yoghurt, full fat yoghurt);
- Any non-yoghurt substance;
- Placebo not including live bacteria.

Studies that compare yoghurt with the following only will not be eligible for inclusion:

- Probiotic yoghurt;
- Fermented buffalo milk.

3.1.5 Outcomes

To be included in this scoping review studies will assess the interventions featured in section 3.1.3 in relation to any of the following outcomes:

- Any health outcome, with particular emphasis on:
    - Bone health (including osteoporosis);
    - Weight management (including satiety outcomes);
    - Metabolic health;
    - Cardiovascular health and risk factors (including obesity, cholesterol/ lipid profiles, hypertension, atherosclerosis, diabetes and insulin resistance);
    - Cancer risk;
    - Malnutrition (including diarrhoea).
    - Gastrointestinal symptoms/digestive health (for example Irritable bowel syndrome; digestive symptoms caused by antibiotics).
    - Prevention of infectious gastrointestinal and respiratory tract diseases in the general population

Studies will be excluded if they only assess the interventions in relation to:

- Faecal count outcomes;
- Outcomes relating to stomach flora;
- Overall assessments of diets where yoghurt is only one factor and not reported separately;
- Dental health
- Lactose intolerance (already agreed by EFSA);
- Contagious diseases;
- Treatment of infectious GI/respiratory tract diseases;
- Studies reporting laboratory or immunological parameters only;
- Inflammatory diseases;
- Auto-immune diseases;

- Eye diseases (e.g. age related macular degeneration) and cataracts;
- Vaginitis;
- Studies of yoghurt interference with antibiotic uptake.

Table 3.1: Summary of inclusion/exclusion criteria

PICOS	Inclusion criteria	Exclusion criteria
Participants	General human population with categorisation by age band	• Subgroups of the general population with specific diseases; • Any animal population; • In vitro studies; • Studies using technologies that mimic stomachs.
Interventions	Yoghurt or yoghurt used in combination with any other non-probiotic yoghurt substance (oral intake only)	• Probiotic yoghurt • Fermented milk, kefir and kumys. • Fermented baby formula; • Milk
Comparators	Where a comparator is assessed it may be: Any non-probiotic yoghurt, non-yoghurt intervention, placebo or control product. Placebos may not contain other active probiotics and/or prebiotics.	• Probiotic yoghurt • Fermented buffalo milk
Outcomes	Any health outcome, with particular emphasis on: • Bone health; • Weight management; • Metabolic health; • Cardiovascular health and risk factors; • Cancer risk; • Malnutrition (including diarrhoea); • GI/digestive health; • Prevention of GI or RT infections.	• Faecal count outcomes; • Stomach flora counts; • Overall assessments of diets where yoghurt is only one factor; • Dental health; • Lactose intolerance • Contagious diseases; • Treatment of infectious diseases • Studies reporting laboratory or immunological parameters only; • Inflammatory diseases; • Auto-immune diseases; • Eye diseases (e.g. age related macular degeneration); • Vaginitis; • Studies of yoghurt interference with antibiotic uptake.
Study types	• Epidemiological studies; • Cohort studies; • Open label studies; • RCTs. Full-papers, abstracts and conference presentations, trial reports and unpublished reports will be eligible.	• Case reports • Letters • Comments • Editorials

3.2 SEARCH STRATEGY

The next stage of the scoping review is to search for relevant studies.

The literature search will be conducted in a range of relevant databases to identify studies investigating the health benefits of yoghurt (Table 3.2). Grey literature will be searched via OAISTER, OpenGrey and NTIS. To identify further unpublished studies, clinical trial registries and conference proceedings will be searched.

Table 3.2: Databases and resources searched

Database	Interface
MEDLINE and MEDLINE In-Process	OvidSP
EMBASE	OvidSP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library/Wiley Interscience
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library/Wiley Interscience
DARE Database of Abstracts of Reviews of Effects (DARE)	CRD interface
Health Technology Assessment Database (HTA)	CRD interface
Science Citation Index (SCI)	Web of Knowledge
Conference Proceedings Citation Index – Science (CPCI-S)	Web of Knowledge
African Index Medicus	http://indexmedicus.afro.who.int/
LILACS	http://search.bvsalud.org/portal/
OAISTER	http://oaister.worldcat.org/
OpenGrey	http://www.opengrey.eu/
NTIS	Proquest Dialog
Biosis	Proquest Dialog
CAB Abstracts	Proquest Dialog
Food Science and Technology Abstracts	Proquest Dialog
ClinicalTrials.gov	www.clinicaltrials.gov
ICTRP (trials)	http://www.who.int/ictrp/en/

Information on ongoing or recently completed studies, unpublished research, and research reported in the grey literature will be identified by searching selected major conference proceedings (from the last three years), as follows:

- ESPEN congress;
- The International Scientific Conference on Nutraceuticals and Functional Foods (Food and function);
- European Nutrition Conference (FENS);
- Federation of American Societies for Experimental Biology (FASEB);
- American Dietetics Association;

- Federation of European Microbiological Societies (FEMS);
- American Society of Microbiology (ASM);
- American College of Gastroenterology (ACG) Annual Scientific Meetings;
- Digestive Disease Week;
- British Society of Gastroenterology meetings;
- United European Gastroenterology Week;
- American Dairy Products Institute (ADPI)
- International Dairy Federation (IDF)
- International Functional Food Conference
- American Society for Nutrition (ASN)
- European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)
- North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)
- International Scientific Association for Probiotics and Prebiotics ISAPP)

Four search strategies to identify studies in the databases MEDLINE and MEDLINE In-Process, Embase, the Central database, and African Index Medicus are presented in Figure 3.1. The strategies do not include the term 'doi', which is very noisy as a search term. It is now the abbreviation for 'digital object identifier', often included in record abstracts and those records are not necessarily about yoghurt.

Figure 3.1 Draft search strategies to identify studies reporting the health benefits of yoghurt

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

1	Yogurt/
2	Streptococcus thermophilus/
3	Lactobacillus delbrueckii/
4	(yogurt$ or yoghurt$ or yoghourt$ or yaourt$ or joghurt$ or yogourt$ or yaghourt$ or yahourth$ or yoghurd$ or joghourt$ or jogourt$).ti,ab.
5	(maas or amasi$1 or dahi$1 or da-hi$1 or dohi$1 or meesti$1 or perugu$1 or thayir$1 or thayiru$1 or mosaru$1 or curd$1 or matsun$1 or matsoon$1 or matsoun$1 or matzoun$1 or madzoon$1 or madzoun$1 or matson$1 or matsoni$1 or dadiah$1 or dadih$1 or stragisto$1 or q?zana$1 or dhahi$1 or dhaunro$1 or juju dhau$1 or rahmjoghurt$ or jameed$1 or zabadi$1 or labni$1 or lebni$1 or labneh$1 or m?st chekide$1).ti,ab.
6	(streptococcus adj3 thermophilus).ti,ab.
7	s thermophilus.ti,ab.
8	(lactococcus adj3 thermophilus).ti,ab.
9	l thermophilus.ti,ab.
10	(lactobacillus adj3 delbruecki$).ti,ab.
11	l delbruecki$.ti,ab.
12	bulgaricus.ti,ab.
13	or/1-12
14	(letter or editorial or comment or case reports).pt.
15	case report.ti.
16	animals/ not (animals/ and humans/)
17	13 not (14 or 15 or 16)

Ovid Embase

1	yoghurt/
2	streptococcus thermophilus/
3	lactobacillus bulgaricus/
4	(yogurt$ or yoghurt$ or yoghourt$ or yaourt$ or joghurt$ or yogourt$ or yaghourt$ or yahourth$ or yoghurd$ or joghourt$ or jogourt$).ti,ab.
5	(maas or amasi$1 or dahi$1 or da-hi$1 or dohi$1 or meesti$1 or perugu$1 or thayir$1 or thayiru$1 or mosaru$1 or curd$1 or matsun$1 or matsoon$1 or matsoun$1 or matzoun$1 or madzoon$1 or madzoun$1 or matson$1 or matsoni$1 or dadiah$1 or dadih$1 or stragisto$1 or q?zana$1 or dhahi$1 or dhaunro$1 or juju dhau$1 or rahmjoghurt$ or jameed$1 or zabadi$1 or labni$1 or lebni$1 or labneh$1 or m?st chekide$1).ti,ab.
6	(streptococcus adj3 thermophilus).ti,ab.
7	s thermophilus.ti,ab.
8	(lactococcus adj3 thermophilus).ti,ab.
9	l thermophilus.ti,ab.
10	(lactobacillus adj3 delbruecki$).ti,ab.
11	l delbruecki$.ti,ab.
12	bulgaricus.ti,ab.
13	or/1-12
14	(letter or editorial).pt.
15	case report/
16	case report.ti.
17	(animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not human/
18	13 not (14 or 15 or 16 or 17)

CENTRAL (Cochrane Library/Wiley Interscience)

ID	Search
#1	MeSH descriptor: [Yogurt] this term only
#2	MeSH descriptor: [Streptococcus thermophilus] this term only
#3	MeSH descriptor: [Lactobacillus delbrueckii] this term only
#4	(yogurt* or yoghurt* or yoghourt* or yaourt* or joghurt* or yogourt* or yaghourt* or yahourth* or yoghurd* or joghourt* or jogourt*)
#5	(maas or amasi* or dahi* or da-hi* or dohi* or meesti* or perugu* or thayir* or thayiru* or mosaru* or curd* or matsun* or matsoon* or matsoun* or matzoun* or madzoon* or madzoun* or matson* or matsoni* or dadiah* or dadih* or stragisto* or q?zana* or dhahi* or dhaunro* or juju next dhau* or rahmjoghurt* or jameed* or zabadi* or labni* or lebni* or labneh* or m?st next chekide*):ti,ab,kw
#6	(streptococcus near/3 thermophilus)
#7	s next thermophilus
#8	(lactococcus near/3 thermophilus)
#9	l next thermophilus
#10	(lactobacillus near/3 delbruecki*)
#11	l next delbruecki*
#12	bulgaricus
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

African Index Medicus **(**http://indexmedicus.afro.who.int/)

Searched using Advanced form interface. Following string searched with Keyword field.

yogurt or yoghurt or yoghourt or yaourt or joghurt or yogourt or yaghourt or yahourth or yoghurd or joghourt or jogourt or yogurts or yoghurts or yoghourts or yaourts or joghurts or yogourts or yaghourts or yahourths or yoghurds or joghourts or jogourts or thermophilus or delbrueckii or bulgaricus [Key Word]

maas or amasi or dahi or da-hi or dohi or doi or meesti or perugu or thayir or thayiru or mosaru or curd or matsun or matsoon or matsoun or matzoun or madzoon or madzoun or matson or matsoni or dadiah or dadih or stragisto or dhahi or dhaunro or juju dhau or rahmjoghurt$ or jameed or zabadi or labni or lebni or labneh or amasis or dahis or da-his or dohis or dois or meestis or perugus or thayirs

or thayirus or mosarus or curds or matsuns or matsoons or matsouns or matzouns or madzoons or madzouns or matsons or matsonis or dadiahs or dadihs or stragistos or dhahis or dhaunros or rahmjoghurts or jameeds or zabadis or labnis or lebnis or labnehs [Key Word]

The searches will not be limited by date or language.

The reference lists of relevant reviews, trials and studies will be searched to identify any further studies.

The results will be loaded into EndNote bibliographic software and deduplicated using several algorithms.

3.3 SELECTION OF ELIGIBLE STUDIES

Record selection will be undertaken using several passes.

The first pass will be undertaken by one reviewer to rapidly remove obviously irrelevant records including those records which report animal studies, address probiotic yoghurts, include ineligible study design features, or report outcomes that are not of interest.

Then initial record selection from the title and abstract will be undertaken by two reviewers independently (second pass). The reviewers will be seeking to identify the studies most likely to contain evidence of the health benefits of yoghurt. If there is uncertainty about whether a record is relevant it will be selected for further checking. At this stage advice on inclusion criteria refinement may be sought from DII.

The full text of potentially relevant studies will then be obtained. The full papers will be assessed for relevance by one reviewer and checked by a second independent reviewer (third pass). Discrepancies will be resolved through discussion or by consulting a third reviewer. Studies that are considered ineligible at this stage will be listed in an 'Excluded Studies' table with reasons for exclusion (EFSA 2010: section 4.1.1.5). This table will be included in the final report. Studies that we are unable to obtain will be listed in another table.

Where questions about study eligibility remain, we will contact the study's primary investigator.

The number of studies identified by the search and excluded at various stages will be recorded and reported in a PRISMA study flow diagram (see Appendix A) following the PRISMA checklist (Appendix B)(5).

3.4 BRIEF DATA EXTRACTION

At the data extraction stage some studies, on close inspection, may prove ineligible. These studies will be described in the 'excluded studies' table with the reasons for exclusion. The

number of records lost at this stage of the review process will be documented in the flow diagram (see Appendix A).

We will develop a data extraction template in Excel. Data likely to be extracted from each study include:

- Study identification information; number, authors, date;
- Study location;
- Study design;
- Study inclusion/exclusion criteria;
- Intervention details (we will collect the definition of yoghurt provided by the authors, strain if provided, administration details and dosage);
- Duration of intervention with yoghurt;
- Comparator details (we will collect the definition provided by the authors, administration details and dosage);
- Population characteristics at baseline (including age, ethnic background, health status, diagnoses, any subgroups for which data are presented separately);
- The number of individuals recruited to the study (total, per treatment group);
- Which eligible outcomes were measured and how were they measured;
- Comments (e.g. significant differences between study groups);

Data will be extracted by one reviewer and checked by a second independent reviewer. Any discrepancies will be resolved through discussion or by consulting a third reviewer.

Where information we need is not presented in the paper we will contact the study authors to ask for the data.

3.5 OVERVIEW OF THE ELIGIBLE STUDIES AND THEIR SUITABILITY FOR REVIEW

The eligible studies will be described in text and presented in tables describing their populations, the interventions and comparators and the study methods.

Studies will be grouped according to their population of focus; the types of intervention used and the outcomes they are assessing.

The feasibility of the eligible studies for the production of a systematic review will be described along with possible subgroups which might be considered. The report will also describe the response rate from study authors who have been asked to provide further information.

Section 4: Report

The final report will be structured as follows and content will be detailed (as far as possible) according to the PRISMA reporting guidelines (5) and EFSA guidance (4) to maximise the opportunities for streamlined transfer into a systematic review:

- Executive summary;
- List of tables and figures;
- Introduction and background to the research question;
- Objectives of the scoping review;
- Description of the research methods;
    - Search strategy;
    - Record selection;
    - Brief study data extraction;
    - Analyses of the results.
- Brief tables providing the results of the scoping review including a flow diagram of the study selection process;
- Discussion of the similarity of studies for production of a SR;
- References;
- Included studies tables;
- Excluded studies tables;
- Forthcoming studies table;
- PRISMA checklist;
- Search strategies

Section 5: Timeline

The project timeline is presented in Table 5.1. The primary objective is to provide DII with a draft report before the 2014 “yoghurt summit”. Given the volume of papers to be reviewed we will make a provisional report available to inform any presentations DII may wish to make. A full final report will then be made available in April 2014. To accommodate this we will begin data extraction in parallel to study selection. The timelines may be impacted by waiting for responses to queries to authors and the client. If we encounter unexpectedly large numbers of records we may discuss prioritisation strategies with DII.

We will respond to DII’s comments on the draft scoping review report within three weeks of receipt: our response will describe how we will respond to comments and the date for completion of the revised report: the time for revision will depend on the scale of the comments. All timings are dependent on timely agreement of the protocol. If there is a delay in agreement of the protocol, then these delays will impact upon the subsequent timings.

Table 5.1: Timeline for the scoping review

Activity	Current estimated date	Current timeline
Project initiation meeting/ Protocol development	31/10/13	Protocol agreed 8 Nov 2013.
Searching	07/11/13	
Record assessment / ordering / further selection	21/11/13	
Full text assessment for relevance	03/01/14	
Record extraction	28/02/14	
Provide provisional draft report	14/03/14	
Provide full draft report	31/03/14	
Revised report (in light of DII comments)	April 2014	

Figure 5.1: Timeline for the scoping review

References

1. Codex Committee on Milk and Milk Products. Codex Standard for Fermented Milks (2nd Ed). In. New Zealand: Codex Alimentarius 2010. p. 11.

2. Meyer AL, Elmadfa I, Herbacek I, Micksche M. Probiotic, as well as conventional yogurt, can enhance the stimulated production of proinflammatory cytokines. Journal of Human Nutrition and Dietetics. 2007;20(6):590-98. Available from: http://dx.doi.org/10.1111/j.1365-277X.2007.00807.x

3. McKinley MC. The nutrition and health benefits of yoghurt. International Journal of Dairy Technology. 2005;58(1):1-12. Available from: http://dx.doi.org/10.1111/j.1471-0307.2005.00180.x

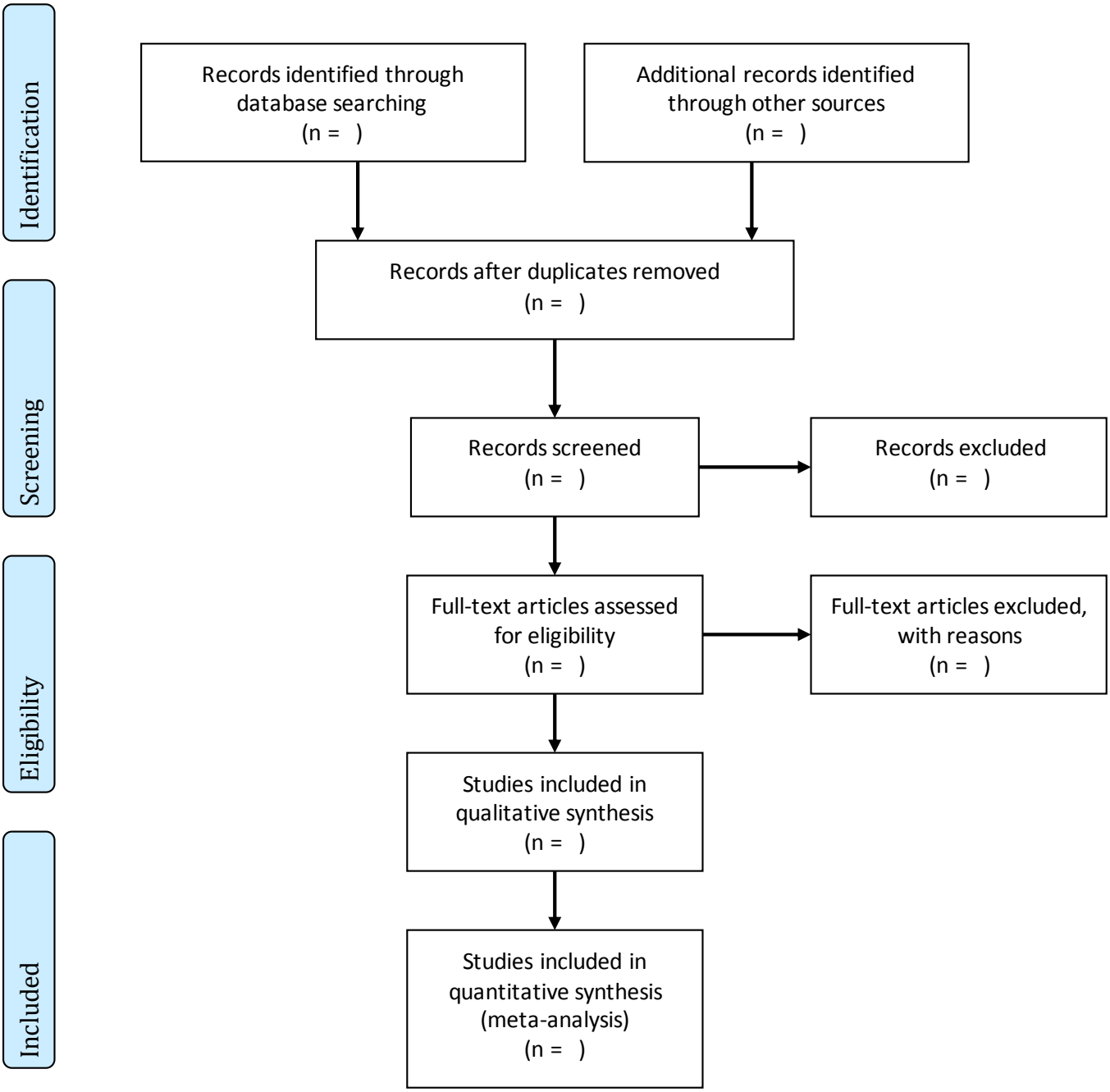
4. European Food Safety Authority. Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA Journal. 2010;8(6):1637. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/1637.htm.

5. Liberati A, Altman D, Tezlaff J, Mulrow C, Gotzsche P, Ioannidis J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.

APPENDIX A

PRISMA flow diagram

PRISMA 2009 Flow Diagram



APPENDIX B

PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	This project was funded by Danone Institute International

APPENDIX C

Protocol Amendments

Protocol clarifications and amendments

The following changes were made:

Section 3.1.3

The following text was added to the list of non-eligible interventions:

- "Fermented baby formula"

The following text was added to clarify eligible/ non-eligible interventions:

"For the purposes of this scoping review, we will consider yoghurt which is reported to contain any other bacteria than *Streptococcus thermophilius* and *Lactobacillus delbrueckii* subsp. *Bulgaricus* to be not eligible for inclusion.

Only studies reporting oral consumption of yoghurt are relevant. Topical application of yoghurt as an intervention is not relevant."

Section 3.1.4

One exclusion criteria was removed after an assessment of the results retrieved:

- Yoghurt used as the carrier base for other substances alone where the other substance is the focus of the study;

On closer inspection of records where yoghurt was a carrier for another active substance, we felt that the purpose of the study did not really impact the investigation of yoghurt compared to another substance as long as there was a comparison of the 'other active substance+yoghurt' versus 'other active substance+another product'. The principle was that it was possible to see the effects of yoghurt compared to another substance or product, despite yoghurt being the carrier in that specific paper.

Section 3.1.5

The following text was added to the list of eligible outcomes:

- "Cancer risk;"

The following eligible outcomes were modified:

- "Cardiovascular health and risk factors (including obesity, cholesterol/ lipid profiles, hypertension, atherosclerosis, diabetes and insulin resistance);

- Gastrointestinal symptoms/digestive health (for example Irritable bowel syndrome; digestive symptoms caused by antibiotics)."

The following text was added to the list of non-eligible outcomes:

- Eye diseases (e.g. age related macular degeneration) and cateracts;
- Vaginitis;
- Studies of yoghurt interference with antibiotic uptake

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