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EXISTE RELAÇÃO ENTRE A ABUNDÂNCIA DE BACTÉRIAS REDUTORAS DE NITRATO E A HIPERTENSÃO ARTERIAL? UMA REVISÃO SISTEMÁTICA

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Orientadora: Profa. Renata Maria Lataro, Dra.

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Este Trabalho de Conclusão de Curso foi julgado adequado para obtenção do título de Bacharel em Farmácia e aprovado em sua forma final pelo Curso de Graduação em Farmácia do Centro de Ciências da Saúde da Universidade Federal de Santa Catarina.

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RESUMO

Contexto: A hipertensão arterial (HA) é uma doença crônica multifatorial caracterizada pelo aumento sustentado da pressão arterial (PA) que afeta em torno de 1,4 bilhão de pessoas no mundo. O óxido nítrico (NO) é uma molécula vasodilatadora que atua no controle da PA, e sua produção pode ocorrer pela redução de nitratos por bactérias redutoras de nitrato orais ou intestinais. Entretanto, a relação entre bactérias redutoras de nitrato e a HA permanece em debate. **Objetivo:** Revisar sistematicamente a relação entre a abundância de bactérias redutoras de nitrato orais e intestinais e o diagnóstico de HA em humanos. **Bases de dados:** MEDLINE (via PubMed), Scopus, Cochrane Library (Central), EMBASE, LILACS, Web of Science e Livivo (bases de dados) e ProQuest e Google Scholar (literatura cinzenta) foram acessados em busca de artigos elegíveis em 14 de maio de 2022, sem limitação da data de publicação. **Extração de dados**: A busca identificou 6598 artigos, e após a aplicação dos critérios de inclusão e exclusão, 23 deles foram incluídos no estudo. **Resultados:** Realizou-se uma análise qualitativa dos dados de 18 artigos que avaliaram a microbiota intestinal, 4 que avaliaram a microbiota oral e 1 que avaliou ambas. Considerando-se a microbiota intestinal, apenas um estudo demonstrou depleção da espécie *Lactobacillus farciminis* na microbiota intestinal de pacientes hipertensos, o que representa baixa expressividade no comprometimento da redução de nitrato pela microbiota intestinal. Na microbiota oral, não se observou redução da abundância de bactérias redutoras de nitrato em pacientes hipertensos. **Conclusão:** Segundo os dados obtidos com esta revisão sistemática, a abundância de bactérias redutoras de nitrato orais e intestinais não está reduzida na HA.

Palavras-chave: óxido nítrico; microbiota; doenças cardiovasculares; disbiose; bactérias entéricas.

ABSTRACT

Context: Arterial hypertension (AH) is a multifactorial chronic disease characterized by a sustained increase in blood pressure (BP) that affects about 1.4 billion people worldwide. Nitric oxide (NO) is a vasodilator molecule acting in BP control, and its production can occur through the reduction of nitrates by oral or intestinal nitrate-reducing bacteria. However, the relationship between nitrate-reducing bacteria and AH remains under debate. **Objective:** To systematically review the relationship between the abundance of oral and intestinal nitrate-reducing bacteria and the diagnosis of AH in humans. **Databases:** MEDLINE (via PubMed), Scopus, Cochrane Library (Central), EMBASE, LILACS, Web of Science and Livivo (databases), and ProQuest and Google Scholar (gray literature) were searched for eligible articles on May 14, 2022, with no publication date restriction. **Data Extraction:** The search identified 6598 articles, and 23 were included in the study after applying the inclusion and exclusion criteria. **Results:** It was conducted a qualitative data analysis of 18 articles that assessed the intestinal microbiota, 4 that assessed the oral microbiota, and 1 that assessed both. In one study, a depletion of the species *Lactobacillus farciminis* was observed in the intestinal microbiota of hypertensive patients, representing low expressiveness in the impairment of nitrate reduction by the intestinal microbiota. In the oral microbiota, there was no reduction in the abundance of nitrate-reducing bacteria in hypertensive patients. **Conclusion:** According to the data obtained from this systematic review, the abundance of oral and intestinal nitrate-reducing bacteria is not reduced in AH.

Keywords: nitric oxide; microbiota; cardiovascular diseases; dysbiosis; enteric bacteria.

SUMÁRIO

CONSIDERAÇÕES INICIAIS

Este Trabalho de Conclusão de Curso foi escrito na forma de artigo científico, visto que há interesse em publicá-lo em periódico científico especializado. Análises subsequentes serão realizadas para complementar os resultados e discussão e, assim, construir um artigo ainda mais robusto que será submetido na revista proposta a seguir:

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EXISTE RELAÇÃO ENTRE A ABUNDÂNCIA DE BACTÉRIAS REDUTORAS DE NITRATO E A HIPERTENSÃO ARTERIAL? UMA REVISÃO SISTEMÁTICA

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Introduction

Arterial hypertension (AH) is a multifactorial chronic disease characterized by a sustained increase in blood pressure (BP),[1] which represents a significant risk factor for myocardial infarction, stroke, renal failure, and peripheral vascular disease.[2] It affects about 1.4 billion people worldwide, two-thirds of them in underdeveloped or developing countries.[3,4] Microbiota refers to the set of microorganisms that coexist peacefully with their hosts.[5] It is estimated that the human microbiome contains up to 10^{14} bacterial cells,[6] forming different communities that are distributed over practically the entire surface of the organism and that are present in the oral cavity, in the respiratory tract, in the skin, in the urogenital tract and, mainly, in the gastrointestinal tract.[7] The microbiota of each individual has unique characteristics,[8] and with all this variability comes the difficulty in determining the components of the normal microbiota.[7] Therefore, it is also difficult to characterize the profile of dysbiosis, which could lead to the development of diseases as AH.[7] AH is mediated by several mechanisms, including the endothelial dysfunction.[9] NO is a vasodilator molecule acting in BP control,[10] and its production can occur through the reduction of nitrates by oral or intestinal nitrate-reducing bacteria.[11,12] The nitrate-nitrite-NO pathway acts by helping and complementing the canonical generation of NO from NOS, especially when in malfunction.[11] In this context, nitrate and nitrite anions can be used as precursors for generating NO and other bioactive nitrogen intermediates. In this case, bacteria are mandatory to convert nitrate to nitrite, the first step in nitrate bioactivation.[13] Although the main and limiting steps of the nitrate-nitrite-NO pathway occur in the oral cavity,[14] the gut microbiome can also reduce nitrate.[12] Considering that nitrate is inert and needs to be reduced by nitrate-reducing bacteria to nitrite to exert any biological function, oral and gut bacteria play a key role in this process.[11,15] In addition, they play an important role in determining plasma levels of nitrite and, therefore, in the physiological control of BP, being related to AH.[16]

Various studies demonstrate acute and chronic BP reduction after nitrate supplementation in humans.[17] For example, Kapil et al[18] conducted a randomized, double-blind, placebo-controlled clinical trial lasting 4 weeks that showed a lasting reduction in BP in hypertensive participants after nitrate ingestion.[18] However, studies indicate that oral microbiota suppression affects systemic nitrite levels and, consequently, BP in humans. [16,19] Kapil et al[16] measured BP (clinic, home, and 24-h ambulatory) in healthy volunteers during an initial control period followed by a treatment period with a chlorhexidine-based antiseptic mouthwash. The treatment reduced oral nitrite production by 90% and plasma nitrite levels by 25%. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) increased by 2 to 3.5 mmHg,[16] suggesting that the reduction of endogenous nitrate produced by oral bacteria plays an important role in determining plasma nitrite levels and, therefore, in the physiological control of BP.[16] Although several studies have shown the effects of nitrate/nitrite on BP control, the relationship between nitrate-reducing bacteria and the development of AH remains under debate.

Therefore, this study was developed to analyze if a lower abundance of nitrate-reducing oral and/or fecal bacteria is associated with hypertension in adults. The present study systematically reviewed the relationship between the abundance of oral and intestinal nitrate-reducing bacteria and the diagnosis of AH in humans.

Methods

This systematic review was performed according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guideline,[20] which is included in Appendix S1. The systematic review protocol was registered on International Prospective Register of Systematic Reviews (PROSPERO) on May 13, 2022.

Eligibility Criteria

The acronym PICOS (Population; Intervention; Comparator; Outcomes; Studies) illustrated in Table 1 was used to define the research question and the inclusion and exclusion criteria for this systematic review. The studies were included if they: (1) were observational studies (cross-sectional, case-control and cohort) and clinical trials (randomized and non-randomized); (2) included adults (≥ 18 years old) with arterial hypertension (SBP ≥ 130 mmHg and/or DBP ≥80 mmHg and/or use of blood pressure lowering medication); (3) compared (or not) to normotensive adults; and (4) used microbiome analysis inferred from next-generation sequencing (NGS) to identify different bacterial taxa in the oral and/or gut nitrate-reducing bacteria. Exclusion criteria consisted of: (1) studies including subjects younger than 18 years; (2) studies not showing NGS data; (3) studies performing previous culture step; (4) studies written in non-Latin alphabet, not possible to translate in a translation application; (5) studies using any alternative study design (case reports, case series); (6) pre-clinical studies (in vitro or in animals); (7) books and books chapters, letters, opinions, reviews (narrative or systematic), guidelines, conferences abstracts.

Literature search

On May 14, 2022, a literature search was performed in the following databases: MEDLINE (via PubMed), Scopus, Cochrane Library (Central), EMBASE, LILACS, Web of Science and Livivo. Gray literature was accessed via ProQuest and Google Scholar databases. Different syntaxes were used to select articles from different databases to fulfill their requirements, as shown in Appendix S2.

Study selection

All identified records were exported to reference manager software Mendeley (1.19.8, Elsevier), used to automatically exclude duplicated records. In the sequence, duplicates were

also searched and deleted manually. The remaining records were exported to Rayyan,[21] where two reviewers (EMP and LFT) independently screened titles and abstracts according to inclusion and exclusion criteria (phase 1). Afterwards, the reviewers proceeded to independent complete text reading of the relevant articles considering inclusion and exclusion criteria (phase 2). The third reviewer (RML) resolved disagreements between the review authors. Reference lists of the elected articles were manually searched to identify other eligible studies.

Data extraction

Data from the included studies were extracted by EMP, while confirmation of the extracted data was performed by RML. Extracted data consisted of: author, year, country, type of study, population (number), population age (mean age with SD), number of drugs (mean and SD), most-used drugs (number and percentage), number of participants using antihypertensive drugs, population with controlled hypertension (number and percentage), body mass index (BMI), blood pressure, region of 16S rRNA sequencing and differential abundance of oral and gut nitrate-reducing bacteria. Any disagreements were resolved via another review of the original articles. Intestinal and oral nitrate-reducing bacteria were identified according to described by Ji X., 1988,[22] Neut C., 1997,[23] Parham N. J., 2000,[24] Sobko T. et al, 2005[25] and Tiso M., 2015[26] and Goh 2019[27] and are listed in Appendix S3 and Appendix S4.

Risk-of-bias assessment

Two independent reviewers (EM and RML) analyzed the risk of bias of included studies using The Joanna Briggs Institute Critical Appraisal (JBI) Tool for prevalence studies.[28] We determined three main questions based on the objectives of this systematic review: Was the sample frame appropriate to address the target population?; Were valid methods used for the

identification of the condition?; Was the condition measured in a standard, reliable way for all participants? The remaining six questions were considered non-critical domains. The study was considered with a high risk of bias when: 1) two or more "no" answers in the main domains; or 2) one "no" and two "unclear" answers in the main domains; or 3) one "no" answer in one main domain and two or more "no" answers in non-critical domains. The criterion for low risk of bias was one "no" answer or two "unclear" answers in non-critical domains. When the study did not fit the high or low risk of bias criteria, it was considered as a moderate risk.

Certainty of evidence assessment

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (https://www.gradepro.org) was used by two reviewers (EMP and RML) to assess the certainty of the evidence of included articles, and any disagreements were solved by discussion. This tool presents five domains: "risk of bias", "inconsistency", "indirectness", "imprecision" and "publication bias". An overall rating of "high", "moderate", "low" or "very low" was given separately to intestinal and oral microbiota to classify the certainty of evidence based on the domains mentioned above.

Results

Search results

The search across the databases identified 6598 articles, of which 6506 were from all databases, and 190 were from gray literature. After automatic removal of duplicated articles, remained 6046 references on all databases and 189 on gray literature. Then a second duplicate removal was carried out manually, remaining 6003 records on all databases and 189 records on gray literature. In the sequence, the articles were assessed by title and abstract reading (phase 1), and 46 records from all databases and 14 from gray literature remained to

be analyzed by full-text reading (phase 2). Full-text reading resulted in 1 report of included article and 23 articles eligible for qualitative analysis (23 from all databases and 8 from gray literature). Considering the inclusion and exclusion criterion, 23 articles were included in this systematic review; 18 analyzed the intestinal microbiota, 4 analyzed the oral microbiota, and 1 analyzed both. Appendix S5 shows the articles excluded in phase 2 and the respective reasons for exclusion. The most important reasons for exclusion were the wrong study design (n = 21) followed by the wrong outcome (n = 2), written in non-Latin alphabet (n = 1) and the wrong publication type (n = 1). The PRISMA flow chart presents a summary of the review's inclusion and exclusion process (Figure 3).

Study characteristics

Intestinal microbiota

The intestinal microbiota studies' characteristics are summarized in Table 2. A total of 19 articles were included on the topic of intestinal microbiota in this systematic review. Of them, 11 were conducted in China,[29,30,39,31–38] 2 in the United States[40,41] and 1 study each in Spain,[42] Russia,[43] United Kingdom,[44] Australia,[45] Finland[46] and Brazil.[47] Most of them are cohort studies (n = 9),[32,36,39,40,43,44,46–48] while the others are case-control studies[30,35,37,38,45] and cross-sectional studies.[29,33,34,49,50] The articles were published between 2017 and 2022. The sample sizes in the studies ranged from a minimum of 47 participants[40] to a maximum of 6953 participants.[46] While 17 articles reported findings of both sexes, 1 study investigated only female participants.[44] Of the reported data, the age (mean ± SD) of participants ranged from 41.1 ± 9.1[49] to 69.322 ± 10.613.[30] The BMI ranged from 20.64 ± 1.85[37] to 30.7 ± 7.0[40] for the normotensive group and from 20.47 ± 2.01[37] to 37.5 ± 13.4[40] for the hypertensive group. In normotensive individuals, SBP (mean ± SD) was 117.99 ± 5.68 and DBP was 74.46 ± 4.21. Considering the hypertensive participants, available data shows SBP as 151.67 ± 14.16 and

DBP as 91.02 ± 8.25. A total of 7 studies assessed individuals not using blood pressure-lowering medication,[32,37,39,43,45,49,50] while 3 studies reported hypertensive groups of which part of the participants was receiving antihypertensive treatment.[29,41,46] Nevertheless, no data was available about antihypertensive treatment for the remaining articles. Only one study reported specific classes of antihypertensive medications used by the participants.[46]

Nine studies[32,37–40,43,45,47,49,50] assessed participants whose blood pressure was uncontrolled (≥ 140/90 mmHg).

The differential abundance data of oral nitrate-reducing bacteria are presented in table 3. Most studies used V3-V4 region of 16S rRNA to assess microbial data,[29,33,50,51,34–36,41,43,45,47,49] while 4 assessed only the V4 region[32,37,39,44] and 3 did not inform the region of analysis.[38,40,46]

The genus *Enterobacter* was found depleted in hypertensive patients in one study,[32] while *Enterobacter*,[31,36,46] *Actinomyces*,[32,46] *Klebsiella*,[32,37,38] *Citrobacter*,[37,46] *Pseudomonas*,[37] *Providencia*[37] and *Proteus*[37] were found increased. Furthermore, genera *Klebsiella* and *Actinomyces* were diminished in control group,[32] while *Staphylococcus* were increased.[30] Also, at a species level, *Bacteroides vulgatus*,[36,49] *Lactobacillus rhamnosus*,[46] *Escherichia coli*[36] and *Klebsiella Pneumoniae*[38] were increased in hypertensive groups *and Lactobacillus farciminis* was depleted[46]. Moreover, species *Bacteroides vulgatus* and *Escherichia coli* were increased in normotensive groups.[40]

Oral microbiota

The oral microbiota studies' characteristics are summarized in Table 4. Five articles were included on the topic of oral microbiota in this systematic review. Of them, 3 were conducted in China,[29,52,53] 1 in the United States[54] and 1 in Qatar.[55] Their designs are cohort studies,[53,55]

cross-sectional[29,52] and prospective cohort.[54] These articles are relatively recent and were published between 2021 and 2022. The sample sizes in the studies ranged from a minimum of 50 participants[52] to a maximum of 909 participants.[54] While most articles reported findings of both sexes, 1 study investigated only female participants.[54] Of the reported data, the age (mean ± SD) of participants ranged from 30.50 ± 5.74[52] to 67.42 ± 1.82.[29] The BMI ranged from 22.81 ± 0.69[29] to 25.1 ± 4.3[54] for the normotensive group and from 24.12 ± 0.57[29] to 28.2 ± 5.9[54] for the hypertensive group. SBP (mean ± SD) was 113.31 ± 6.10 and DBP (mean ± SD) was 69.6 ± 4.36 for the normotensive group. Relative to hypertension groups, available data shows SBP (mean ± SD) of 131.71 ± 5.58 and DBP (mean ± SD) of 80.38 ± 9.31 for these groups. Only one of the records did not report participants' ages, BMI and BP.[55] One study only assessed antihypertensive treatment-naive participants,[53] while 1 article reported a hypertension group in which part of the participants was receiving antihypertensive treatment[29] and for other 2 studies all participants of hypertension group were receiving antihypertensive treatment.[54,55] The remaining article[52] did not report how many (or if) participants were treating hypertension. Three studies[29,52,53] assessed participants whose blood pressure was uncontrolled (≥ 140/90 mmHg), while the others[54,55] did not report this information.

The differential abundance data of oral nitrate-reducing bacteria are presented in table 5. All studies analyzed the V3-V4 region of 16S rRNA to assess microbial data. Genera *Neisseria*,[29,52,53] *Haemophilus*,[29,52] *Veillonella*,[52,56] *Fusobacterium*,[52] *Leptotrichia*,[52] *Prevotella*[56] and *Actinomyces*[56] were found increased in hypertensive groups compared to normotensive groups. It was found that genera *Prevotella* and *Veillonella* were increased in the subgingival plaques and saliva of the control group,[29] while *Neisseria* was increased only in the subgingival plaques compared to hypertensive participants.[29] Also, genera *Prevotella*,[52]

206 *Actinomyces*,[52] *Porphyromonas*,[52] *Granulicatella*[52] and *Fusobacterium*[56] were increased in
207 oral samples of the normotensive group. In addition, at a species level, one study[54] found an
208 increase of *Veillonella atypica*, *Veillonella dispar*, *Veillonella parvula*, *Neisseria sicca*,
209 *Selenomonas noxia*, *Prevotella melaninogenica*, *Prevotella salivae* and *Rothia mucilaginosa*
210 in the hypertensive group. Moreover, species *Corynebacterium durum*, *Granulicatella*
211 *adiacens*, *Actinomyces naeslundii*, *Haemophilus parainfluenzae*, *Rothia dentocariosa*,
212 *Corynebacterium matruchotti*, *Neisseria subflava* and *Neisseria flavescens* were found
213 increased in normotensive group.[54]
214
215 **Risk of bias assessment**
216 The risk of bias assessment is summarized in Table 6. In the intestinal microbiota, 12 articles
217 were judged to have a moderate risk of bias, 7 were judged to have a low risk of bias, and
218 none had a high risk of bias. In addition, in the oral microbiota, there were 4 studies with a
219 moderate risk of bias and 1 with low risk of bias, while none had a high risk of bias.
220
221 **Certainty of evidence assessment**
222 We evaluated the certainty of the evidence of the studies on the intestinal and oral microbiota
223 separately. However, the overall results from intestinal and oral microbiota were similar. The
224 risk of bias was considered serious, while inconsistency, indirectness and imprecision were
225 judged as not serious. On the topic of other considerations, it was considered that the fecal
226 sample quality was uncertain and that may influence certainty assessment. Overall, the
227 certainty of evidence assessed through the GRADE approach was low for both intestinal and
228 oral microbiota. Appendix S6 presents GRADE analysis.
229
230 **Discussion**
231 There is growing interest in the potential role of the microbiota in BP regulation and
232 hypertension development.[57] This systematic review was developed to analyze if a lower

abundance of nitrate-reducing oral and/or fecal bacteria is associated with hypertension in adults. Three cross-sectional,[29,49,50] 3 cohort[32,36,46] and 3 case-control[30,37,38] brought information relative to nitrate-reducing bacteria of intestinal microbiota (Table 3). In addition, five studies[29,52–54,56] brought information about nitrate-reducing bacteria of oral microbiota (Table 5).

Intestinal microbiota

In hypertensive patients, the genus *Enterobacter* was found depleted in one study[32] and increased in three studies.[31,36,46] Furthermore, *Actinomyces*,[32,46] *Klebsiella*,[32,37,38] *Citrobacter*,[37,46] *Pseudomonas*,[37] *Providencia*[37] and *Proteus*[37] were found increased in hypertensive patients. The genera *Klebsiella* and *Actinomyces* were diminished in the control group,[32] while *Staphylococcus* were increased.[30] *Enterobacter* is well documented to induce pro-inflammatory responses and is associated with gut microbiota dysbiosis.[58] *Klebsiella* is a pathogen routinely found in the human gut that causes pneumonia, diarrhea, and urinary tract infection and is related to gut dysbiosis.[38] The genus *Citrobacter* is involved with carnitine metabolism,[59] which originates the gut microbiota-derived metabolite trimethylamine N-oxide (TMAO).[60] TMAO is related to the progression of atherosclerosis[60] and possibly to AH.[61] Although *Enterobacter*, *Klebsiella*, and *Citrobacter* are nitrate-reducing bacteria,[23,24] they may contribute to dysbiosis in AH through pro-inflammatory effects and/or TMAO production.[38,58–62]

At a species level, *Bacteroides vulgatus*,[36,49] *Lactobacillus rhamnosus*,[46] *Escherichia coli*[36] and *Klebsiella pneumoniae*[38] were increased while *Lactobacillus farciminis* was depleted in the hypertensive groups.[46] Furthermore, species *Bacteroides vulgatus* and *Escherichia coli* were also abundant in normotensive individuals.[40] No depleted bacteria were found in normotensive groups. *Bacteroides vulgatus* is one of the dominant species of genus

Bacteroides in human gut microbiota[63] and is capable of dissimilatory nitrate reduction (DNRA) in the gut, which produces NO.[24] However, it is enhanced in a model of intestinal inflammation in mice.[64] In vitro, NO generation by mono-inoculated bacteria plates added with nitrate showed that *Escherichia coli* produced low NO levels.[25] However, another culture experiment showed *Escherichia coli* as one of the predominant nitrate-reducing species.[24] In another study, nitrite generation in vitro by *Lactobacillus rhamnosus* was small, but considerable.[26] *Klebsiella pneumoniae* is the medically most important species of its genus, responsible for the most significant number of nosocomial infections.[65] *Lactobacillus farciminis* is a probiotic species[66] that demonstrated ex vivo NO production in the colonic lumen of rats.[67] Overall, it was found a depletion of nitrate-reducing species *Lactobacillus farciminis* and an increase of *Bacteroides vulgatus*, *Lactobacillus rhamnosus*, *Escherichia coli* and *Klebsiella pneumoniae* in the hypertensive group. Species *Bacteroides vulgatus* and *Escherichia coli* were also increased in the normotensive groups. Given the overlap of nitrate-reducing bacteria that are increased in hypertensive and normotensive individuals, these bacteria are unlikely to impact nitrate reduction. Furthermore, the impact of *Lactobacillus farciminis* depletion in the intestinal microbiota of the hypertensive group in the impairment of nitrate reduction by the intestinal microbiota is improbable. Moreover, it is interesting to highlight that this reduction was observed only in one study. Thus, our data suggested that the abundance of nitrate-reducing bacteria might not be compromised in AH.

Oral microbiota

Genera *Neisseria*,[29,52,53] *Haemophilus*,[29,52] *Veillonella*,[52,56] *Fusobacterium*,[52] *Leptotrichia*,[52] *Prevotella*[56] and *Actinomyces*[56] were found increased in hypertensive groups compared to normotensive groups. No depleted bacteria were found in hypertensive groups. However, in the normotensive groups, another study also found genera *Prevotella* and *Veillonella* increased in the subgingival plaques and saliva,[29] and *Neisseria* increased in the subgingival

plaques.[29] Furthermore, it was also found genera *Prevotella*,[52] *Actinomyces*,[52] *Porphyromonas*,[52] *Granulicatella*,[52] and *Fusobacterium*[56] increased in oral samples of the normotensive group. No depleted bacteria were found in the normotensive groups. Genera *Neisseria*, *Haemophilus*, *Veillonella*, *Leptotrichia*, *Prevotella* and *Granulicatella* are some of the most abundant nitrate-reducing bacteria of oral microbiota.[68–71] Excluding *Granulicatella*, the others were abundant in hypertensive patients. It is known that there is a link between periodontal disease and AH, as there is a higher presence of periodontitis in patients with AH than in those without AH.[72] *Veillonella* is associated with caries[73] and *Prevotella* is linked to bacteria plaques,[74] gingivitis,[75] periodontitis,[75] halitosis[76] and cardiovascular disease.[77] Similarly, *Neisseria* and *Haemophilus* are highly abundant in saliva in periodontitis.[78] Therefore, although *Prevotella*, *Neisseria* and *Haemophilus* are nitrate-reducing bacteria increased in hypertensive patients, they are also related to periodontitis.

In addition, at a species level, one study[54] found an increase of *Veillonella atypica*, *Veillonella dispar*, *Veillonella parvula*, *Neisseria sicca*, *Selenomonas noxia*, *Prevotella melaninogenica*, *Prevotella salivae* and *Rothia mucilaginosa* in the hypertensive group. Moreover, species *Corynebacterium durum*, *Granulicatella adiacens*, *Actinomyces naeslundii*, *Haemophilus parainfluenzae*, *Rothia dentocariosa*, *Corynebacterium matruchotti*, *Neisseria subflava* and *Neisseria flavescens* were found increased in normotensive group.[54] These species, except for *Corynebacterium durum*, *Actinomyces naeslundii* and *Corynebacterium matruchotti*, are some of the most important nitrate-reducing bacteria of oral microbiota.[68–71,79] However, it is important to note that these species data were extracted from a single study.

Overall, considering species, it was not found depleted nitrate-reducing bacteria in the hypertensive group. However, there was an increase in the nitrate-reducing bacteria both in hypertensive and normotensive groups. Genera *Neisseria*, *Haemophilus* and *Prevotella*, which are related to periodontitis, were increased in hypertensive groups, while only *Prevotella* was increased in normotensive groups. Furthermore, genera *Veillonella*, *Fusobacterium*, *Leptotrichia* and *Actinomyces* were found increased in hypertensive groups, and *Veillonella*, *Actinomyces*, *Porphyromonas*, *Granulicatella* and *Fusobacterium* increased in normotensive groups. Moreover, *Veillonella atypica*, *Veillonella dispar*, *Veillonella parvula*, *Neisseria sicca*, *Selenomonas noxia*, *Prevotella melaninogenica*, *Prevotella salivae* and *Rothia mucilaginosa* were increased in the hypertensive group; and *Corynebacterium durum*, *Granulicatella adiacens*, *Actinomyces naeslundii*, *Haemophilus parainfluenzae*, *Rothia dentocariosa*, *Corynebacterium matruchotti*, *Neisseria subflava* and *Neisseria flavescens* were increased in the normotensive group. Considering that the number of increased genera and species is the same between the hypertensive and the normotensive groups, and that three of the increased species in the normotensive group are not listed among the main nitrate-reducing bacteria in the oral microbiota, it is not possible to state that there is a reduction of oral nitrate-reducing bacteria in AH. Thus, our data do not support the hypothesis that the oral abundance of nitrate reducing bacteria is compromised in AH. Furthermore, the remaining studies[33–35,39,41,43,44,47,80] did not find a differential abundance of fecal and/or oral nitrate-reducing bacteria in hypertensive patients.

In the intestinal microbiota, 12 articles were judged to have a moderate risk of bias, 7 were judged to have a low risk of bias and none had a high risk of bias. In addition, in the oral microbiota, there were 4 studies with a moderate risk of bias and 1 with a low risk of bias.

Overall, the certainty of evidence assessed through the GRADE approach was low for both intestinal and oral microbiota.

Conclusion

The data obtained with this systematic review supports the concept that intestinal and oral abundance of nitrate-reducing bacteria is not reduced in AH. However, the depletion of *Lactobacillus farciminis* in the intestinal microbiota of the hypertensive group, observed in one study, has to be investigated.

Registration

The systematic review protocol was registered on PROSPERO on May 13, 2022, under the identification number CRD42022315891.

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Author contributions. RML, NDT and CMS developed the research question and prepared the systematic review protocol, and EMP performed the literature search. EMP and LFT proceeded with the studies selection. Data extraction and analysis was performed by EMP. RML contributed with data analysis and interpretation. EMP wrote the manuscript. RML critically assessed and approved the final version of the manuscript.

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Declaration of Interest. The authors declare no competing interests.

Supporting information

The following Supporting Information will be available through the online version of this article at the publisher's website.

Appendix S1 - PRISMA 2020 checklist

Appendix S2 - Databases and search strategies

Appendix S3 - List of intestinal nitrate-reducing bacteria.

Appendix S4 - List of oral nitrate-reducing bacteria.

Appendix S5 - Excluded articles and reasons for exclusion

Appendix S6 - Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

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Table Legend

Table 1 - PICOS criteria for inclusion of studies.

Table 2 - Characteristics of included studies analyzing intestinal microbiota (n = 19).

Table 3 - Characteristics of included studies analyzing intestinal microbiota (n = 19).

Table 4 - Characteristics of included studies analyzing oral microbiota (n = 5).

Table 5 - Characteristics of included studies analyzing oral microbiota (n = 5).

Table 6 - Assessment of methodological quality of individual studies using the JBI Critical Appraisal Checklist for prevalence studies

Figure Legend

Figure 1 - PRISMA 2020 flow diagram of the literature search process.

TABLES AND FIGURES

Table 1 - PICOS criteria for inclusion of studies.

Parameter	Inclusion criteria	Exclusion criteria
Participants	Adults (≥ 18 years old)	Subjects younger than 18 years
Intervention or exposition	Arterial hypertension (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 80 mmHg and/or use of blood pressure lowering medication)	
Comparison or control	Normotensive group (systolic blood pressure ≤ 120 mmHg and diastolic blood pressure ≤ 80 mmHg) or no control group	
Outcome measure(s)	The differential abundance of oral and/or gut nitrate-reducing bacteria, inferred from NGS data	Studies not showing NGS data; Studies performing previous culture step
Types of **S**tudies included	Observational studies (cross-sectional, case-control and cohort) and clinical trials (randomized and non-randomized – only baseline data).	Studies written in non-Latin alphabet, not possible to translate in a translation application; Studies using any alternative study design (case reports, case series); Pre-clinical studies (in vitro and in animals); Books and books chapters, letters, opinions, reviews (narrative or systematic), guidelines, conferences abstracts

Table 2 - Characteristics of included studies analyzing intestinal microbiota (n = 19).

Author, year, Country	Type of study	Population (n)				Population mean age with SD		Number of drugs, mean SD		Most-used drugs, n (%)	Participants using antihypertensive drugs (n)	Controlled HTN, n (%)		BMI		BP (Systolic/diastolic)		Sequencing, 16S rRNA region
		N		H		N	H	N	H			N	H	N	H	N	H	
		F	M	F	M													
Calderón-Pérez, L.. et al, 2020, Spain	Cross-sectional	n = 16	n = 16	n = 10	n = 19	41.1 ± 9.1	53.7 ± 9.6	-	0	0	0	-	0	23.8 ± 2.7	26.2 ± 2.5	BP = 109.7 ± 7.1; DBP = 65.7 ± 6.7	SBP = 153.1 ± 14.6; DBP = 91.0 ± 8.8	V3–V4
Chen, B-Y. et al, 2022, China	Cross-sectional	n = 16	n = 7	n = 27	n = 9	62.87 ± 2.03	67.42 ± 1.82	-	NR	NR	30	-	0	22.81 ± 0.69	24.12 ± 0.57	SBP= 118.6 ± 2.64; DBP = 75.55 ± 1.56	SBP = 126.1 ± 2.25; DBP = 77.82 ± 1.32	V3–V4
Dan, X. et al, 2019, China	Case-control	n = 41	n = 26	n = 33	n = 29	69.492 ± 9.630	69.322 ± 10.613	-	NR	NR	NR	-	NR	25.051 ± 4.436	26.089 ± 3.112	SBP = 122.935 ± 6.902; DBP = 76.209 ± 6.902	SBP = 153.298 ± 14.917; DBP = 84.313 ± 10.739	V3–V4
Kashtanova, D. A. et al, 2018, Russia	Cohort	n = 58		n = 34		NR	NR	-	0	0	0	-	NR	NR	NR	NR	NR	V3–V4
Li, H. et al, 2019, China	Cross-sectional	n = 25	n = 17	n = 28	n = 35	59.3 ± 9.2	58.4 ± 10.2	-	0	0	0	-	0	25.3 ± 2.9	27.0 ± 3.6	SBP = 122.3 ± 11.5; DBP = 77.0 ± 7.6	SBP = 149.8 ± 11.6; DBP = 92.5 ± 8.4	V3–V4
Li, J. et al, 2017, China	Cohort	n = 9	n = 32	n = 6	n = 93	53.7 ± 5.9	53.6 ±5.5	-	0	0	0	-	0	25.2 ± 3.3	26 ± 3.5	SBP = 115.3 ± 7.4; DBP = 74.1 ± 6.5	SBP = 148.8 ± 14.2; DBP = 94.7 ± 9.2	V4

Lin, Y. et al, 2022, China	Cross-sectional	NC	NC	n = 9[1]; n = 10[2]; n = 9[3]	n = 11[1]; n = 10[2]; n = 11[3]	-	54.23 ± 4.12[1]; 56.32 ± 3.29[2]; 55.86 ± 5.29[3]	-	NR	R	NR	-	NR	-	25.52 ± 3.94[1]; 24.85 ± 4.85[2]; 25.02 ± 5.74[3]	-	NR	V3–V4
Louca, P. et al, 2021, UK	Cohort	n = 474	-	n = 397	-	52.41 ± 11.9	60.33 ± 8.72	-	NR	NR	NR	-	NR	24.19 ± 3.77	28.14 ± 5.41	SBP = 109.24 ± 6.76; DBP = 69.05 ± 6.21	SBP = 138.98 ± 15.01; DBP = 83.48 ± 10.14	V4
Lu, S. et al, 2021, China	Cross-sectional	NC	NC	n = 29[4]; n = 21[5]	n = 31[4]; n = 47[5]	-	68.23[4]; 69.56[5]	-	NR	NR	NR	-	R		24.75[4]; 25.40[5]	-	NR	V3–V4
Mushtaq, N. et al, 2019, China	Case-control	n = 14	n = 16	n = 22	n = 28	60.5 ± 11	62.5 ± 10.4	-	NR	NR	NR	-	NR	NR	NR	SBP = 122.83 ± 7.6; DBP = 79.63 ± 6.8	SBP = 180.34 ± 15.44; DBP = 106.88 ± 10.1	V3–V4
Nakai, M. et al, 2021, Australia	Case-control	n = 31	n = 16	n = 8	n = 15	59.2 ± 7.7	60.3 ± 6.6	-	0	0	0	-	0	24.9 ± 3.0	26.0 ± 2.6	SBP = 122.3 ± 12.5; DBP = 75.5 ± 8.3	SBP = 135.6 ± 18.0; DBP = 82.2 ± 10.5	V3–V4
Palmu, J. et al, 2020, Finland	Cohort	n = 3662		n = 3291		NR	NR	-	NR	D = 3,3; BB = 10,3; CCB = 4,2; ARB = 8,2	1253	-	NR	NR	NR	NR	NR	NR
Qu, L. et al, 2022, China	Cohort	n = 16	n = 18	n = 17[5]; n = 14[4]	n = 14[5]; n = 184	59.15 ± 6.21	60.52 ± 4.84[5]; 59.13 ± 4.354	-	NR	NR	NR	-	NR	24.82 ± 2.28	25.70 ± 2.90[5]; 26.11 ± 2.99[4]	SBP = 123.67 ± 5.83; DBP = 77.31 ± 7.90	SBP = 157.03 ± 19.50; DBP = 89.41 ± 12.72[5];	V3–V4

																	SBP = 161.03 ± 21.25 DBP = 93.48 ± 12.93[4]	
Silveira-Nunes, G. et al, 2020, Brazil	Cohort	n = 25	n = 7	n = 34	n = 14	63.3 ± 15.0	65.3 ± 15.5	-	NR	NR	NR	-	0	NR	NR	NR	NR	V3–V4
Stevens, B.R. et al, 2021, USA	Cohort	n = 13[6]; n = 4[7]	n = 8[6]; n = 3[7]	n = 10[8]; n = 5[9]	n = 8[8]; n = 3[9]	53.0 ± 14.8[6]; 63.8 ± 6.2[7]	59.9 ± 17.6[8]; 67.0 ± 10.7[9]	-	NR	NR	NR		0	30.7 ± 7.0[6]; 27.3 ± 5.9[7]	37.5 ± 13.4[8]; 34.2 ± 10.5[9]	NR	NR	NR
Sun, S. et al, 2019, USA	Cohort	n = 343		n = 186		NR	NR	-	NR	NR	154	-	NR	NR	NR	NR	NR	V3–V4
Wan, C. et al, 2021, China	Case-control	n = 135	n = 165	n = 157	n = 143	62.02 ± 11.79	61.60 ± 11.92	-	0	0	0	-	0	20.64 ± 1.85	20.47 ± 2.01	NR	NR	V4
Yan, Q. et al, 2017, China	Case-control	n = 28	n = 32	n = 25	n = 35	56.0 ± 8.6	57.0 ± 9.6	-	NR	NR	NR	-	0	23.4 ± 2.6	23.5 ± 2.9	SBP = 111 ± 6; DBP = 71 ± 7	SBP = 165 ± 20; DBP = 101 ± 11	NR
Zuo, K. et al, 2019, China	Cohort	n = 4	n = 11	n = 3	n = 31	58	54.5	-	0	0	0	-	0	25.64	25.56	SBP = 120; DBP = 78	SBP = 151; DBP = 95.5	V4

SD, standard deviation; HTN, hypertension; BMI, body mass index; BP, blood pressure; N, normotensive; H, Hypertensive; F, female; M, male; -, not applicable; SBP, systolic blood pressure; DBP, diastolic blood pressure; NR, not reported; NC, no control group; ARB, angiotensin II receptor blockers; BB, beta blockers; CCB, calcium-channel blockers; D, Diuretics;

[1]Grade 1 AH

[2]Grade 2 AH

[3]Grade 3 AH

[4]Group AH without cognitive impairment

[5]Group AH with cognitive impairment

[6]Control group

[7]Group depressive disorder only

[8]Group AH only

[9]Group AH and depressive disorder

Table 3 - Characteristics of included studies analyzing intestinal microbiota (n = 19).

Author, year, Country	Intestinal nitrate-reducing bacteria, differential abundance							
	N				H			
	G		S		G		S	
	D	I	D	I	D	I	D	I
Calderón-Pérez, L.. et al, 2020, Spain								*Bacteroides Vulgatus*
Chen, B-Y. et al, 2022, China								
Dan, X. et al, 2019, China		*Staphylococcus*						
Kashtanova, D. A. et al, 2018, Russia								
Li, H. et al, 2019, China						*Enterobacter*		
Li, J. et al, 2017, China	*Klebsiella, Actinomyces*				*Enterobacter*	*Actinomyces*, *Klebsiella*		
Lin, Y. et al, 2022, China	NC	NC	NC	NC				
Louca, P. et al, 2021, UK								
Lu, S. et al, 2021, China	NC	NC	NC	NC				
Mushtaq, N. et al, 2019, China								
Nakai, M. et al, 2021, Australia								
Palmu, J. et al, 2020, Finland						*Citrobacter, Enterobacter, Actinomyces*	*Lactobacillus farciminis*	*Lactobacillus rhamnosus*
Qu, L. et al, 2022, China						*Enterobacter*[1]		*Escherichia coli, Bacteroides vulgatus*[2]
Silveira-Nunes, G. et al, 2020, Brazil								
Stevens, B.R. et al, 2021, USA				*Bacteroides vulgatus*[3] *Escherichia coli*[4] *Bacteroides vulgatus*[5]				
Sun, S. et al, 2019, USA								
Wan, C. et al, 2021, China						*Citrobacter, Pseudomonas, Providencia, Proteus,*		

						Klebsiella		
Yan, Q. et al, 2017, China						*Klebsiella*		*Klebsiella Pneumoniae*
Zuo, K. et al, 2019, China								

N, normotensive; H, Hypertensive; G, Genera; S, Specie-level; D, depleted; I, increased; NC, no control group.

[1]AH group with cognitive impairment and AH group without cognitive impairment

[2]AH group with cognitive impairment

[3]Control groups compared to group AH with depression

[4]Control group compared to groups AH and AH with depression

[5]Control group compared to AH

Table 4 - Characteristics of included studies analyzing oral microbiota (n = 5).

Author, year, Country	Type of study	Population (n)				Population mean age with SD		Number of drugs, mean SD		Most-used drugs, n (%)	Participants using antihypertensive drugs (n)	Controlled HTN, n (%)		BMI		BP (Systolic/diastolic)		Sequencing, 16S rRNA region
		N		H		N	H	N	H			N	H	N	H	N	H	
		F	M	F	M													
Chen, B-Y. et al, 2022, China	Cross-sectional	n = 16	n = 7	n = 27	n = 9	62.87 ± 2.03	67.42 ± 1.82	-	NR	NR	30	-	0	22.81 ± 0.69	24.12 ± 0.57	SBP= 118.6 ± 2.64; DBP = 75.55 ± 1.56	SBP = 126.1 ± 2.25; DBP = 77.82 ± 1.32	V3–V4
Chen, X. et al, 2022, China	Cross-sectional	n = 27		n = 23		30.50 ± 5.74	36.22 ± 10.20	-	NR	NR	NR	-	0	24.60 ± 3.08	26.63 ± 3.04	SBP = 118.07 ± 12.12; DBP = 70.15 ± 11.09	SBP = 139.04 ± 16.39; DBP = 93.87 ± 12.30	V3–V4
LaMonte, M. J. et al, 2022, USA	Cohort	n = 429	-	n = 480	-	64.5 ± 6.4	68.1 ± 7.1	-	NR	NR	480	-	NR	25.1 ± 4.3	28.2 ± 5.9	SBP = 106 ± 8.1; DBP = 66.3 ± 6.3	SBP = 129 ± 17.8; DBP = 72.5 ± 9.5	V3–V4
Li, S. et al, 2021, China	Cohort	n = 68	n = 19	n = 36	n = 11	44.26 ± 9.895	44.14 ± 8.39	-	0	0	0	-	0	24.8 ± 4.49	26.86 ± 4.61	SBP = 110.57 ± 12.89; DBP = 66.38 ± 8.72	SBP = 132.69 ± 23.6; DBP = 77.34 ± 15	V3–V4
Sohail, M. U., Hedin, L., Al-Asmakh, M., 2021, Qatar	Cohort	n = 21	n = 19	n = 32	n = 24	NR	NR	-	NR	NR	56	-	NR	NR	NR	NR	NR	V3–V4

SD, standard deviation; HTN, hypertension; BMI, body mass index; BP, blood pressure; N, normotensive; H, Hypertensive; F, female; M, male; SBP, systolic blood pressure; DBP, diastolic blood pressure; NR, not reported; -, not applicable

Table 5 - Characteristics of included studies analyzing oral microbiota (n = 5).

Author, year, Country	Oral nitrate-reducing bacteria, differential abundance							
	N				H			
	G		S		G		S	
	D	I	D	I	D	I	D	I
Chen, B-Y. et al, 2022, China		Saliva and subgingival plaques: *Prevotella, Veillonella* Subgingival plaques: *Neisseria*				Saliva: *Neisseria, Haemophilus*		
Chen, X. et al, 2022, China		*Prevotella, Actinomyces, Porphyromonas, Granulicatella*				*Neisseria, Haemophilus, Veillonella, Fusobacterium, Leptotrichia*		
LaMonte, M. J. et al, 2022, USA				*Corynebacterium durum, Granulicatella adiacens, Actinomyces naeslundii, Haemophilus parainfluenzae, Rothia dentocariosa, Corynebacterium matruchotti, Neisseria subflava, Neisseria flavescens*				*Veillonella atypica, Veillonella dispar, Veillonella parvula, Neisseria sicca, Selenomonas noxia, Prevotella melaninogenica, Prevotella salivae, Rothia mucilaginosa*
Li, S. et al, 2021, China						*Neisseria*[1]		
Sohail, M. U., Hedin, L., Al-Asmakh, M., 2021, Qatar		*Fusobacterium*				*Prevotella, Veillonella and Actinomyces*		

N, normotensive; H, Hypertensive; G, Genera; S, Specie-level; D, depleted; I, increased

[1]Group AH with periodontitis compared to group control with periodontitis

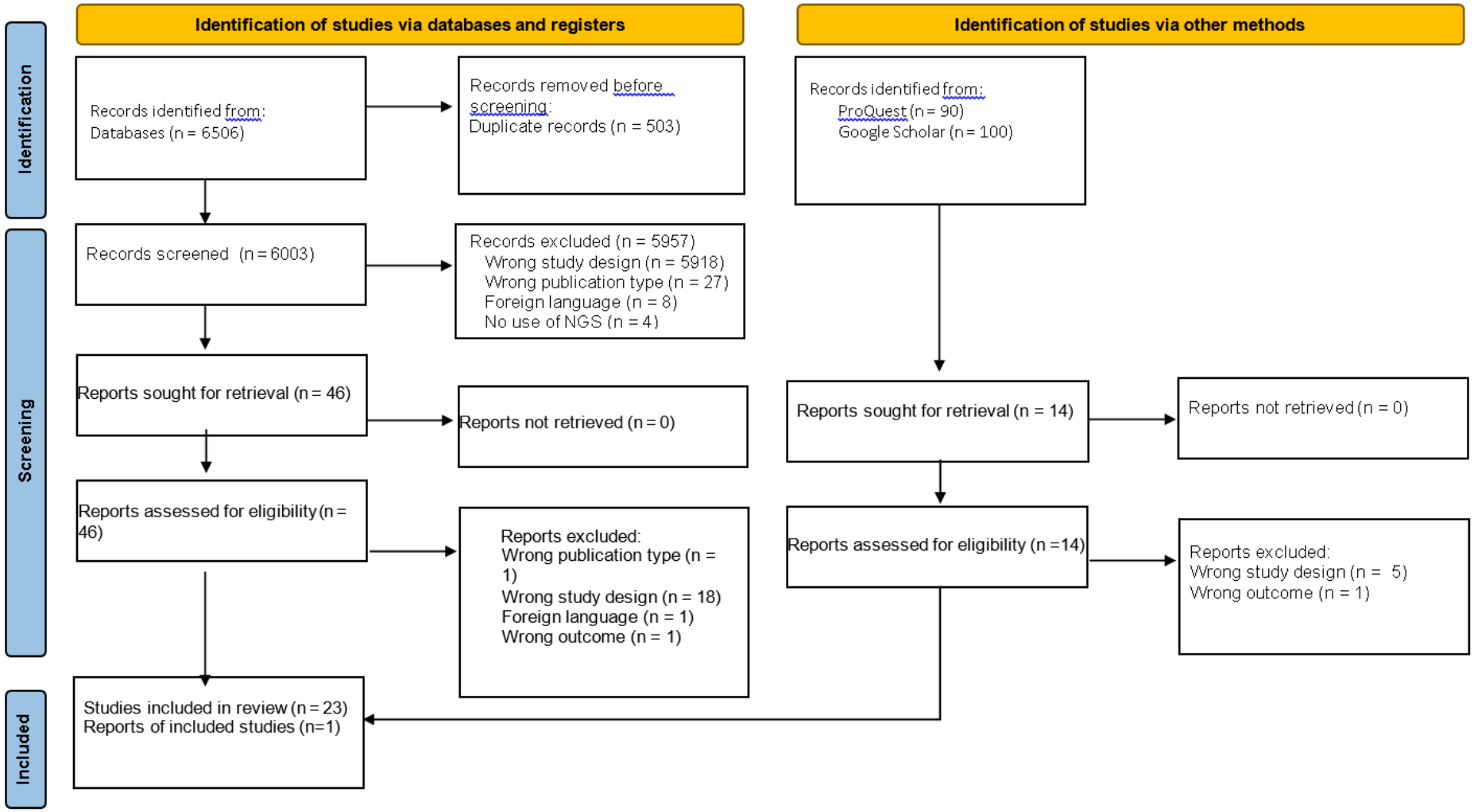
Table 6 - Assessment of methodological quality of individual studies using the JBI Critical Appraisal Checklist for prevalence studies

Author, year	**1. Was the sample frame appropriate to address the target population?**	2. Were study participants sampled in an appropriate way?	3. Was the sample size adequate?	4. Were the study subjects and the setting described in detail?	5. Was the data analysis conducted with sufficient coverage of the identified sample?	**6. Were valid methods used for the identification of the condition?**	**7. Was the condition measured in a standard, reliable way for all participants?**	8. Was there appropriate statistical analysis?	9. Was the response rate adequate, and if not, was the low response rate managed appropriately?	**Overall appraisal:** LOW, MODERATE, OR HIGH
Chen, B-Y. et al 2022	**Y**	N	U	N	N	**Y**	**Y**	Y	U	**MODERATE**
Chen, X. et al 2022	**N**	U	U	U	Y	**Y**	**Y**	Y	U	**MODERATE**
LaMonte, M. J. et al 2022	**N**	Y	U	Y	Y	**Y**	**Y**	Y	Y	**MODERATE**
Li, S. et al 2021	**Y**	Y	U	Y	Y	**Y**	**Y**	Y	U	**LOW**
Sohail, M. U., Hedin, L., Al-Asmakh, M. 2021	**Y**	Y	U	Y	N	**Y**	**Y**	Y	U	**MODERATE**
Calderón-Pérez, L. et al 2020	**Y**	Y	U	Y	Y	**Y**	**Y**	Y	Y	**LOW**
Dan, X. et al 2019	**Y**	N	U	N	Y	**Y**	**Y**	Y	U	**MODERATE**
Kashtanova, D. A. et al 2018	**Y**	Y	U	Y	U	**Y**	**Y**	Y	U	**MODERATE**
Li, H. et al 2019	**Y**	Y	U	Y	Y	**Y**	**Y**	Y	U	**LOW**
Li, J. et al 2017	**Y**	N	U	N	Y	**Y**	**Y**	Y	U	**MODERATE**
Lin, Y. et al 2021	**Y**	Y	U	Y	Y	**Y**	**Y**	Y	U	**LOW**
Louca, P. et al 2021	**N**	Y	U	N	Y	**Y**	**Y**	U	U	**MODERATE**
Lu, S. et al 2021	**N**	Y	U	Y	U	**Y**	**Y**	U	Y	**MODERATE**
Mushtaq, N. et al 2019	**Y**	U	U	N	Y	**Y**	**Y**	U	U	**MODERATE**
Nakai, M. et al 2021	**Y**	Y	U	Y	Y	**Y**	**Y**	Y	Y	**LOW**
Palmu, J. et al 2020	**Y**	Y	Y	Y	Y	**Y**	**Y**	Y	Y	**LOW**
Qu, L. et al 2022	**Y**	Y	U	N	Y	**Y**	**Y**	Y	U	**MODERATE**
Silveira-Nunes, G. et al 2020	**Y**	Y	U	Y	N	**Y**	**Y**	U	U	**MODERATE**
Stevens, B.R. et al 2021	**Y**	U	U	N	Y	**Y**	**Y**	Y	U	**MODERATE**
Sun, S. et al 2019	**Y**	Y	Y	Y	Y	**Y**	**Y**	Y	Y	**LOW**
Wan, C. et al 2021	**Y**	Y	U	Y	Y	**Y**	**Y**	Y	U	**LOW**
Yan, Q. et al 2017	**Y**	U	U	N	Y	**Y**	**Y**	Y	U	**MODERATE**
Zuo, K.et al 2019	**Y**	Y	U	N	N	**Y**	**Y**	Y	U	**MODERATE**

1. Was the sample frame appropriate to address the target population? **MAIN DOMAIN**
2. Were study participants sampled in an appropriate way? **NON-CRITICAL DOMAIN**
3. Was the sample size adequate? **NON-CRITICAL DOMAIN**
4. Were the study subjects and the setting described in detail? **NON-CRITICAL DOMAIN**
5. Was the data analysis conducted with sufficient coverage of the identified sample? **NON-CRITICAL DOMAIN**
6. Were valid methods used for the identification of the condition? **MAIN DOMAIN**
7. Was the condition measured in a standard, reliable way for all participants? **MAIN DOMAIN**
8. Was there appropriate statistical analysis? **NON-CRITICAL DOMAIN**
9. Was the response rate adequate, and if not, was the low response rate managed appropriately? **NON-CRITICAL DOMAIN**

Y, yes; N, no; U, uncertain

Figure 1 - PRISMA 2020 flow diagram of the literature search process



SUPPLEMENTARY MATERIAL

Appendix S1 - PRISMA 2020 checklist

Section/topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	01
ABSTRACT			
Structured summary	2	Provide a structured summary including: background, objectives, eligibility criteria, information sources, risk of bias, synthesis of results, limitations of evidence, interpretation and important implications, registration.	-
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	02
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	03
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	04, Table 1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	04
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	04, Appendix S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	04, 05
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	05
Data items	10	a. List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	05

		b. List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	05, 06
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13	a. Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). b. Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. c. Describe any methods used to tabulate or visually display results of individual studies and syntheses. d. Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. e. Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, metaregression). f. Describe any sensitivity analyses conducted to assess robustness of the synthesised results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	06
RESULTS			
Study selection	16	a. Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. b. Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	06, 07, Figure 3, Appendix S3
Study characteristics	17	Cite each included study and present its characteristics.	07-10, Tables 02, 03, 04, 05
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	10, Table 6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	-
Results of Synthesis	20	a. For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-

		b. Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. c. Present results of all investigations of possible causes of heterogeneity among study results. d. Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	10, Appendix S4
DISCUSSION			
Discussion	23	a. Provide a general interpretation of the results in the context of other evidence. b. Discuss any limitations of the evidence included in the review. c. Discuss any limitations of the review processes used. d. Discuss implications of the results for practice, policy, and future research.	10-14
Other information			
Registration and protocol	24	a. Provide registration information for the review, including register name and registration number, or state that the review was not registered. b. Indicate where the review protocol can be accessed, or state that a protocol was not prepared. c. Describe and explain any amendments to information provided at registration or in the protocol.	15
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	15
Competing interests	26	Declare any competing interests of review authors.	15

Appendix S2 – Databases and search strategies

Database	Search strategy	Results May 14th 2022
MEDLINE (via PubMed)	("Gastrointestinal Microbiome"[MeSH Terms] OR "Gastrointestinal Microbiome"[All Fields] OR "Gastrointestinal Microbiomes"[All Fields] OR "Gut Microbiome"[All Fields] OR "Gut Microbiomes"[All Fields] OR "Gut Microflora"[All Fields] OR "Gut Microbiota"[All Fields] OR "Gut Microbiotas"[All Fields] OR "Gastrointestinal Flora"[All Fields] OR "Gut Flora"[All Fields] OR "Gastrointestinal Microbiota"[All Fields] OR "Gastrointestinal Microbiotas"[All Fields] OR "Gastrointestinal Microbial Community"[All Fields] OR "Gastrointestinal Microbial Communities"[All Fields] OR "Gastrointestinal Microflora"[All Fields] OR "Gastric Microbiome"[All Fields] OR "Gastric Microbiomes"[All Fields] OR "Intestinal Microbiome"[All Fields] OR "Intestinal Microbiomes"[All Fields] OR "Intestinal Microbiota"[All Fields] OR "Intestinal Microbiotas"[All Fields] OR "Intestinal Microflora"[All Fields] OR "Intestinal Flora"[All Fields] OR "Enteric Bacteria"[All Fields] OR "gut bacteria"[All Fields] OR "Dysbiosis"[MeSH Terms] OR "Dysbiosis"[All Fields] OR "Dysbioses"[All Fields] OR "Disbiosis"[All Fields] OR "Disbioses"[All Fields] OR "Dysbacteriosis"[All Fields] OR "Dysbacterioses"[All Fields] OR "Disbacteriosis"[All Fields] OR "Oral microbiome"[All Fields] OR "oral microbiota"[All Fields] OR (("bacteria"[MeSH Terms] OR "bacteria"[All Fields] OR "bacteriae"[All Fields] OR "bacterias"[All Fields] OR "Eubacteria"[All Fields]) AND ("Mouth"[MeSH Terms] OR "Mouth"[All Fields] OR "oral"[Title/Abstract] OR "Cavitas Oris"[All Fields] OR "Cavitas oris propria"[All Fields])) OR "fecal microbiome"[All Fields] OR "Faecal microbiome"[All Fields] OR "fecal microbiota"[All Fields] OR "Faecal microbiota"[All Fields] OR ("nitrate reducing bacteria"[All Fields] OR (("bacteria"[MeSH Terms] OR "bacteria"[All Fields] OR "bacteriae"[All Fields] OR "bacterias"[All Fields] OR "Eubacteria"[All Fields]) AND ("Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[All Fields] OR "Nitrogen Monoxide"[All Fields] OR "Endothelium-Derived Nitric Oxide"[All Fields] OR "Endogenous Nitrate Vasodilator"[All Fields] OR "Mononitrogen Monoxide"[All Fields])))) AND ("Hypertension"[MeSH Terms] OR "High Blood Pressure"[All Fields] OR "High Blood Pressures"[All Fields] OR "blood pressure"[All Fields])	1,095
Embase	('gastrointestinal microbiome'/de OR 'gastrointestinal microbiome' OR 'gastrointestinal microbiomes' OR 'gut microbiome'/de OR 'gut microbiome' OR 'gut microbiomes' OR 'gut microflora' OR 'gut microbiota'/de OR 'gut microbiota' OR 'gut microbiotas' OR 'gastrointestinal flora'/de OR 'gastrointestinal flora' OR 'gut flora' OR 'gastrointestinal microbiota'/de OR 'gastrointestinal microbiota' OR 'gastrointestinal microbiotas' OR 'gastrointestinal microbial community' OR 'gastrointestinal microbial communities' OR 'gastrointestinal microflora' OR 'gastric microbiome' OR 'gastric microbiomes' OR 'intestinal microbiome' OR 'intestinal microbiomes' OR 'intestinal microbiota'/de OR 'intestinal microbiota' OR 'intestinal microbiotas' OR 'intestinal microflora'/de OR 'intestinal microflora' OR 'intestinal flora'/de OR 'intestinal flora' OR 'enteric bacteria'/de OR 'enteric bacteria' OR 'gut bacteria'/de OR 'gut bacteria' OR 'dysbiosis'/de OR dysbiosis OR dysbioses OR disbiosis OR disbioses OR 'dysbacteriosis'/de OR dysbacteriosis OR dysbacterioses OR disbacteriosis OR 'oral microbiome'/de OR 'oral microbiome' OR 'oral microbiota'/de OR 'oral microbiota' OR (('bacteria'/de OR bacteria OR bacteriae OR bacterias OR 'eubacteria'/de OR eubacteria) AND ('mouth'/de OR mouth OR oral OR 'cavitas oris' OR 'cavitas oris propria')) OR 'fecal microbiome'/de OR 'fecal microbiome' OR 'faecal microbiome' OR 'fecal microbiota'/de OR 'fecal microbiota' OR 'faecal microbiota'/de OR 'faecal microbiota' OR 'nitrate reducing bacteria' OR (('bacteria'/de OR bacteria OR bacteriae OR bacterias OR 'eubacteria'/de OR eubacteria) AND ('nitric oxide'/de OR 'nitric oxide' OR 'nitrogen monoxide'/de OR 'nitrogen monoxide' OR 'endothelium-derived nitric oxide'/de OR 'endothelium-derived nitric oxide' OR 'endogenous nitrate vasodilator' OR 'mononitrogen monoxide'))) AND ('hypertension'/de OR 'high blood pressure'/de OR 'high blood pressure' OR 'high blood pressures' OR 'blood pressure'/de OR 'blood pressure')	3,104
Scopus	TITLE-ABS-KEY("Gastrointestinal Microbiome" OR "Gastrointestinal Microbiomes" OR "Gut Microbiome" OR "Gut Microbiomes" OR "Gut Microflora" OR "Gut Microbiota" OR "Gut Microbiotas" OR "Gastrointestinal Flora" OR "Gut Flora" OR "Gastrointestinal Microbiota" OR "Gastrointestinal Microbiotas" OR "Gastrointestinal Microbial Community" OR "Gastrointestinal Microbial Communities" OR "Gastrointestinal Microflora" OR "Gastric Microbiome" OR "Gastric Microbiomes" OR "Intestinal Microbiome" OR "Intestinal Microbiomes" OR "Intestinal Microbiota" OR "Intestinal Microbiotas" OR "Intestinal	2,873

	Microflora" OR "Intestinal Flora" OR "Enteric Bacteria" OR "gut bacteria" OR Dysbiosis OR Dysbioses OR Disbiosis OR Disbioses OR Dysbacteriosis OR Dysbacterioses OR Disbacteriosis OR "Oral microbiome" OR "oral microbiota" OR ((bacteria OR bacteriae OR bacterias OR Eubacteria) AND (mouth OR oral OR "Cavitas Oris" OR "Cavitas oris propria")) OR "fecal microbiome" OR "Faecal microbiome" OR "fecal microbiota" OR "Faecal microbiota" OR "nitrate reducing bacteria" OR ((bacteria OR bacteriae OR bacterias OR Eubacteria) AND ("Nitric Oxide" OR "Nitrogen Monoxide" OR "Endothelium-Derived Nitric Oxide" OR "Endogenous Nitrate Vasodilator" OR "Mononitrogen Monoxide"))) AND TITLE-ABS-KEY(Hypertension OR "High Blood Pressure" OR "High Blood Pressures" OR "blood pressure")	
Web of Science	TS=("Gastrointestinal Microbiome" OR "Gastrointestinal Microbiomes" OR "Gut Microbiome" OR "Gut Microbiomes" OR "Gut Microflora" OR "Gut Microbiota" OR "Gut Microbiotas" OR "Gastrointestinal Flora" OR "Gut Flora" OR "Gastrointestinal Microbiota" OR "Gastrointestinal Microbiotas" OR "Gastrointestinal Microbial Community" OR "Gastrointestinal Microbial Communities" OR "Gastrointestinal Microflora" OR "Gastric Microbiome" OR "Gastric Microbiomes" OR "Intestinal Microbiome" OR "Intestinal Microbiomes" OR "Intestinal Microbiota" OR "Intestinal Microbiotas" OR "Intestinal Microflora" OR "Intestinal Flora" OR "Enteric Bacteria" OR "gut bacteria" OR Dysbiosis OR Dysbioses OR Disbiosis OR Disbioses OR Dysbacteriosis OR Dysbacterioses OR Disbacteriosis OR "Oral microbiome" OR "oral microbiota" OR ((bacteria OR bacteriae OR bacterias OR Eubacteria) AND (mouth OR oral OR "Cavitas Oris" OR "Cavitas oris propria")) OR "fecal microbiome" OR "Faecal microbiome" OR "fecal microbiota" OR "Faecal microbiota" OR "nitrate reducing bacteria" OR ((bacteria OR bacteriae OR bacterias OR Eubacteria) AND ("Nitric Oxide" OR "Nitrogen Monoxide" OR "Endothelium-Derived Nitric Oxide" OR "Endogenous Nitrate Vasodilator" OR "Mononitrogen Monoxide"))) AND TS=(Hypertension OR "High Blood Pressure" OR "High Blood Pressures" OR "blood pressure")	2,070
LILACS	("Gastrointestinal Microbiome" OR "Gastrointestinal Microbiomes" OR "Gut Microbiome" OR "Gut Microbiomes" OR "Gut Microflora" OR "Gut Microbiota" OR "Gut Microbiotas" OR "Gastrointestinal Flora" OR "Gut Flora" OR "Gastrointestinal Microbiota" OR "Gastrointestinal Microbiotas" OR "Gastrointestinal Microbial Community" OR "Gastrointestinal Microbial Communities" OR "Gastrointestinal Microflora" OR "Gastric Microbiome" OR "Gastric Microbiomes" OR "Intestinal Microbiome" OR "Intestinal Microbiomes" OR "Intestinal Microbiota" OR "Intestinal Microbiotas" OR "Intestinal Microflora" OR "Intestinal Flora" OR "Enteric Bacteria" OR "gut bacteria" OR dysbiosis OR dysbioses OR disbiosis OR disbioses OR dysbacteriosis OR dysbacterioses OR disbacteriosis OR "Oral microbiome" OR "oral microbiota" OR "Microbioma Gastrointestinal" OR "Bactérias Entéricas" OR "Comunidade Microbiana Gastrointestinal" OR "Comunidades Microbianas Gastrointestinais" OR "Flora Gastrointestinal" OR "Flora Gástrica" OR "Flora Intestinal" OR "Microbioma Gástrico" OR "Microbioma Intestinal" OR "Microbioma do Estômago" OR "Microbioma dos Intestinos" OR "Microbiomas Gástricos" OR "Microbiota Gastrointestinal" OR "Microbiota Gástrica" OR "Microbiota Intestinal" OR "Microbiota do Estômago" OR "Microbiota dos Intestinos" OR "Microflora Gastrointestinal" OR "Microflora Intestinal" OR "Comunidad Microbiana Gastrointestinal" OR "Comunidades Microbianas Gastrointestinales" OR "Flora de Estómago" OR "Flora de Intestino" OR "Flora de los Intestinos" OR "Flora del Estómago" OR "Flora del Intestino" OR "Microbioma de los Intestinos" OR "Microbioma del Estómago" OR "Microbioma del Intestino" OR "Microbiota de los Intestinos" OR "Microbiota del Estómago" OR "Microbiota del Intestino" OR "Microflora del Estómago" OR disbiose ((bacteria OR bacteriae OR bacterias OR eubacteria) AND (mouth OR oral OR "Cavitas Oris" OR "Cavitas oris propria" OR boca OR "Cavidade Bucal" OR boca)) OR "fecal microbiome" OR "Faecal microbiome" OR "fecal microbiota" OR "Faecal microbiota" OR "nitrate reducing bacteria" OR ((bacteria OR bacteriae OR bacterias OR eubacteria) AND ("Nitric Oxide" OR "Nitrogen Monoxide" OR "Endothelium-Derived Nitric Oxide" OR "Endogenous Nitrate Vasodilator" OR "Mononitrogen Monoxide" OR "Óxido Nítrico"))) AND (hypertension OR "High Blood Pressure" OR "High Blood Pressures" OR "blood pressure" OR hipertensão OR "Pressão Arterial Alta" OR "Pressão Sanguínea Alta" OR hipertensión OR "Presión Sanguínea Alta") AND (db:("LILACS"))	24
Livivo	("Gastrointestinal Microbiome" OR "Gastrointestinal Microbiomes" OR "Gut Microbiome" OR "Gut Microbiomes" OR "Gut Microflora" OR "Gut Microbiota" OR "Gut Microbiotas" OR "Gastrointestinal Flora" OR "Gut Flora" OR "Gastrointestinal Microbiota" OR "Gastrointestinal Microbiotas" OR "Gastrointestinal Microbial Community" OR "Gastrointestinal Microbial Communities" OR "Gastrointestinal Microflora" OR "Gastric Microbiome" OR "Gastric Microbiomes" OR "Intestinal Microbiome" OR "Intestinal Microbiomes" OR "Intestinal Microbiota" OR "Intestinal Microbiotas" OR "Intestinal Microflora" OR "Intestinal Flora" OR	1,294

	"Enteric Bacteria" OR "gut bacteria" OR Dysbiosis OR Dysbioses OR Disbiosis OR Disbioses OR Dysbacteriosis OR Dysbacterioses OR Disbacteriosis OR "Oral microbiome" OR "oral microbiota" OR ((bacteria OR bacteriae OR bacterias OR Eubacteria) AND (mouth OR oral OR "Cavitas Oris" OR "Cavitas oris propria")) OR "fecal microbiome" OR "Faecal microbiome" OR "fecal microbiota" OR "Faecal microbiota" OR "nitrate reducing bacteria" OR ((bacteria OR bacteriae OR bacterias OR Eubacteria) AND ("Nitric Oxide" OR "Nitrogen Monoxide" OR "Endothelium-Derived Nitric Oxide" OR "Endogenous Nitrate Vasodilator" OR "Mononitrogen Monoxide"))) AND (Hypertension OR "High Blood Pressure" OR "High Blood Pressures" OR "blood pressure")	
Cochrane Library	("Gastrointestinal Microbiome" OR "Gastrointestinal Microbiomes" OR "Gut Microbiome" OR "Gut Microbiomes" OR "Gut Microflora" OR "Gut Microbiota" OR "Gut Microbiotas" OR "Gastrointestinal Flora" OR "Gut Flora" OR "Gastrointestinal Microbiota" OR "Gastrointestinal Microbiotas" OR "Gastrointestinal Microbial Community" OR "Gastrointestinal Microbial Communities" OR "Gastrointestinal Microflora" OR "Gastric Microbiome" OR "Gastric Microbiomes" OR "Intestinal Microbiome" OR "Intestinal Microbiomes" OR "Intestinal Microbiota" OR "Intestinal Microbiotas" OR "Intestinal Microflora" OR "Intestinal Flora" OR "Enteric Bacteria" OR "gut bacteria" OR Dysbiosis OR Dysbioses OR Disbiosis OR Disbioses OR Dysbacteriosis OR Dysbacterioses OR Disbacteriosis OR "Oral microbiome" OR "oral microbiota" OR ((bacteria OR bacteriae OR bacterias OR Eubacteria) AND (mouth OR oral OR "Cavitas Oris" OR "Cavitas oris propria")) OR "fecal microbiome" OR "Faecal microbiome" OR "fecal microbiota" OR "Faecal microbiota" OR "nitrate reducing bacteria" OR ((bacteria OR bacteriae OR bacterias OR Eubacteria) AND ("Nitric Oxide" OR "Nitrogen Monoxide" OR "Endothelium-Derived Nitric Oxide" OR "Endogenous Nitrate Vasodilator" OR "Mononitrogen Monoxide"))):ti,ab,kw AND (Hypertension OR "High Blood Pressure" OR "High Blood Pressures" OR "blood pressure"):ti,ab,kw	494
ProQuest Dissertation and Thesis	noft("Gastrointestinal Microbiome" OR "Gastrointestinal Microbiomes" OR "Gut Microbiome" OR "Gut Microbiomes" OR "Gut Microflora" OR "Gut Microbiota" OR "Gut Microbiotas" OR "Gastrointestinal Flora" OR "Gut Flora" OR "Gastrointestinal Microbiota" OR "Gastrointestinal Microbiotas" OR "Gastrointestinal Microbial Community" OR "Gastrointestinal Microbial Communities" OR "Gastrointestinal Microflora" OR "Gastric Microbiome" OR "Gastric Microbiomes" OR "Intestinal Microbiome" OR "Intestinal Microbiomes" OR "Intestinal Microbiota" OR "Intestinal Microbiotas" OR "Intestinal Microflora" OR "Intestinal Flora" OR "Enteric Bacteria" OR "gut bacteria" OR Dysbiosis OR Dysbioses OR Disbiosis OR Disbioses OR Dysbacteriosis OR Dysbacterioses OR Disbacteriosis OR "Oral microbiome" OR "oral microbiota" OR ((bacteria OR bacteriae OR bacterias OR Eubacteria) AND (mouth OR oral OR "Cavitas Oris" OR "Cavitas oris propria")) OR "fecal microbiome" OR "Faecal microbiome" OR "fecal microbiota" OR "Faecal microbiota" OR "nitrate reducing bacteria" OR ((bacteria OR bacteriae OR bacterias OR Eubacteria) AND ("Nitric Oxide" OR "Nitrogen Monoxide" OR "Endothelium-Derived Nitric Oxide" OR "Endogenous Nitrate Vasodilator" OR "Mononitrogen Monoxide"))) AND noft(Hypertension OR "High Blood Pressure" OR "High Blood Pressures" OR "blood pressure")	90
Google Scholar	(Hypertension OR "High Blood Pressure") AND ("Gastrointestinal Microbiome" OR "Gut Microbiota" OR Dysbiosis OR "oral bacteria")	100

Search strategies were performed for each database by using specific words combinations and truncations with the support of a librarian.

Appendix S3 – List of intestinal nitrate-reducing bacteria

Genera	**Species**
Actinomyces[1]	*Aeromonas hydrophila*[3]
Citrobacter[1]	*Bacteroides vulgatus*[2]
Diphtheroids[1]	*Bifidobacterium adolescentis*[4]
Enterobacter[1]	*Bifidobacterium bifidus*[4]
Klebsiella[2]	*Bifidobacterium breve*[4]
Morganella[1]	*Bifidobacterium infantis*[4]
Peptostreptococcus[1]	*Bifidobacterium longum infantis*[5]
Proteus[1]	*Clostridium clostridioforme/Enterocloster clostridioformis*[1]
Providencia[1]	*Clostridium perfringens*[1]
Pseudomonas[1]	*Clostridium ramosum*[2]
Serratia[1]	*Enterobacter aerogenes*[3]
Staphylococcus[1]	*Enterobacter cloacae*[2]
	Enterobacter dissolvens[2]
	Escherichia coli[1–3,5]
	Eubacterium lentum[1]
	Klebsiella pneumoniae[2,3]
	Lactobacillus acidophilus[4,5]
	Lactobacillus casei[4]
	Lactobacillus casei shirota[4]
	Lactobacillus farciminis[4]
	Lactobacillus plantarum[4,5]
	Lactobacillus paracasei[4]
	Lactobacillus reuteri[4]
	Lactobacillus rhamnosus[4,5]
	Salmonella typhimurium[3]
	Serratia grimesii[3]
	Shigella dysenteriae[2]
	Shigella sonnei[3]

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Appendix S4 – List of oral nitrate-reducing bacteria[1]

Genera[2]	**Species**
Actinomyces	Actinomyces naeslundii[3]
Brevibacillus	Actinomyces odontolyticus[2,3]
Fusobacterium	Actinomyces oris/Actinomyces naeslundii genospecies[2]
Granulicatella	Actinomyces viscious[2,3]
Haemophilus	Brevibacillus brevis/ Bacillus brevis[2]
Leptotrichia	Capnocytophaga sputigena[3]
Neisseria	Corynebacterium durum[3]
Porphyromonas	Corynebacterium matruchotii[3]
Prevotella	Eikenella corrodens[3]
Veillonella	Granulicatella adiacens[2,3]
Unclassified genus of Gemellaceae family	Haemophilus parainfluenzae[2,3]
	Haemophilus segnis[3]
	Microbacterium oxydans[3]
	Neisseria flavescens[2]
	Neisseria mucosa[2]
	Neisseria sicca[2]
	Neisseria subflava[2]
	Prevotella melaninogenica[2]
	Prevotella salivae[2]
	Propionibacterium acnes[3]
	Rothia dentocariosa[3]
	Rothia mucilaginosa[3]
	Staphylococcus epidermidis[3]
	Staphylococcus hemolyticus[3]
	Selenomonas noxia[3]
	Veillonella dispar[2,3]
	Veillonella parvula[2]
	Veillonella atypica[2,3]

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3. Doel J, Benjamin N, Hector M, et al. Evaluation of bacterial nitrate reduction in the human oral cavity. *Eur J Oral Sci*. 2005;113:14-19.

Appendix S5 - Excluded articles and reasons for exclusion.

Author, year	Reason for exclusion
Burleigh, M. C., 2020	1
Chervinets, M. M.; Chervinets, Y. V.; Kravchuk, E. S., 2020	2
Cortés-Martín, A. et al, 2020	1
De La Cuesta-Zuluaga, J. et al., 2018a	1
De La Cuesta-Zuluaga, J. et al., 2018b	1
Fei, N. et al, 2019	1
Jiao, J. et al, 2021	1
Joishy, T. K. et al, 2022	1
Ko, C.-Y. et al, 2021	1
Lin, Y.-T., 2021	3
Lira-Junior, R. et al, 2018	1
Nowak, C.; Arnlov, J., 2021	1
Okamoto, S. N. et al, 2020	1
Pircalabioru, G. G. et al, 2022	1
Ried, K.; Travica, N.; Sali, A., 2018	1
Seong, E. et al, 2021	1
Stevens, B. R. et al, 2019	4
Takagi, T. et al, 2020	1
Tindall, A., 2019	1
Verhaar, B. J. H. et al, 2020	3
Waleijko, J. M. et al, 2018	1
Wang, P. et al, 2021a	1
Wang, P. et al, 2021b	1
Xu, J., 2015	1
Yu, Y., 2018	1

1- Wrong study design (n = 21); 2- Foreign language (n = 1); 3- Wrong outcome (n = 2); 4- Wrong publication type (n = 1).

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1. Burleigh, M. C. Interactions between diet and oral bacteria in the regulation of cardiovascular and oral health. Ann arbor: *University of the West of Scotland (United Kingdom).* 2020.
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5. De La Cuesta-Zuluaga, J. et al. Body size phenotypes comprehensively assess cardiometabolic risk and refine the association between obesity and gut microbiota. *International Journal of Obesity*. 2018b; v. 42, n. 3, p. 424–432.
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7. Jiao, Jie, et al. Profile of gut flora in hypertensive patients with insufficient sleep duration. *Journal of Human Hypertension*. 2022; v. 36, n. 4, p. 390-404.
8. Joishy, T. K. et al. Human Gut Microbes Associated with Systolic Blood Pressure. *International Journal of Hypertension*. 2022; v. 2022.
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10. Lin, Y.-T. Proteomic, Metabolomic, and Microbiome Studies of Blood Pressure. *Ann Arbor: Uppsala Universitet (Sweden)*. 2021.
11. Lira-Junior, Ronaldo, et al. Salivary microbial profiles in relation to age, periodontal, and systemic diseases. *PloS one. 2018;* v. 13, n. 3, e0189374.
12. Nowak, C.; Arnlov, J. Association between the gut microbiota and kidney function. *Journal of the American Society of Nephrology*. 2021; v. 32, p. 38.
13. Okamoto, S. N. et al. Impact of Gut Microbiome on Hypertensive Patients With Low-Salt Intake. *Frontiers in Medicine*. 2020; v. 7.
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20. Verhaar, B. J. H. et al. Associations between gutmicrobiota, faecal short-chain fatty acids, and blood pressure across ethnic groups: the HELIUS study. *EUROPEAN HEART JOURNAL*. 2020; v. 41, n. 44, p. 4259–4267.
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Appendix S6 - Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (https://www.gradepro.org)

Certainty assessment							№ of patients		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hypertensive group**	**Normotensive group**	
Intestinal Microbiota 19	Observational studies	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	n = 4989	n = 5288	⊕⊕◯◯ Low
Oral Microbiota 5	Observational studies	Serious[b]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	n = 642	n = 606	⊕⊕◯◯ Low

Explanations

a. In total, 12 studies presented moderate risk of bias and 7 presented low risk of bias
b. In total, 4 studies presented moderate risk of bias and 1 presented low risk of bias
1. The quality of fecal samples was uncertain, and this factor may influence the certainty assessment

ANEXO A – Normas da revista

1) Scope and audience

Nutrition Reviews is a highly cited, monthly, international, peer-reviewed journal that specializes in the publication of authoritative, innovative, and critical literature reviews that provide new insights on current and emerging topics in nutritional sciences, food sciences, clinical nutrition, community nutrition, and nutrition policy. Readers of *Nutrition Reviews* include nutrition scientists, biomedical researchers, clinical and dietetic practitioners, and advanced students of nutrition.

Articles selected for publication will be consistent with the journal's mission and should clearly outline both the biological and practical nutritional implications of a timely topic, so the reader obtains a clear understanding of both the topic's nature and its relevance. The journal does not publish primary research. Reviews and commentaries on current cutting-edge nutrition topics are eligible for consideration, provided they are prepared in accordance with established guidelines. Unsolicited submissions written in English are welcome from all countries from individual scientists and research teams.

2) Mission and history

Nutrition Reviews was founded in 1942 in response to a recognized need for expert analysis and synthesis of the vast amounts of nutrition science research being generated worldwide. Today, that need is greater still and *Nutrition Reviews* continues to serve it with the same goal in mind: To help nutrition scientists, scholars, practitioners, and policy makers stay abreast of significant developments in the field through concise reports prepared with objectivity and a critical focus.

3) Article types

Nutrition Reviews publishes five types of review articles in both the narrative and systematic review formats. Additionally, commentaries about recent nutrition issues and events along with letters to the editor are also published. All review articles must address a clearly defined research question that is articulated in an abstract; they must also follow recognized approaches to the literature selection, analysis, and conclusions, as outlined in accepted guidelines. It is recommended that authors consult existing literature on what constitutes various types of reviews. *Nutrition Reviews* does not publish original research articles. Authors are required to identify the type of article that is being submitted according the following categories:

Scoping Reviews provide an evaluation of the type and amount of research available on a topic, as well as potential knowledge gaps. These reviews should address the big picture of an issue to present new concepts and frameworks being proposed for the field of nutrition.

Narrative Reviews provide critical reviews that explain and summarize the literature on a specific nutrition topic that adds new knowledge to the current literature. Manuscripts that describe a concept or a process (e.g., a biochemical pathway, nutrition mechanism, or methodology) are well suited to be submitted as a narrative review. Narrative reviews do not require any specific guidance for determining which papers are used for the reviews but need to provide a critical and balanced review of the topic. Nutritional topics for which there is a significant amount of data and peer reviewed publications should be addressed by systematic reviews.

Systematic Reviews provide a comprehensive review on a specific topic that has not been addressed, or include new literature that either substantiates past findings or provides new insight for the nutrition field. Systematic reviews need to follow and describe a structured approach for identifying a comprehensive search of the literature, and should analyze the literature based on accepted methodology so the approach can be replicated and compared with past reviews. Systematic reviews can include papers that have used qualitative, quantitative, or mixed method approaches to study a nutrition topic. Systematic reviews should be conducted by a research team.

Meta-Analyses provide a systematic review of the literature that quantitatively combines data to provide an overall evaluation that supports or refutes the probability of a cause-and-effect nutrition relationship. Meta-analyses are especially helpful to determine a nutrition-disease link or the potential impact of nutrition interventions.

Umbrella Reviews evaluate exiting systematic reviews and meta-analyses. These reviews should summarize the similarities and differences in the methods and conclusions from past reviews to help readers better understand a topic for which there have not been consistent results between previous reviews.

Commentaries provide a discussion on the importance of a current method, study, or group of studies in nutrition research presented in the context of the larger body of research on that topic.

Letters to the Editor are welcome. Letters should address issues related to a recently published review in the *Nutrition Reviews*. Letters should add to the discourse regarding the article by highlighting factors that may have influenced the outcome of a review. Upon acceptance of a letter, authors of the published review will be provided the opportunity to respond to the issues raised in the letter.

Identification of Nutrition Topics
Papers will be published under the type of review that was conducted. Upon submission, authors need to provide 5-7 key words to identify the nutrition topic that is being addressed by the manuscript.

4) Terms of consideration

All manuscripts submitted to the journal must be original works of authorship that are not

under simultaneous consideration elsewhere and do not infringe the intellectual property rights of any individual or organization. All previously published information, whether by the authors themselves or other individuals, groups, or entities, must be appropriately cited. The final version must have been read and approved by all of the individuals named as authors. The work must present novel information that differs substantially from that presented in works published by the authors previously. Authors should attest to these terms in their cover letter.

5) Authorship and originality

To qualify for authorship, individuals *must meet all of the following criteria*: 1) contributed significantly to the work's conception, design, data collection (as applicable), or data interpretation and analysis; 2) participated in the writing or critical revision of the article in a manner sufficient to establish ownership of the intellectual content; and 3) read and approved the version of the manuscript being submitted. All authors share responsibility for ensuring the manuscript complies with the journal's style requirements and terms of consideration. Any requests for changes to author names, or order of appearance, that are received post submission will need to be approved in writing by all authors.

6) Funding and sponsorship

All sources of funding for the article's research, preparation, and publication should be noted in the article's Acknowledgments section under the subheading "Funding" and be acknowledged in the cover letter. The full name of the funding agency should be provided and grant numbers should be supplied. If grants or other funding were given to specific authors, the relevant individuals should be identified by their initials in parentheses.
The role any sponsor played in the study design, data collection and analysis, manuscript preparation and revision, and publication decisions should be made clear in the Funding declaration in the Acknowledgments section. Authors should also indicate whether they received complete access to data pertaining to the publication that was owned by the sponsor.

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7) Declaration of Interests

All authors are required to disclose relevant competing interests by noting them in the Acknowledgments section of the manuscript under the subheading "Declaration of Interest." Guidelines regarding what constitutes a competing interest are included in the Declaration of Interest form. Completed Declaration of Interest forms for each author should be uploaded as supporting Information at the time of manuscript submission.

8) Manuscript preparation

Cover letter. The cover letter should address the following topics: description of the work and its novelty; authorship; and originality. The description of the work should clearly indicate what novel contribution the submitted article makes to the existing literature. A statement should indicate that all listed authors meet the criteria for authorship (see *Authorship and*

Originality entry above) and that no individual meeting these criteria has been omitted. Regarding originality, the following should be declared or, if untrue, explained: 1) the submitted article represents the original work of the authors; 2) the article is not currently under consideration elsewhere, nor has it been previously published in the same or substantially similar form; and 3) no copyright to any other work was breached in the manuscript's creation.
Manuscript format. Manuscripts should be prepared electronically using word-processing software, preferably Microsoft Word. Article pages should be formatted as double-spaced and left-justified text with 1-inch margins and 12-point type. Pages and lines must be numbered.

Length restrictions. Articles in any category must be formatted as indicated in the *Manuscript format* guidelines section and reviews may not exceed 50 double-spaced pages in length, including references and illustrative material. Each article should provide a focused, concise, and objective investigation of a clearly defined topic. Commentaries should be less than 2000 words and letters to the editors should be less than 500 words.

Supplemental information. The option to publish certain material as "Supplemental Information" in an online-only format is provided. Authors are encouraged to make use of this option to accommodate material that may be of interest to the reader but is not integral to the work itself. Examples would include extensive summary tables and appendices. It is particularly important that the main text of an article include everything essential for a complete understanding of the review and that the main text stands alone from the Supplemental Information. Readers should not need to toggle between documents to obtain or understand information. If references are included in Supporting information documents, they should be listed at the end of each document and appear in a numerical sequence pertaining solely to that document.

Cover page. The following information should be included on the cover page:

- *Article type.* Choose one of the article types in which the journal specializes. Editors may change this designation if they find the article is better suited to another category.
- *Title.* The title of the article should be short (200 characters or less), specific, and accurately describe the topic of the work. Abbreviations and acronyms should not be used unless they are widely recognized and generally understood, e.g. HIV, DNA. Articles and phrases such as "the use of," "the treatment of," and "a report of" should be avoided.
- *Author names.* Please list the first name, middle initial(s), last name and academic degrees of each author in descending order of their contributions to the article. Each author should provide an ORCID identification. Individuals who provided technical or administrative support should be recognized in the Acknowledgments section.
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- Objectives that describes the primary reason for the review
- Background that identifies the justification for the review
- Methods of data sourcing and extraction and data synthesis (as applicable)
- Results that summarizes the main findings
- Conclusion that identifies the contribution the paper has made to the literature and recommendations as appropriate.
- *Key words.* At least three to five key words or phrases need to be provided.

a. Sections and headings

Scoping and Narrative Reviews

Each manuscript should contain at a minimum the following sections in addition to the abstract:

- Introduction that includes the justification and objectives for the review.
- Methods used to review the literature by describing how you identified what papers were used. There is no set format for this section.
- Discussion regarding the topic being reviewed.
- Conclusion (at the end of the text).
- Acknowledgements (after the Conclusion).
- Funding and sponsorship (as part of the Acknowledgments).
- Declaration of interest (as part of the Acknowledgments).
- References (after the Acknowledgments).
- List of any Supporting Information included (after the acknowledgements and before the reference list)
- Table Legend and Figure Legend listing the tables and figures included in the manuscript (after the reference list)
- Between the Introduction and Conclusion, additional headings and subheadings are at the discretion of the author. Headings and subheadings should be used to organize the text and guide the reader.

Systematic reviews and Meta-Analyses

Articles of this type should be prepared in accordance with relevant, existing guidelines (e.g., PRISMA or MOOSE checklists) and be structured accordingly. If the guidelines used include a checklist, the completed checklist should be uploaded as Supporting Information during the manuscript submission process. Questions regarding the acceptability of chosen guidelines can be sent to the journal's editorial office via e-mail (nutritionreviews@ilsi.org). Each manuscript should contain at a minimum the following sections:

- A structured, concise abstract containing the following subheadings: Context, Objective, Data Sources, Data Extraction, Data Analysis, Conclusions.
- Introduction that includes a sufficient amount of background information to justify the review, and the objectives for the review including the question(s) being addressed by the review.
- Methods used to review and evaluate the literature using standardized procedures. This should include the databases used for the review, the key search terms, the criteria for excluding or including previous studies, and how the studies were evaluated and by whom. Finally, the methods should include how the data were

analyzed including the statistical methods for any meta-analyses that were conducted.
- PICOS criteria (participants, interventions, comparisons, outcomes, and study design) used to define the research question as Table 1 and cite the table at an appropriate place in the text.
- A flow chart of the literature search process.
- A completed MOOSE/PRISMA checklist as part of the Supporting Information.
- Results to report what previous papers were identified, reviewed and included in study (number and types of articles). An analysis should include the methods used to determine the quality of the studies. Key characteristics of the studies used for the review should be included within a table (e.g. study designs, characteristics of subjects, sample size, risk of bias and outcomes). Meta-analyses need to include the results of the statistical analyses and should illustrate the results using appropriate graphic presentations.
- Discussion that summarizes the main results of the review, compares the findings of the review to existing literature, and states limitations of the review. The discussion section also includes the author's interpretation of the results and their implications for policy, practice and future research
- Conclusion that summarizes the impact of the review and provides recommendations for studies, policy, and practice as appropriate
- Acknowledgements (after the Conclusion
- Funding and sponsorship (as part of the Acknowledgments
- Declaration of interest (as part of the Acknowledgments
- References (after the Acknowledgments)
- List of any Supporting Information included (after the acknowledgements and before the reference list
- Table Legend and Figure Legend listing the tables and figures included in the manuscript (after the reference list)

Umbrella

Articles of this type should be presented as a systematic review of previous reviews. Thus, the sections are the same as a systematic review. Each manuscript should contain at a minimum the following sections in addition to the abstract:

- A structured, concise abstract containing the following subheadings: Context, Objective, Data Sources, Data Extraction, Data Analysis, Conclusions.
- Introduction that includes a sufficient amount of background information to justify the review, and the objectives for the review including the question(s) being addressed by the review.
- Methods used to review and evaluate the literature using standardized procedures. This should include the databases used for the review, the key search terms, the criteria for excluding or including previous studies, and how the studies were evaluated and by whom. Finally, the methods should include how the data were analyzed including the statistical methods for any meta-analyses that were conducted.
- PICOS criteria (participants, interventions, comparisons, outcomes, and study design) used to define the research question as Table 1 and cite the table at an appropriate place in the text.
- A flow chart of the literature search process.
- A completed MOOSE/PRISMA checklist as part of the Supporting Information.

- Results to report what previous papers were identified, reviewed and included in study (number and types of articles). An analysis should include the methods used to determine the quality of the studies. Key characteristics of the studies used for the review should be included within a table (e.g. study designs, characteristics of subjects, sample size, risk of bias and outcomes). Meta-analyses need to include the results of the statistical analyses and should illustrate the results using appropriate graphic presentations.
- Discussion that summarizes the main results of the review, compares the findings of the review to existing literature, and states limitations of the review. The discussion section also includes the author's interpretation of the results and their implications for policy, practice and future research.
- Conclusion that summarizes the impact of the review and provides recommendations for studies, policy, and practice as appropriate.
- Acknowledgements (after the Conclusion)
- Funding and sponsorship (as part of the Acknowledgments)
- Declaration of interest (as part of the Acknowledgments)
- References (after the Acknowledgments).
- List of any Supporting Information included (after the acknowledgements and before the reference list)
- Table Legend and Figure Legend listing the tables and figures included in the manuscript (after the reference list)

Commentaries and Letters to the Editor

Commentaries and *Letters to the Editor* do not have a set format for submission. Submissions should use prose to convey their message. Tables and figures are not usually provided but may be acceptable and their applicability will be determined. References should be limited to less than 10 citations. Commentaries and Letters to the Editor must still include an abstract and key words.

Other Guidelines

Abbreviations and acronyms. Abbreviations and acronyms should not be used unless they are widely recognized and generally understood, e.g. BMI, FDA. These should only be used for terms used more than four times in the text. If that criterion is met, the term should be spelled out on first use followed by the abbreviation or acronym in parentheses. The abbreviated form should be used consistently thereafter, except in section headings, where it should continue to be spelled out.

References. The number of references cited should be tailored to the material being reviewed and be from reputable sources. As a general rule, should not include more than 200 references for reviews and not more than 10 references for commentaries and letters to the editor. References should be numbered sequentially upon first appearance in text, tables, and figures. They should be typed as superscripts and placed after commas and periods but before colons and semicolons. When citing a series of consecutive numbers, provide the first and last with a dash between them (e.g., [5–7]). When referring to a group of authors in the text, the format "Smith et al.[23]" should be used. Reference numbers should not be surrounded by brackets or parentheses.
References cited only in figure or table legends should be numbered according to the first mention of the graphic in the text and should be cited immediately after the first reference to

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The reference list should be formatted according to AMA (American Medical Association) style. For each citation, sufficient information must be provided to allow a reader to know in what medium the material appeared and to access the information. Please list all authors if there are six or fewer; for seven or more authors, list the first three followed by “et al.” Examples of AMA style are as follows:

Journal article: Gordon KB, Papp KA, Hamilton TK, et al, for the Efalizumab Study Group. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. JAMA. 2003;290:3073–3080.

Chapter in a book: Dybul M, Connors M, Fauci AS. Immunology of HIV infection. In: Paul WE, ed. Fundamental Immunology. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2003:1285–1318.

Entire book: Gibson GR, Rastall RA. Prebiotics: Developments and Application. Hoboken, NJ: Wiley; 2006.

Government bulletin: Guidance on Labeling of Foods That Need Refrigeration by Consumers. College Park, MD: Office of Food Labeling, US Food and Drug Administration; 1997. Docket No. 96D-0513.

Internet citation: American College of Surgeons. National Trauma Data Bank Report 2006, Version 6.0. Chicago, USA. Available at: http://www.facs.org/trauma/ntdb/ntdbannualreport2006.pdf. Accessed on October 22, 2007.

More detailed guidance on Internet citations is provided in the recommendations of the Library of Medicine.

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Tables and illustrations should be numbered in the sequence in which they appear in the text. They should appear in sequence after the reference list.

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Where ethically feasible, *Nutrition Reviews* strongly encourages authors to make all data and software code on which the conclusions of the paper rely available to readers. We suggest that data be presented in the main manuscript or additional supporting files, or deposited in a public repository whenever possible. This includes the complete list of all papers identified for systematic reviews whether they are used or not used for evaluating the literature. For information on general repositories for all data types, and a list of recommended repositories by subject area, please see Choosing where to archive your data.

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information recommended by DataCite:

- [dataset]* Authors, Year, Title, Publisher (repository or archive name), Identifier

*The inclusion of the [dataset] tag at the beginning of the citation helps us to correctly identify and tag the citation. This tag will be removed from the citation published in the reference list.

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9) Procedures

Manuscript processing

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