JOURNAL OF ORAL MICROBIOLOGY
2025, VOL. 17, 2459919
https://doi.org/10.1080/20002297.2025.2459919

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RESEARCH ARTICLE

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The association between the oral microbiome and hypertension: a systematic review

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ABSTRACT

Background: This study systematically reviewed the available evidence regarding the potential association between oral microbiota and hypertension.
Methods: A comprehensive search of online databases was conducted by two independent investigators for all relevant articles. All observational studies that assessed the association between oral microbiota and hypertension were included. Quality appraisal was conducted using the NOS tool.
Results: A total of 17 studies comprising 6007 subjects were included. The studies varied with respect to sample type and microbial analysis method. All studies, except one, found significant differences in microbial composition between hypertensive and normotensive subjects. However, there were substantial inconsistencies regarding the specific differences identified. Still, a few taxa were repeatedly found enriched in hypertension including *Aggregatibacter*, *Kingella*, *Lautropia*, and *Leptotrachia* besides the red complex periodontal pathogens. When considering only studies that controlled for false discovery rates and confounders, *Atopobium*, *Prevotella, and Veillonella* were identified as consistently associated with hypertension.
Conclusion: There are significant differences in the oral microbiome between hypertensive and normotensive subjects. Despite the heterogeneity between the included studies, a subset of microbial taxa seems to be consistently enriched in hypertension. Further studies are highly recommended to explore this association.
Registration: PROSPERO database (ID: CRD42023495005).

ARTICLE HISTORY
Received 6 September 2024
Revised 12 December 2024
Accepted 2 January 2025

KEYWORDS
Oral microbiota; dysbiosis; hypertension; blood pressure; association; dysbiosis; mouth

Introduction

Hypertension is a significant public health problem affecting a large proportion of the general population worldwide [1]. According to the WHO, it is estimated that more than 1.28 billion adults (32% of the population) aged between 30 and 79 years in 2021 had hypertension, most of whom are in low and middle-income countries [1]. With the projected increase in the elderly population in developed and developing countries, it is estimated that the burden of hypertension and its associated complications will continue to increase substantially by 20,230 [1]. Hypertension is associated with great morbidity and mortality as well as a huge economic burden [1,2].

Despite extensive research, the etiopathogenesis of hypertension remains complex and not fully understood [1]. Recognized risk factors include age, gender, ethnicity, dietary factors, sedentary life, smoking, and overweight/obesity [1]. In recent years, the role of human microbiome in various systemic diseases, including cardiovascular diseases has gained a lot of interest [3,4]. Numerous studies have investigated the relationship between human gut microbiome and hypertension, and found that microbiome dysbiosis may contribute to the development of hypertension and can also modify the response to anti-hypertension medications [4–8]. The evidence also reveals that the fecal microbiota transfer between healthy individuals and hypertensive patients show a causal role of gut microbiota in regulating blood pressure [8,9].

Similarly, there has been growing interest in the role of oral microbiome in hypertension. Certain oral bacteria are capable of reducing salivary and dietary nitrate into nitrite, which is further reduced internally into NO (Figure 1). Therefore, a depletion in nitrate-reducing members of the oral microbiome may reduce NO bioavailability, and consequently increases blood pressure [10]. Another possible mechanism by which oral bacteria can contribute to hypertension is through triggering systemic inflammation, which is

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/20002297.2025.2459919

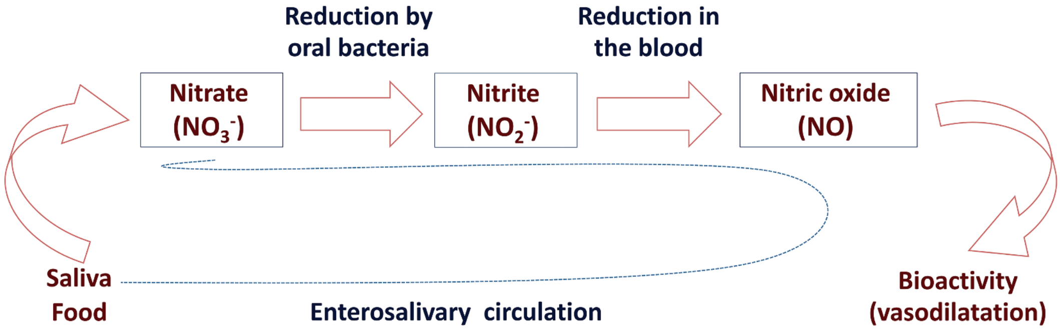

Figure 1. Contribution of oral bacteria to bioavailability of nitric oxide.

known to contribute to endothelial dysfunction [11,12].

Several studies have investigated the alterations in the composition of the oral microbiome associated with hypertension [13–30]. Regardless of sample type and microbial analysis method used, the majority of these studies found significant differences in the composition of the oral microbiome between hypertensive and normotensive subjects. However, the results of these studies have not been systematically reviewed to assess consistency and delineate the exact nature of oral microbial dysbiosis potentially involved in hypertension. Therefore, the purpose of the present systematic review was to analyze the results of previous microbiome studies and define the key oral microbial features associated with hypertension based on overall evidence.

Methods

The present systematic review adhered to and followed the PRISMA 2020 guidelines and PECO (Population, Intervention, Comparison, Outcomes) principles. The research focused questions were: 1) Is there a significant association between oral microbiota and hypertension? And, more specifically, 2) What are the key oral microbial features consistently associated with hypertension?

Eligibility criteria

Inclusion criteria

All observational studies (cross-sectional, cohort, and case–control studies) that assessed the oral microbiota in relation to hypertension in humans were included, namely those that involved the following: 1) Adult hypertensive patients, 2) A control group with individuals with no history of hypertension, and 3) Oral microbial assessment.

Exclusion criteria

Case reports, post-mortem studies, studies with no control groups, animal studies, control subjects with history of hypertension, experimental studies, review articles, commentaries, studies with no microbial data, studies focused on preeclampsia, and studies that involved hypertensive subjects with other comorbidities (e.g. diabetes mellitus, kidney diseases, sleep apnea, stroke, etc.).

Search strategy and information sources

We conducted a comprehensive online search in four databases: PubMed, Embase, Scopus, and Web of Science on December 30th for all relevant studies published from inception until 30 December 2023. The grey literature was also searched through ProQuest. All searches were conducted with no date or language restrictions. The following MeSH (Medical Subject Headings) terms and free keywords were used: (‘Oral microbiome’ OR ‘Oral microbiota’ OR ‘Oral microorganisms’ OR ‘Oral microflora’ OR ‘Oral flora’ OR ‘salivary microbiome’ OR ‘salivary microbiota’ OR ‘oral dysbiosis’ OR ‘oral biofilm’ OR ‘oral pathogen*’ OR ‘periodontal pathogen*‘ OR “periopathogen* OR ‘oral bacteria’) AND (‘Hypertension’[Mesh] OR hypertension OR ‘blood pressure’ OR ‘cardiovascular diseases’ OR ‘antihypertensive’) (Supplementary Table S1). The online search was also supplemented with a manual search of the references of retrieved studies for any additional studies. All searches were conducted by two independent investigators (SA, GA), and any disagreement was solved with discussion.

Screening and selection process

All retrieved articles were exported to EndNote program V. 20, after which duplicates were eliminated. After that, the title and abstracts of all articles were cross-examined against the eligibility criteria by two independent investigators (SA, GA), and irrelevant articles were removed. The full-texts of all potentially eligible articles were sought and carefully evaluated for inclusion.

Data extraction

All relevant data were extracted and tabulated by two independent investigators (AA, RB). The extracted data included the following: study details (the author, year, and country of publication), study design, study group characteristics (age, gender, case definition, and sample size), type and site of the sample, microbiome sequencing technique, bioinformatic/statistical methods (including whether or not adjustment for multiple comparisons and/or confounders was performed), and the main results (differences in diversity and microbial abundances). Any data related to analysis of non-oral samples or study groups other than hypertension and healthy controls were not extracted. The authors of the primary studies were contacted for any missing data or for any clarification.

Quality assessment

The quality of all studies was evaluated using the Newcastle Ottawa Scale (NOS) for assessing the quality of non-randomized studies [31]. The quality appraisal was done by two independent investigators, and all disagreements were resolved by discussion. Rated on a 0–9 star scale, the overall quality of each study was rated as either: high quality, seven stars or more; moderate quality, 4–6 stars; or poor quality, 0–3 stars [31].

Addressing heterogeneity

Microbiome studies are known for their high heterogeneity as elaborated on in the discussion. Meta-analysis requires obtaining the raw sequencing data for the original studies and re-analyzing them using a standard bioinformatic workflow, which is beyond the scope of this review. As an alternative, we developed here the following consistency criteria to define key bacterial taxa that can be implicated with some confidence in hypertension: 1) Taxa identified in studies that controlled for FDR and confounders; and 2) Taxa that were found to be associated with hypertension in one direction (i.e. depleted or enriched) in two or more studies but not in the opposite direction in any study with the same sample type.

Results

Study selection

Figure 2 depicts the search strategy of the present review. The online searches yielded a total of 2885 articles, of which 1790 were duplicates and thus excluded. The titles and abstracts of the remaining 1095 articles were cross-checked for eligibility. Of these, 1045 records were irrelevant. The fulltext of the remaining 50 potentially eligible articles was sought and thoroughly cross-checked. Accordingly, 33 were excluded for various reasons (Supplementary Table S2). Eventually, 17 studies were eligible for inclusion and were further processed for data extraction (Figure 2).

General characteristics of the included studies

General characteristics of the included studies are detailed in Table 1. This systematic review included 17 case-controlled studies comprising 6007 participants aged between 30.5 and 80 years [13–18,20–22,24–27,28,29,30,32]. These studies were published between 2010 and 2023. The number of subjects in each included study ranged from 41 [25] and 1215 [24]. Geographically, five of these studies were conducted in China [15–18,30] and five in the USA [20–

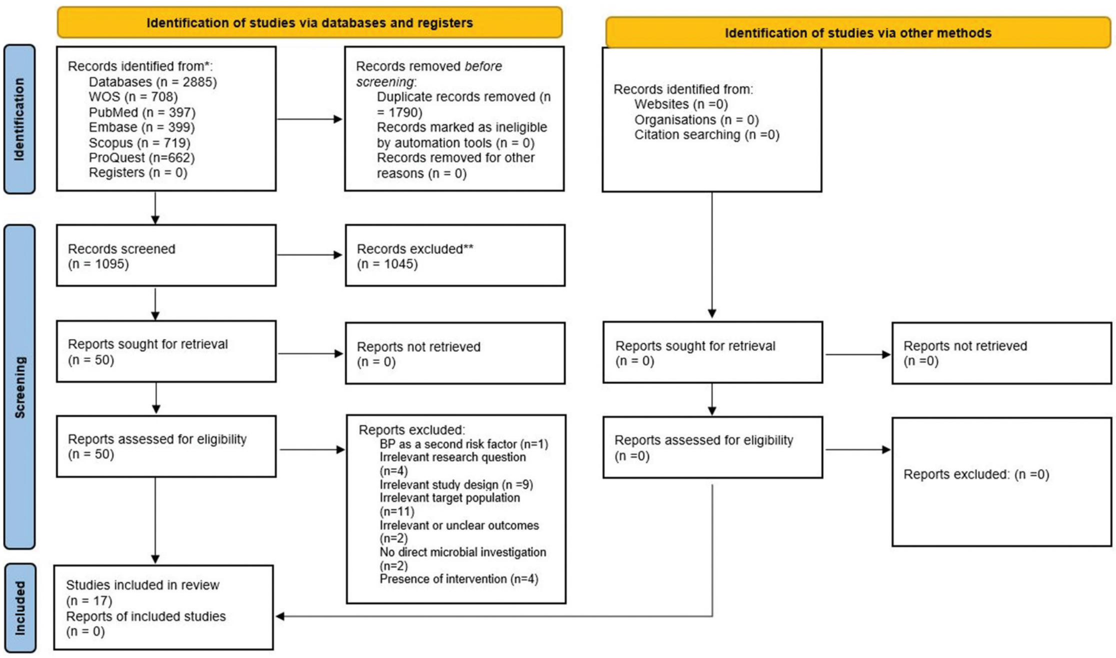

Figure 2. Flow diagram of the search strategy.

Table 1. General characteristics of published studies that investigated the oral microbiome associated with hypertension.

Author (country)	Study Design*	Study groups and case definition	No. of males/females); age (mean±SD or range)	Definition of HTN	Sample type	Microbiome analysis method	Adjustment for confounders (Yes/No)	Differential abundance analysis method	FDR (Yes/No)	Quality	Reporting Funding/ Conflict of interest
1- Murugesan & Al Khodor [26] (Qatar)	Case-control	G1: Normotensive ($n = 336$) G2: Elevated BP ($n = 357$) G3: Stage I HTN ($n = 336$) G4: Stage II HTN ($n = 161$)	G1: 220/116; (34.39 ± 10.12) G2: 207/150; (41.63 ± 12.60) G3: 220/116; (46.31 ± 10.27) G4: 78/83; (52.43 ± 10.14)	Following the American Heart Association Guidelines 2017 HTN with SBP ≥130 mmHg and/or DBP ≥80 mmHg	Saliva	16S rRNA gene seq. (V1–V3)	No	Univariate Wilcoxon test	No	Moderate	Yes/Yes
2- Chen et al. [16] (China)	Case-control	Initial cohort: G1: Normotensive ($n = 39$) G1a: No-PD ($n = 23$) G1b: PD ($n = 16$) G2: HTN ($n = 95$) G2a: No-PD ($n = 36$) G2b: PD ($n = 59$) Follow-up cohort** (after 6 months): G1: Normotensive ($n = 26$) G2: HTN ($n = 52$)	Initial cohort: G1a: No-PD: 7/16; (62.87 ± 2.03) G1b: PD: 5/11; (67.38 ± 1.56) G2a: No-PD: 9/27; (67.42 ± 1.82) G2b: PD: 27/32; (68.14 ± 0.79) Follow-up cohort (after 6 months): Not reported	Following the 2018 ESC/ESH Guidelines HTN with SBP ≥140 mmHg and/or DBP ≥90 mmHg	Saliva Subgingival plaque Feces	16S rRNA gene seq. (V3–V4) Shotgun metagenome seq. (for species-level profiling)	No	Kruskal-Wallis rank-sum test LEfSe (LDA score > 2) Spearman's correlation with BP	Yes	High	Yes/Yes
3- Lamonte et al. (USA) [24]	Case-control	G1: Normotensive ($n = 429$) G2: Undiagnosed elevated BP ($n = 306$) G3: Prevalent HTN (480)	G1: 429 females (no males); (64.5 ± 6.4) G2: 306 females (no males); (67.5 ± 6.8) G3: 480 females (no males); (68.1 ± 7.1)	Following the American Heart Association Guidelines 2017	Subgingival plaque	16S rRNA gene seq. (V3–V4)	Yes	ANOVA test Multivariable Cox regression analyses	Yes	High	Yes/Yes
4-Barbadoro et al. [14] (Italy)	Case-control	G1: Normotensive ($n = 25$) G2: HTN ($n = 23$)	G1: 9/16 <65 years ($n = 12$), 65–70 years ($n = 8$), >70 years ($n = 5$) G2: 14/9 <65 years ($n = 0$), 65–70 years (n=$n = 12$), >70 years ($n = 11$)	NM	Supragingival plaque Biofilm under dental prosthesis Subgingival plaque	PCR for selected bacterial species (*A. actinomycetemcomitans, Prevotella intermedia, Tannerella forsythia, Porphyromonas gingivalis, Trepomena denticola, Streptococcus mutans, Streptococcus sanguinis, Veillonella dispar, and Neisseria. subflava*)	Yes	Multiple logistic regression models	No	Low	Yes/Yes
5- Chen et al. [17] (China)	Case-control	G1: Normotensive ($n = 24$) G2: HTN ($n = 36$)	25/35; (67.73 ± 6.81; 45–79) G1: Not reported G2: Not reported	Following the 2018 ESC/ESH Guidelines HTN with SBP ≥140 mmHg and/or DBP ≥90 mmHg	Saliva Subgingival plaque Feces	Shotgun metagenome seq.	No	LEfSe (LDA score > 2) Kruskal-Wallis test Spearman's correlation with BP	Yes	Moderate	Yes/Yes
6- Chen et al. [15] (China)	Case-control	G1: Normotensive ($n = 24$) G2: HTN ($n = 52$)	G1: 9/15; (66.29 ± 1.42) G2: 22/30; (69.21 ± 0.69)	HTN with SBP ≥140 mmHg and/or DBP ≥90 mmHg	Saliva Subgingival plaque Feces Blood	16S rRNA gene seq. (V3–V4) Shotgun metagenome seq.	No	Spearman's correlation with HTN-associated metabolome	Yes	Moderate	Yes/Yes

(*Continued*)

Table 1. (Continued).

Author (country)	Study Design*	Study groups and case definition	No. of males/females); age (mean±SD or range)	Definition of HTN	Sample type	Microbiome analysis method	Adjustment for confounders (Yes/No)	Differential abundance analysis method	FDR (Yes/ No)	Quality	Reporting Funding/ Conflict of interest
7- Chen et al. [18] (China)¶	Case-control	G1: Normotensive ($n = 27$) G2: HTN ($n = 23$)	G1: 27 males (no females); (30.50 ± 5.74) G2: 23 males (no females); (36.22 ± 10.20)	HTN with SBP ≥140 mmHg and/or DBP ≥90 mmHg	Saliva	16S rRNA gene seq. (V3-V4)	No	Kruskal – Wallis tests LEfSe (LDA score > 2) Multivariate linear regression	No	High	Yes/Yes
8- Gordon et al. [22] (USA)	Case-control	G1: Normotensive ($n = 179$) G2: Elevated/stage I HTN ($n = 106$) G3: Stage II HTN ($n = 42$) G4: HTN medication use ($n = 119$)	G1: 179 females (no males); (65.8 ± 6.3) G2: 106 females (no males); (68.3 ± 6.7) G3: 42 females (no males); (69.4 ± 6.9) G4: 119 females (no males); (68.4 ± 7.3)	Following the American Heart Association Guidelines 2017 HTN with SBP ≥130 mmHg and/or DBP ≥80 mmHg	Subgingival plaque	16S rRNA gene seq. (V3-V4)	No	Kruskal-Wallis test	Yes	High	Yes/Yes
9- Goh et al. [21] (USA)	Case-control	G1: Normotensive ($n = 187$) G2: HTN ($n = 93$)	G1: 34/153; (32 ± 9) G2: 26/67; (37 ± 11)	Following the American Heart Association Guidelines 2017 HTN with SBP ≥130 mmHg and/or DBP ≥80 mmHg	Subgingival plaque	16S rRNA gene seq. (V3-V4) Analysis limited to 20 nitrate-reducing taxa (summary score)	Yes	Multivariate linear regression	No	Moderate	Yes/Yes
10- Sohail et al. [28] (Qatar)	Case-control	G1: Normotensive ($n = 40$) G2: HTN ($n = 56$)	43/53; (47.5; 30–60) G1: Not reported G2: Not reported	HTN with SBP ≥140 mmHg and/or DBP ≥90 mmHg	Saliva	16S rRNA gene seq. (V3-V4)	Yes	Mann – Whitney U-test Spearman correlation and stepwise linear regression analysis between clinical measurements and microbial taxa count	Yes	Low	Yes/Yes
11- Aoyama et al. [13] (Japan)	Case-control	G1a: 61–70-year Normotensive ($n = 132$) G1b: 71–80-year Normotensive ($n = 67$) G2a: 61–70-year HTN ($n = 189$) G2b: 71–80-year HTN ($n = 223$)	G1a: 85 males (65.3 ± 2.9); 47 females (66.2 ± 3.2) G1b: 47 males (74.7 ± 2.6); 20 females (74.7 ± 2.9) G2a: 147 males (65.6 ± 2.9); 42 females (66.2 ± 2.7) G2b: 166 males (74.9 ± 2.8); 57 females (74.6 ± 2.4)	NM	Saliva Subgingival plaque	PCR for selected periodontal pathogens: *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, and Prevotella intermedia*	Yes	Wilcoxon test Multivariate logistic regression	No	Moderate	Yes/Yes
12- Marchi-Alves et al. [25] (Brazil)	Case-control	G1: Normotensive ($n = 20$) G2: HTN ($n = 21$)	G1: 2/18; (60.05 ± 7.51) G2: 3/18; (65.57 ± 7.78)	Self-reported and confirmed by the registers in the patient history at the health service or the prescribed use of medications	Saliva	Culture media for total aerobic microorganisms, Staphylococci, Streptococci and Candida species,	No	Mann–Whitney test	No	Low	No/Yes

(*Continued*)

Table 1. (Continued).

Author (country)	Study Design*	Study groups and case definition	No. of males/females); age (mean±SD or range)	Definition of HTN	Sample type	Microbiome analysis method	Adjustment for confounders (Yes/No)	Differential abundance analysis method	FDR (Yes/No)	Quality	Reporting Funding/ Conflict of interest
13- SU et al. [29] (Japan)	Case-control	G1: Normotensive ($n = 50$) G2: HTN ($n = 20$)	23/47; (69.5; 45–92) G1: NR G2: NR	NM	Tongue dorsum	PCR for selected periodontal pathogens: *Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola*	No	Mann–Whitney test Spearman's rank correlation between bacterial number with age and moisture level	Yes	Moderate	Yes/Yes
14- Fei et al. [20] (Ghana, South Africa, Jamaica, and the United States) ¶	Case-control	G1: Ghana ($n = 196$) Normotensive ($n = 190$) and HTN ($n = 6$) G2: South Africa ($n = 176$) Normotensive ($n = 150$) and HTN ($n = 26$) G3: Jamaica ($n = 92$) Normotensive ($n = 91$) and HTN ($n = 1$) G4: United States ($n = 191$) Normotensive ($n = 166$) and HTN ($n = 25$)	Gender for the whole cohort: 393 females and 262 males. Not reported for the individual groups. Age G1: 35.8 ± 6.6 G2: 33.3 ± 5.9 G3: 33.9 ± 6.2 G4: 36.0 ± 6.3	Elevated blood pressure (≥130/85 mm Hg), or receiving treatment	Saliva (620 samples) Feces	16S rRNA gene seq. (V4)	Yes	Analysis of composition of microbiomes (ANCOM)	Yes	High	Yes/Yes
15- Shanker et al. [27] (India) ¶	Case-control	G1: Gingivitis subjects ($n = 25$) Normotensive ($n = 20$) and HTN ($n = 5$) G2: Periodontitis subjects ($n = 54$) Normotensive ($n = 44$) and HTN ($n = 10$)	G1: 21/4; (41.48 ± 1.37) G2: 43/11; (48.46 ± 0.77)	Self-report of physician's diagnosis and/or use of antihypertensive drugs along with perusal of their medical records	Saliva	PCR for *Porphyromonas gingivitis*	Yes	Univariate analysis Binary logistic regression analysis	No	Moderate	Yes/Yes
16- Desvarieux et al. [32] (USA)	Case-control	Normotensive ($n = 247$) and HTN ($n = 406$)	Gender and age for the whole cohort: 259; (70 ± 9) for males/394; (67 ± 8) for females. Not reported for the individual groups.	HTN with SBP ≥140 mm Hg or a DBP ≥90 mm Hg or the patient's self-report of a history of antihypertensive use	Subgingival plaque	Checkerboard DNA-DNA hybridization for 11 periodontal bacteria: *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Trepomena denticola, Campylobacter rectus, Eikenella corrodens, Fusobacterium nucleatum, Parvimonas micra, Prevotella intermedia. Actinomyces naeslundii and Veillonella parvula*	Yes	Linear logistic regression models	No	High	Yes/No

(*Continued*)

Table 1. (Continued).

Author (country)	Study Design*	Study groups and case definition	No. of males/females); age (mean±SD or range)	Definition of HTN	Sample type	Microbiome analysis method	Adjustment for confounders (Yes/No)	Differential abundance analysis method	FDR (Yes/No)	Quality	Reporting Funding/ Conflict of interest
17- Ye et al. [30] (China)	Case-Control	G1a: Normotensive (no-HTN no PD) ($n = 14$) G1b: Normotensive and PD (PD no HTN) ($n = 10$) G2a: HTN and no PD (HTN no PD) ($n = 16$) G2b: HTN and PD (HTN-PD) ($n = 20$)	G1a: 4/10; (66.79 ± 9.3) G1b: 4/6; (68.7 ± 6.3) G2a: 8/8; (68.8 ± 5.96) G2b: 9/11; (67.05 ± 5.4)	Following the 2018 ESC/ ESH Guidelines HTN with SBP ≥140 mmHg and/or DBP ≥90 mmHg	Saliva Subgingival plaques Feces	Shotgun metagenome seq.	Yes	MaAsLin2, Limma Voom, and Wilcoxon test	Yes	Moderate	Yes/Yes

*: Studies differed in describing the study design although all used the same design, so we describe them all here as case-control for consistency. **: The follow-up cohort was still cross-sectional on a subset of the original cohort. ¶: The study included multiple disease groups; only groups relevant to the scope of this review are presented.

FDR: False discovery rate, HTN: Hypertension, PD: Periodontitis, No-PD: No periodontitis, RCDP: Removable Complete Dental Prosthesis, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ESC/ESH: European Society of Cardiology and the European Society of Hypertension.

22,24,32]. The rest were conducted in Japan [13,29], Qatar [26, 28], Brazil [25], India [27], Italy [14], and one study included subjects from multiple regions (USA, Jamaica, South Africa, and Ghana) [20]. Regarding the definition of hypertension, four studies followed the 2017 American Heart Association Guidelines (AHA) [21,22,24,26], while three followed the 2018 European Society of Cardiology and the European Society of Hypertension (ESC/ESH) [16,17,30]. On the other hand, five studies specified measurement references for defining hypertension without citing specific guidelines [15,18,20,28,32], two other studies relied on self-reporting and/or the recorded diagnosis on the system [25,27], while three studies didn't specify their reference for the definition of hypertension [13,14,29].

Some studies considered additional clinical factors. Four studies stratified by cases and controls by periodontitis [27,30,32], while one study included obstructive sleep apnea [18]; the data for the latter were extracted solely for the standalone hypertension and normotensive groups. All studies enrolled both genders except for two studies that enrolled only females [22,24], and one study that enrolled males [18].

With respect to sample type, five studies collected samples from both saliva and subgingival plaque [13,15–17,30], six studies collected saliva only [18,20,25–27,28], and four studies collected subgingival plaque [21,22,24,32]. Additionally, one study collected supra- and subgingival plaques [14], and one study involved swabs from the dorsum of the tongue [29]. In addition to the oral samples, five studies collected fecal samples [15–17,20,30], and one collected blood samples [15]. The data for these samples (fecal and blood) were not considered in this review.

Various methods were employed for microbial analysis. The majority of the included studies used 16S rRNA gene sequencing [18,20–22,24,26,28], four studies used PCR for selected types of bacteria [13,14,27,29], two studies used shotgun metagenome sequencing (SMS) [17,30], one study used culture-based method [25], one study used checkerboard DNA–DNA hybridization for specific periodontal bacteria [32], and two studies used both 16S ribosomal RNA gene sequencing and SMS [15,16]. In 13 studies, the analysis was limited to the profiling of bacterial communities; one study used the SMS data to profile fungi only [17], and two studies performed analysis for both oral bacteria and fungi [15,25], while one study analyzed the virome only [30].

Regarding the assessment of confounders, two studies conducted comprehensive adjustments utilizing different regression models for assessment [21,32], whereas seven studies attempted some sort of adjustments, but not all clinical factors were taken into account [13,14,20,24,27,30,28]. Regarding correction for multiple comparisons, nine studies employed false discovery rates (FDR) to define significant microbial differences between the study groups [15–17,20,22,24,29,30,28].

Quality of the included studies

As can be seen in Table 1, the overall NOS scores of the included studies ranged from 3 to 9, with six studies being rated as high-quality studies, eight studies as moderate, and three as low quality. The most common methodological limitations were related to selection and comparison shortcomings.

Changes in oral microbial alpha and beta diversity in hypertension

As summarized in Table 2, eight of the included studies examined differences in alpha diversity between hypertensive and normotensive patients [16–18,20,24,26,30,28], mostly using Shannon's and/or Chao1 indexes. Four studies found no significant changes in alpha diversity in association with hypertension [17,20,24,28], while four studies reported significant changes [16,18,26,30]. Among the latter, the results were conflicting, with two studies reporting lower alpha diversity in hypertensive individuals compared to normotensive individuals [18,26], and the other two reported higher alpha diversity in hypertensive patients [16,30]. Furthermore, one study reported no significant change in alpha diversity in the study's initial cohort; however, a significant change was observed after the 6-months follow-up [16].

Seven studies assessed differences in beta diversity [16–18,20,26,30,28], using principal coordinate analysis (PCoA) based on various distance matrices (Table 2); however, two of these studies [26,30] did not perform formal statistical testing of the differences (PERMANOVA or ANOSIM). Three studies found significant differences between hypertension and normotensive groups [17,18,28], while another study didn't find significant differences [20]. Interestingly, one study reported no significant change in beta diversity except in subgingival samples, and this difference was only observed at the study's initial cohort, but not after the 6-month follow-up period [16].

Bacterial composition differences between hypertensive and normotensive subjects

All 15 studies that focused on the bacterial component of the microbiome, except for one [29], found some level of significant differences in microbial composition between hypertensive and normotensive subjects as summarized in Table 2, although the

Table 2. Summary of the microbial findings of the included studies.

Study	α-Diversity differences	β-Diversity differences	Taxa enriched in the cases	Taxa depleted in the cases	Diagnostic accuracy or AUC	Association summary
1- Murugesan & Al Khodor [26] (Qatar)	**Significant** HTN had lower diversity than normotensive (Simpson and Shannon Indices)	**Significance not reported*** (PCoA based on Bray – Curtis distance)	Phyla: Frimcuites, Actinobacteria TM7 (Stage 1) Genera: *Bacteroides, Lactobacillus, and Atopobium* Species: Not reported	Phyla: Proteobacteria, Bacteriodetes Genera: *Prevotella, Neisseria, and Haemophilus* Species: Not reported	Machine learning using random forest AUC = 89%-91%	Salivary microbiome composition significantly differed between the normal, elevated, stage-1, and stage-2 HTN groups.
2- Chen et al. [16] (China)	**- Initial cohort**: **Not significant** (Chao1, Faith's phylogenetic diversity, Shannon index, and Pielou's evenness) **- Follow-up cohort**: **Significant** HTN had higher than normotensive in saliva and subgingival plaque (Chao1, Faith's phylogenetic diversity)	**- Initial cohort**: **Not significant** for saliva and **significant** for subgingival plaque (PCoA based on Bray-Curtis distance; PERMANOVA test) **- Follow-up cohort**: **Not significant** (PCoA based on Bray-Curtis distance; PERMANOVA test)	**Oral bacterial taxa that differed significantly according to HTN or BP**: **- Initial cohort**: **Saliva** Phyla: Proteobacteria Genera: *Burkholderia, Euzebya, Neisseria, Lautropia, Haemophilus, Cupriavidus, Ralostonia, Moraxella, Pelomonas, Butyrivibrio, Actinobacillus, and, Rothia* Species:** *Neisseria_sicca, Neisseria elongate, Fusobacterium_sp_CM22-, Neisseria mucosa, Lachnoanaerobaculum_sp_ MSX33, Actinomyces oricola, Eikenella_sp_HMSCO61C02, Neisseria sp_HMSC064E01, Ottowia_sp_Marseille P4747, Streptococcus_sp_JS71, Ottowia_sp_oral taxon 894, Neisseria_sp_HMSC058F07, Neisseria_sp_KEM232, Capnocytophaga_leadbetteri, Neisseria_sp_HMSC072F04* **Subgingival plaque** Phyla: Proteobacteria Genera: *Kingella, Rothia, Lautropia, Aggregatibacter, Capnocytophage, Pasteurella, Desulfomicrobium, Eikenella, Rothia* Species: ** *Porphyromonas gingivalis, Tannerella forsythia, Ottowia_sp_Marsellle P4747, Ottowa_sp oral taxon_894, Treponema denticola, Treponema_phagedenis, Bergeyella cardium, Actinomyces_SP_oral _taxon_448, Lachnoanaerobaculum_sp_MSX33, Porphyromonas endodontalis, Campylobacter_showae, Capnocytophaga_sp_oral_taxon_863, Campylobacter_rectus, Capnocytophaga_sp_oral_taxon_332, Prevotella_sp_KCOM_3155, Neisseria_sp_KEM232* **- Follow-up cohort (after 6 months)**: **Saliva**: Genera: *Lautropia, Leptotrachia, Lactobacillus* **Subgingival plaque**: Genera: *Polyangium*	**Oral bacterial taxa that differed significantly according to HTN or BP**: **- Initial cohort**: **Saliva** Phyla: Firmicutes Genera:, *Veillonilla, and Streptococcus, Catonella, Megasphaera, Prevotella, mycoplasma* Species:** *Prevotella_sp_HMSC077E09, Actinomyces_sp_oral taxon 171, Streptococcus_sp_HMSC034E03, Streptococcus sp F0442, Rothia_dentocariosa, Actinomyces_sp_oral_taxon_181, Prevotella_dentalis, Actinomyces_sp_S6_Spd3, Trueperella_pyogenes, Streptococcus_constellatus, Provetella_sp_ oral_ taxon 376, veillonella_parvula, Schaalia georgiae, Streptococcus _parasanguinis, Actinomyces_sp_ph3, Mogibacterium_diversum* **Subgingival plaque** Phyla: Firmicutes Genera: *Selenomonas, Dialister, Prevotella, Veillonella, Bulleidia, Polyangium, Olsenella, Atopobium, Neisseria, Oribacterium* Species:** *Actinobaculum_sp_oral taxon 183, Veillonella parvula, Rothia dentocariosa, Actinomyces_sp_oral taxon 170, Selenomonas noxia, Ralstonia_sp MD27, Leptotrichia_wadei, Veillonella_sp_T14073 2, Streptococcus cristatus, Streptococcus sp 263 SSPC, Streptococcus_sp_UMB1385, Streptococcus oralis, Lachnoanerobaculum_saburreum, Veillonella_sp_T11011_6, Veillonella rogosae* **- Follow-up cohort (after 6 months)**: **Saliva**: Genera: *Ochrobactrum, Anaerovorax, Mobilunucs* **Subgingival plaque**: Genera: *TG5, Veilonilla, Oribacterium, Moryella,*	Not reported	PD and oral microbiota were strongly associated with HTN

(*Continued*)

Table 2. (Continued).

Study	α-Diversity differences	β-Diversity differences	Taxa enriched in the cases	Taxa depleted in the cases	Diagnostic accuracy or AUC	Association summary
3- Lamonte et al. (USA) [24]	**Not significant** (Chao1, Shannon index)	Not reported	**Bacterial species that differed significantly according to HTN and BP**: Species: - G2: None - G3: *Treponema socranskii, Oribacterium oral taxon 078, Veillonellaceae G1 sp. oral taxon 155, Prevotella buccae, Pseudoramibacter alactolyticus, Bifidobacterium dentium, Campylobacter gracilis, and Peptostreptococcaceae_[XI][G-1] [Eubacterium] _infi*	**Bacterial species that differed significantly according to HTN and BP**: Species: G2: *TM7 G1 sp. oral taxon 869* G3: *TM7 G1 sp. oral taxon 869, Leptotrichia sp. oral taxon 212, Rothia aeria, and Streptococcus sanguinis*	Not reported	Specific oral bacteria were associated with baseline BP status and risk of HTN development among postmenopausal females.
4-Barbadoro et al. [14] (Italy)	Not reported	Not reported	Lack of detailed microbial results/ambiguous results; only ***Neisseria subflava*** was reported to be statistically significantly more abundant in normotensive individuals.		Not reported	HTN had an association with oral microbiome and salivary nitric oxide
5- Chen et al. [17] (China)	**Not significant** (Choa1, Shannon and ACE indexes)	**Significant** (PCoA; based on Bary-Curtis distance; PERMANOVA test)	**Oral fungal taxa that differed significantly according to HTN or BP**: **Saliva**: Genera: *Kluyveromyces, Tetrapisispora, Agaricus* Species: *Exophiala spinifera, Agaricus-bisporus, Saccharomycopsis fibuligera, Colletotrichum_orchidophilum, Chaetomium_thermophilum, Penicillium rubens, Lodderomyces elongisporus, Wickerhamomyces ciferrii, Ascoidea rubescens* **Subgingival Plaque**: Genera: *Nannizzia, Blastomyces, Wallemia* Species: *Nannizzia_gypsea, Verticillium_dahliae, Blastomyces_gilchristii, Kwoniella_pini, Wallemia_mellicola, Trichoderma gamsii, Aspergillus candidus*	**Oral fungal taxa that differed significantly according to HTN or BP**: **Saliva**: Genera: *Sugiyamaella, Materhizium, uc_Hypocreomycetidae, Zymoseptoria, Melampsora* Species: *Sugiyamaella lignohabitans, uc_Hypocreomycetidae, Zymoseptoria tritici, Melampsora_larici_populina, Aspergillus_bombyccis, uc_Magnaporthe* **Subgingival Plaque**: Genera: *Pestalotiopsis, Leptosphaeria, Saccharomycopsis, Gaeumannomyces, Scheffersomyces, Torulaspora, uc_Hypocreales* Species: *Pestalotiopsis fici, Saccharomycopsis fibuligera, Scheffersomyces stipitis, Gaeumannomyces tritici, uc_Hypocreales Cryptococcus neoformans, Alternaria alternate, Torulaspora delbrueckii, Chaetomium globosum, Leptoshaeria biglobosa, uc_Saccharomycopsis, Diplodia corticola, Candida albicans, Anthracocystis flocculosa*	Not reported	There were significant correlations between oral fungi and HTN, including its clinical parameters.
6- Chen et al. [15] (China)	Not reported	Not reported	**Taxa positively correlating with at least two HTN-associated plasma metabolites ¶**: **Saliva** Bacterial genera: *Streptococcus, Polyangium, Neisseria, Moraxella, Aggregatibacter, Actinomyces* Fungal genera: *Ustilago, Cladophiaophora, Torulaspora, Ogataea, Capronia, Thielavia* **Sublingual plaque:** Bacterial genera: *Corynebacterium, Leptotrichia, Actinomyces, Polyangium, Cupriavidus, Aggregatibacter* Fungal genera: *Tetrapisispora, Phaeoacremonium,*	**Taxa negatively correlating with at least two HTN-associated plasma metabolites¶**: **Saliva:** Bacterial genera: *Sphingomonas, [Prevotella], Agrobacterium, Lachoanaerobaculum, Treponema, Tannerella,* Fungal genera: *Trametes, Tetrapisispora, Eremothecium, Exophialia, Aspergillus, Ascoidea,* **Sublingual plaque:** - Bacterial genera: *Prevotella, Bacteroides, Oribacterium, Porphyromonas, Filifactor, Fusobacteriume, Schwartzia, Tannerella, Parvimonas, Lactobacillus,Treponema, Megasphaera, Butyrivibrio, Roseomonas, Bulleidia, Atopobium, Desulfovibrio, Peptostreptococcus* Fungal genera: *Saitoella, Paraphaeosphaeria, Ustilago, Schizosaccharomyces*	Not reported	microbial community composition had significant correlations with HTN-associated metabolites.

(*Continued*)

Table 2. (Continued).

Study	α-Diversity differences	β-Diversity differences	Taxa enriched in the cases	Taxa depleted in the cases	Diagnostic accuracy or AUC	Association summary
7- Chen et al. [18] (China)¶	**Significant** HTN had lower diversity (Chao1 and Richness indexes)	**Significant** (PCoA based on Bary-Curtis distance; ANOSIM test)	Genera By Kruskal – Wallis tests and LEfSe: *Rothia, Neisseria, Haemophilus, Lautropia.* By LEfSe alone: *Campylobacter, Kingella, Cardiobacterium, Ralstonia, Flavitalea, Anaeroglobus*	Genera By Kruskal – Wallis tests: *Actinomyces, Peptostreptococcus, Absconditabacteria-(SR1)-[G1-]* By LEfSe: *Solobacterium, Lachnoanaerobaculum, Segetibacter, Lactobacillus, Cronobacter, Delftia, Fastidiosipila*	Not reported	There were significant alterations in the salivary microbiome in patients with HTN
8- Gordon et al. [22] (USA)	Not reported	Not reported	Species: None	Species: G4: *Prevotella oral taxon 317 and Streptococcus oralis*	Not reported	Two bacterial species demonstrated lower, significantly different relative abundances among females taking HTN medication compared to those with normal BP.
9- Goh et al. [21] (USA)	Not reported	Not reported	*Actinomyces naeslundii was associated with* HTN prevalence ratio Higher levels of *Neisseria flavescens, Haemophilus parainfluenzae, Neisseria sicca* were associated with lower BP in normotensive subjects but no association with HTN.		Not reported	Higher nitrate-reducing taxa summary score was associated with lower BP in normotensive subjects, particularly systolic BP.
10- Sohail et al. [28] (Qatar)	**Not significant** (faith_PD index)	**Significant** between normotensive female and HTN male and female subjects (PCoA based on weighted unifrac distance; PERMANOVA test)	Phyla: Firmicutes Families: Atopobiacea, Veillionellaceae, Prevotellaceae, Genera: *Prevotella, Veillonella, Atopobium*	Phyla: Fusobacteria, Proteobacteria Families: Fusobacteriaceae Genera: *Fusobacterium*	Not reported	There was a strong association between salivary microbial dysbiosis and HTN
11- Aoyama et al. [13] (Japan)	Not reported	Not reported	Species: *G2a: Aggregatibacter actinomycetemcomitans (for saliva and subgingival plaque in males only)* *G2b: Prevotella intermedia* (only for subgingival plaque particularly in males)	None	Not reported	Specific periopathogens were significantly associated with HTN in males, but not in females.
12- Marchi-Alves et al. [25] (Brazil)	Not reported	Not reported	Genera: *Streptococci and staphylococci*	None	Not reported	There is a significantly higher microbial load of certain bacteria in HTN patients compared to normotensive patients.
13- SU et al. [29] (Japan)	Not reported	Not reported	None	None	Not reported	No significant association with HTN.
14- Fei et al. [20] (Ghana, South Africa, Jamaica, and the United States) ¶	**Not significant** in all groups (Shannon index)	**Not significant** in all groups (PCoA of weighted uniFrac distance; PERMANOVA test)	Genera: *Atopobium* (Male and Female), *Fusobacterium* (South Africa), *Veillonella* (Male, Ghana), *Prevotella* (female)	Genera: *Neisseria* (Male), *Rothia* (female)	Not reported	Gender- and ethnicity-specific microbiota was associated with HTN
15- Shanker et al. [27] (India) ¶	Not reported	Not reported	**Species**: *Porphyromonas. gingivalis in G2*	**None**	Not reported	Mean *Porphyromonas gingivalis* expression level was significantly associated with HTN in patients with periodontitis
16- Desvarieux et al. [32] (USA) ¶	Not reported	Not reported	**'Etiological Bacteria burden' – 4 species summed together**: *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola* (in all 4 statistical models)	**'Putative Bacteria burden' – 5 species summed together**: *Campylobacter rectus, Eikenella. corrodens, Fusobacterium nucleatum, Parvimonas micra, Prevotella intermedia* (in only one statistical model)	Not reported	There was a significant association of pathologic bacterial load with prevalent HTN and BP.

(*Continued*)

Table 2. (Continued).

Study	α-Diversity differences	β-Diversity differences	Taxa enriched in the cases	Taxa depleted in the cases	Diagnostic accuracy or AUC	Association summary
17- Ye et al. [30] (China)	- **Significant** Only for HTN-PD in sub-gingival plaque; higher diversity than no-HTN no-PD (Shannon diversity and Pielou evenness index)	**Significance not reported*** (PCoA based on Bray-curtis distance)	**HTN no PD (G2a) compared to no HTN no PD (G1a)**: **Saliva** Families: *Myoviridae* Genera: *Torbevirus* **Subgingival plaques** Families: None Genera: *Salacisavirus, Coralvirus* **HTN-PD(G2b) compared to no HTN no PD (G1a)**: **Saliva** Families: *Myoviridae* Genera: *Torbevirus, Reyvirus* **Subgingival plaques** Families: *Mimiviridae* Genera: *Reyvirus, Flaumdravirus, Emaravirus, Yatapoxvirus, Kungbxnavirus, Salacisavirus, Firehammervirus*	**HTN no PD (G2a) compared to no HTN no PD (G1a)**: **Saliva** Families: None Genera: *Tybeckvirus* **Subgingival plaques** Families: None Genera: *Gillianvirus, Hepatovirus, Alphatorquevirus, Pepyhexavirus, Liefievirus* **HTN-PD(G2b) compared to no HTN no PD (G1a)**: **Saliva** Families: None Genera: *Capripoxvirus* **Subgingival plaques** Families: *Siphoviridae* Genera: *Gillianvirus, Likavirus, Lymphocryptovirus, Pepyhexavirus*	Not reported	There were significant alterations in the oral virome in HTN.

*: No formal test (PERMANOVA or ANOSIM) was used to assess the statistical differences between groups. **: Only the top 15 species listed here. ESVs: Exact Sequences Variances. BP: Blood pressure. ¶: Eight metabolites were identified in that study as HTN-associated. HTN: Hypertension, PD: Periodontitis, No-PD: No periodontitis, PCoA: principal coordinate analysis.

differences varied from being limited to a single or two species [13,21,22,25,27] to involving tens of species [15,16,18,20,24,26,32,33]. Below is a digest of findings from these studies regardless of whether they were controlled for FDRs and/or confounders.

Bacterial genera that were found to be enriched in hypertension in two or more studies, but not depleted in any other study include *Aggregatibacter* (subgingival plaque and saliva) [15,16], *Moraxella* (saliva) [15,16], *Kingella* (subgingival plaque and saliva) [16,18], *Lautropia* (subgingival plaque and saliva) [16,18], and *Leptotrachia* (subgingival plaque and saliva) [15,16]. On the other hand, bacterial genera that were found to be depleted in hypertension in two or more studies, but not enriched in any other study include *Megasphaera* (subgingival plaque and saliva) [15,16], *Oribacterium* (subgingival plaque) [15,16], and *Peptostreptococcus* (subgingival plaque) [15,18] . At the species level, the red complex periopathogens *Porphyromonas gingivalis* (subgingival plaque and saliva) [*16,27,32], Tannerella forsythia* (subgingival plaque) [16,32], and *Treponema denticola* (subgingival plaque) [16,32], in addition to *Actinobacillus actinomycetemcomitans* [13,32], were found to be associated with hypertension in two or more studies, but not in the opposite direction in any study, while *Streptococcus oralis* (subgingival plaque) [16,22] was found to be depleted in two studies, but not enriched in any other study.

Nevertheless, there were substantial inconsistencies and conflicting results among the studies. At the genus level, *Neisseria*, for example, was found to be enriched in the saliva of individuals with hypertension according to some studies [15,16,18] and depleted in both saliva and subgingival plaque according to others [16,20,26]. Similarly, *Prevotella* was found to be enriched in two studies [20,28] and depleted in three [15,16,26]. Similar conflicting results were found for *Haemophilus* [16,18,26], *Streptococcus* [16,15], *Rothia* [16,18,20] and *Veillonella* [16,20,28]. Like-wise at the species level. For example, *Prevotella intermedia* was found to be enriched in the subgingival plaque in one study [13] and depleted in another [32]. The same inconsistency was found for *Campylobacter rectus* [16,32] and *Oribacterium* oral taxon 078 [16,24]. Furthermore, some bacterial taxa were reported to be enriched in one sample type but depleted in another. For instance, *Atopobium* [20,26,28] and *Bacteroides* [26] were found to be enriched in the saliva of individuals with hypertension but depleted in subgingival plaque samples [15,16,26].

A number of additional interesting results are worth noting. One study, for example, found no significant association between the nitrate-reducing bacteria summary score and hypertension but reported an association between the nitrate-reducing taxa summary score and lower BP in normotensive individuals [21]. Another study reported gender-specific findings, showing that certain periopathogens (*Aggregatibacter actinomycetemcomitans*, and *Prevotella intermedia*) were significantly associated with hypertension in males but not in females [13]. A third study demonstrated, using a random forest classifier, that microbial signatures could serve as hypertension biomarkers, the model achieved an accuracy, measured in terms of area under the curve (AUC), ranging from 89% to 91% [26].

The oral mycobiome and virome in hypertension

Out of the 17 included studies, two studies profiled the oral mycobiome [15,17] and one study analyzed the oral virome [30] potentially associated with hypertension. The key findings from these studies are presented in Table 2. Among oral fungi that were found to be associated with hypertension include *Kluyveromyces, Nannizzia*, Cladophiaophora and *Torulaspora*. Fungal genera that were found to be depleted in hypertension include *Sugiyamaella, Materhizium, Zymoseptoria, Trametes and Ustilago*. As with bacteria, contradictory results were also observed. For example, *Tetrapisispora* was found to be enriched in the saliva of hypertensive patients in one study [17] depleted in another study [15]. Similarly, *Ustilago* was enriched in saliva but depleted in subgingival plaque of hypertensive cases in the same study [15]. As far as the virome is concerned, the single conducted study [30] found *Torbevirus, Reyvirus*, and *Salacisavirus* among others to more abundant in hypertension, while *Tybeckvirus, Gillianvirus, and Capripoxvirus*, to be less abundant than in normotensive subjects.

Key taxa consistently associated with hypertension

Applying the consistency criteria described in the methods section, three bacterial genera were found to be consistently enriched in hypertension: *Atopobium*, *Prevotella, and Veillonella* [20,28] while no bacterial genera were found to be consistently depleted (Table 3). Similarly, it shows no consistently reported species among studies that were either enriched or depleted.

Discussion

With over 700 different bacterial taxa, fungi, and viruses, oral microbiome is the second most diverse microbial community after the gut [22,33, 34]. Imbalance in the composition or function of oral microbiome, commonly referred to as 'dysbiosis', has been linked to many systemic diseases including hypertension [22,24,35,36]. While the role of gut

Table 3. Bacterial taxa consistently associated with hypertension*.

Bacterial genera	
Enriched Genera in Hypertension *Atopobium* (Saliva) [28,20] *Prevotella* (Saliva) [20,28] *Veillonella* (Saliva) [20,28]	**Depleted Genera in Hypertension** None
Bacterial species	
Enriched Species in Hypertension None	**Depleted Species in Hypertension** None

*Criteria are described in the text.

microbiome in hypertension has been extensively studied and well-established in the literature [4,5,37], the role of oral microbiome in cardiovascular diseases in general and hypertension in particular is still under investigation and has gained momentum in recent years. In this context, a number of observational studies explored the potential association between oral dysbiosis and elevated blood pressure [13–30] but the results from these studies have not been critically analyzed. Hence, the purpose of this first-of-its-kind systematic review was to answer the following focused questions: 1) Is there a significant association between oral microbiota and hypertension? 2) What are the key oral microbial features consistently associated with hypertension?

The majority of the included studies revealed significant differences in the composition of oral microbiota between hypertensive patients and healthy controls, a finding which corroborates the available evidence regarding the potential role of human microbiome (e.g. gut microbiome) in blood pressure regulation and hypertension development [5,7,37]. The findings are also consistent with previous systematic reviews that found association between oral microbiota and other systemic diseases including cardiovascular diseases (e.g. atherosclerosis), pneumonia and many others [38–40]. Nevertheless, comparison of differentially abundant taxa between cases and controls revealed significant inconsistencies across the studies, i.e. in terms of what set of taxa were found to be associated with hypertension. These inconsistencies can be explained by the high heterogeneity inherent to microbiome data. Such heterogeneity includes study design variations (inclusion criteria, study groups, sample type/collection, etc.), technical variations (DNA extraction method, primer selection, sequencing chemistry, bioinformatic analysis pipeline, etc.), population variations (race/ethnicity, lifestyle, etc.), and importantly, how effect size is reported (fold change, odd ratio, LDA, mean difference, etc.). The only viable way to perform meta-analysis on them is to obtain the raw sequencing data of the original studies and re-analyze them using a standard bioinformatic analysis pipeline, which is out of the scope of the current review. To circumvent that, we devised a set of criteria to define taxa consistently associated with hypertension with some confidence (see methods section).

Applying those criteria, three bacterial genera were found to be consistently enriched in hypertension, namely *Atopobium*, *Prevotella, and Veillonella*, yet none were found to be consistently depleted. *Atopobium* species are anaerobic bacterial normal commensals of the oral cavity, gut, and vagina. Previous studies have reported higher abundance of *Atopobium* in cardiovascular diseases and metabolic disorders including atherosclerosis, obesity and diabetes mellitus [41,42]. Certain species of *Atopbium*, e.g. *A. rimae*, are associated with periodontitis [43], so this could be a potential pathway through which are involved in hypertension. This applies to *Prevotella* which includes known periodontal pathogens such as *P. intermedia*, pathogens. In fact, one of the studies included *P. intermedia* to be associated with hypertension, although only in males [13]. *Prevotella* have also been previously reported to be associated with cardiometabolic and cardiovascular disorders [44,45]. Interestingly, a recent study utilizing a representative data from the National Health and Nutrition Examination Survey found a significant association between increase in blood pressure and levels of antibodies against *Prevotella* and *Veillonella* [46]. It's however unclear how the latter may be involved in hypertension since it is typically associated with periodontal health, and as mentioned above, is also a nitrate reducer.

While the exact mechanism underlying the role of oral microbiota in hypertension is still unclear, two mechanisms have been proposed. The first mechanism is through nitrate-nitrite-NO pathway [47]. Oral microbiota has been reported to play an important role in nitric oxide (NO) bioavailability through reducing dietary nitrate into nitrite and subsequently NO [10,38,48]. NO plays a crucial role in vascular tone and integrity and is associated with lower blood pressure and lower cardiovascular diseases risk [10]. Important oral nitrate-reducing bacteria include species of the genera *Veillonella*, *Actinomyces*, *Rothia*, *Prevotella*, *Neisseria*, and *Haemophilus* [47–49]. It would then be expected that hypertension is associated with a depletion of these taxa. However, the current review found conflicting results among the included studies in this respect, with some studies showing them to be depleted and other studies showing them to be enriched. Interestingly, one study found that a summary score of nitrate-reducing taxa was associated with lower BP in normotensive but not hypertensive individuals [21], suggesting that nitrate reduction may be in important factor in regulating BP only in healthy subjects.

Another mechanism by which the oral microbiome may contribute to hypertension is through triggering chronic inflammation and subsequently endothelial dysfunction [12,50]. Periodontal pathogens can induce a systemic inflammatory response and production of cytokines such as c-reactive protein, tumor necrosis factor alpha, interleukin-6, among others, which in turn lead to endothelial dysfunction and negatively impact on blood pressure [12,50,51]. Several studies found significant association between periodontal infections and systemic inflammation and endothelial dysfunction [11,12,52,53]. In line with this, four of the studies included in this review found one or more periodontal pathogens to be enriched in saliva and/or subgingival plaque samples of hypertensive patients including *Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola* and *Actinobacillus actinomycetemcomitans* [13,16,27,32]. Indeed, a recent systematic review and meta-analysis of 25 clinical trials found that periodontal therapy was associated with a significant improvement in endothelial function in patients with periodontitis, substantiating the correlation of periodontitis (bacterial-induced inflammatory disease) with cardiovascular diseases [54].

It is cogent that the value of any evidence obtained from any systematic review is heavily reliant on the quality of the primary studies. Hence, we thoroughly cross-examined and appraised the quality of all included studies using NOS, a very effective appraisal tool for non-randomized studies. The results revealed that only seven of the included studies were of high quality, while the remaining were either moderate or low quality. The current review was limited by several other factors. One major factor is the remarkable heterogeneity between the studies, which is inherent to microbiome studies as discussed above, which limited comparability. Another important limitation is that most of the included studies failed to adjust for confounders and/or control for false discovery rate (FDR) during data analysis, which is a major weakness. For the future, high-quality, multi-center studies with standard study protocols, including reliable statistical analysis plans, are required to further explore the association between the oral microbiome and hypertension. A shift from metataxonomic (e.g. 16S) and even metagenomic approaches to more functional approaches (e.g. metatranscriptomics or metabolomics) is recommended.

Conclusion

The present systematic review demonstrates an association between oral microbiota and hypertension. The nature of compositional differences between normotensive and hypertensive subject, however, vary considerably among studies, most likely due to methodological inconsistencies across the studies. Nevertheless, a subset of microbial taxa seems to be consistently enriched in hypertension. Further works are warranted to validate and explore their role in hypertension.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The present work is supported by Qatar University, grant No: [QUHI-CDM-24/25–437].

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