Effects of metformin on the gut microbiota: A systematic review

Pavlo Petakh [1,2,*], Iryna Kamyshna [3], Aleksandr Kamyshnyi [2,**]

ABSTRACT

Background: The gut microbiota is increasingly recognized as a crucial factor in human health and disease. Metformin, a commonly prescribed medication for type 2 diabetes, has been studied for its potential impact on the gut microbiota in preclinical models. However, the effects of metformin on the gut microbiota in humans remain uncertain.
Scope of review: We conducted a systematic review of clinical trials and observational studies to assess the existing knowledge on the impact of metformin on the gut microbiota in humans. The review focused on changes in bacterial composition and diversity following metformin treatment.
Major conclusions: Thirteen studies were included in the analysis. The results revealed alterations in the abundance of bacterial genera from various phyla, suggesting that metformin may selectively influence certain groups of bacteria in the gut microbiota. However, the effects on gut microbiota diversity were inconsistent across populations, with conflicting findings on changes in alpha and beta diversity measures.
Overall, the use of metformin was associated with changes in the abundance of specific bacterial genera within the gut microbiota of human populations. However, the effects on gut microbiota diversity were not consistent, highlighting the need for further research to understand the underlying mechanisms and clinical significance of these changes.

1. INTRODUCTION

The gut microbiota is a diverse and dynamic community of microorganisms that inhabit the gastrointestinal tract and have a significant impact on human health and disease [1]. These microorganisms play a vital role in the digestion and absorption of nutrients, the regulation of the immune system, and the production of essential metabolites [2]. The composition and function of the gut microbiota are influenced by a variety of factors, including diet, lifestyle, and medication use [3].

Metformin is a first-line medication widely used for the treatment of type 2 diabetes [4—7]. In recent years, there has been growing interest in the potential effects of metformin on the gut microbiota [8—11]. Preclinical studies have demonstrated that metformin alters the gut microbiota composition and function, and there is evidence to suggest that these changes may be beneficial for metabolic and immune health [12].

Despite the growing interest in this topic, the impact of metformin on the gut microbiota in humans remains unclear [13]. While some studies have reported significant changes in the gut microbiota following metformin treatment, others have found no significant effects [14,15]. Furthermore, there is conflicting evidence regarding the direction and magnitude of the effect. Therefore, a comprehensive and up-to-date systematic review is needed to synthesize the available evidence from human studies and provide a critical assessment of the effects of metformin on the gut microbiota.

This systematic review aims to summarize and evaluate the existing knowledge on the impact of metformin on the gut microbiota in humans. By synthesizing the available evidence, this review will identify knowledge gaps and inform future research directions. The results of this review may also have important implications for the use of metformin as a therapeutic agent, as the gut microbiota plays a critical role in metabolic and immune functions. Overall, the findings of this review will provide valuable insights into the potential effects of metformin on the gut microbiota and their impact on human health.

2. MATERIALS AND METHODS

2.1. Literature search

Our search strategies were designed to incorporate the PICOS framework, which focused on population, intervention, comparisons, outcomes, and study design. Specifically, we aimed to investigate the impact of metformin on the gut microbiota of humans, including both healthy individuals and those with conditions such as obesity,

[1]Department of Biochemistry and Pharmacology, Uzhhorod National University, Uzhhorod, Ukraine [2]Department of Microbiology, Virology, and Immunology, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine [3]Department of Medical Rehabilitation, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine

*Corresponding author. Department of Microbiology, Virology, and Immunology, I. Horbachevsky Ternopil National Medical University, 46001 Ternopil, Ukraine.
E-mail: pavlo.petakh@uzhnu.edu.ua

**Corresponding author. E-mail: alexkamyshnyi@gmail.com (A. Kamyshnyi).

prediabetes, and diabetes. We conducted a systematic search of the PubMed, EMBASE, and SCOPUS databases from January 1, 2000, to January 1, 2023, using relevant keywords and search terms aligned with the PICOS criteria [16]. Additionally, we manually searched reference lists of relevant review papers to identify any additional publications of interest. Our search focused primarily on clinical trials and observational studies, as recommended for systematic reviews.

2.2. Study selection criteria

We adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to ensure that our review was conducted in a transparent and rigorous manner [17]. Our inclusion criteria specified that we only included human studies that reported original data on the gut microbiota following treatment with metformin, and that analyzed gut microbiota from feces or colonic content specimens. Additionally, studies had to be written in English. We excluded studies that did not provide data on individual bacterial taxa or were only available in the form of conference abstracts or proceedings.

2.3. Selection of studies

At the outset, we screened the titles and abstracts of all potentially relevant articles, and subsequently evaluated the full-text articles to determine their eligibility. Two authors carried out this process independently, with any disagreements being resolved through consensus between the two authors, and, if needed, by consulting two additional authors.

2.4. Data extraction

Data extraction was conducted using a standardized form in a Microsoft Excel file, which included details such as study characteristics, participant information, treatment and comparison details, microbiome analysis methods, and outcome measures. One author extracted the data, while another reviewed it. Any discrepancies were resolved through consensus among the authors involved, and if necessary, a third or fourth author was consulted.

2.5. Quality assessment

To evaluate the risk of bias in the selected randomized trials, we utilized the Robvis tool [18]. Three authors extracted the risk of bias data, and in cases of disagreement, the remaining authors reached a consensus.

2.6. Outcomes of assessment

In addition to summarizing the features of the analyzed human studies, our main focus was to investigate the variation in the levels or alterations of specific intestinal bacterial taxa, classified into two widely used taxonomic groups [Phylum (P), Genus (G)], in relation to metformin intake, across the included human studies. The secondary outcomes of interest were disparities in microbial diversity following the administration of metformin.

2.7. Data synthesis

The primary and secondary outcomes were divided into three categories: significant increase, significant decrease, and no significant difference. At least two human studies were used to synthesize the changes of each taxon. Specifically, we compared the effects of metformin on specific taxa among the evaluated human studies. These results were further categorized based on the targeted research populations, such as obese, pre-diabetic, newly diagnosed type 2 diabetes (T2D), and prevalent T2D.

3. RESULTS

3.1. Reviewed studies

A total of 2301 citations were initially identified, and after screening and evaluation, 13 human studies were included in the final analysis (see Figure 1). Most of the studies were published in or after 2017, and the duration of metformin treatment varied across the studies, ranging from a few days to several months. Out of the 13 studies, six (46.15%) were randomized controlled trials, while the remaining seven studies (53.8%) included either newly diagnosed or prevalent type 2 diabetes patients [13,19—24]. The other participants in the studies were obese individuals [25—27], healthy participants [28,29], and gestational diabetes mellitus patients [30] (Table 1).

3.2. Methods of analysis for gut microbiota composition in human studies

In all the human studies included in the analysis, fecal specimens were collected and analyzed for gut microbiota composition. Among the various methods used for analysis, 16S rRNA gene sequencing was found to be the most commonly used method, as presented in Table 1.

3.3. The risk of bias

In the selected randomized trials, two studies had a high risk of bias in performance, detection, and attrition. Four studies had unclear risks in most domains. Among quasi-experimental studies, three had a low risk of bias in all domains, while one had a serious risk of bias in confounding, selection of participants, and classification of interventions. All three cross-sectional studies had a serious risk of bias in several domains, including confounding, selection of participants, and classification of intervention (as illustrated in Figure 2)

3.4. Outcomes of assessment

3.4.1. Changes in bacterial genera induced by metformin treatment

Thirteen studies were included in this systematic review to investigate the effects of metformin on the gut microbiota. Overall, the use of metformin was associated with changes in the abundance of several bacterial genera (Figure 3) (Figure 4).

In the Bacteroidetes phylum, the abundance of *Bacteroides* was found to increase in one study [25] and decrease in another [13,20], while *Parabacteroides* showed an increase in one study [22]. *Alistipes* decreased in one study [13], while *Prevotella* decreased in one study [25] and increased in another [23].

In the Firmicutes phylum, *Bacillus* decreased in one study [27], while *Blautia* [13,25] and *Butyrivibrio* [23,25] increased in two studies each. *Faecalibacterium* decreased in one study [25], while *Ruminococcus* increased in one study [26]. *Streptococcus* increased in one study [25], while *Oscillibacter* [13] and *Lactobacillus* decreased in one study [25]. *Catenibacterium* increased in one study [22], while *Clostridium* decreased in two studies [28,29], and *Intestinibacter* in four studies [24—26,29]. *Roseburia* decreased in one study [26] and increased in another [25].

In the Proteobacteria phylum, *Escherichia* increased in two studies [24,26]. In the Actinobacteria phylum, one study reported a decrease in this phylum [27], while *Adlercreutzia* increased in one study [21] and *Bifidobacterium* increased in one study [23].

Finally, in the Verrucomicrobia phylum, *Akkermansia* decreased in two studies [13,25] and increased in two studies [19,23], while in the Thermodesulfobacteriota phylum, *Bilophila* increased in two studies [19,29].
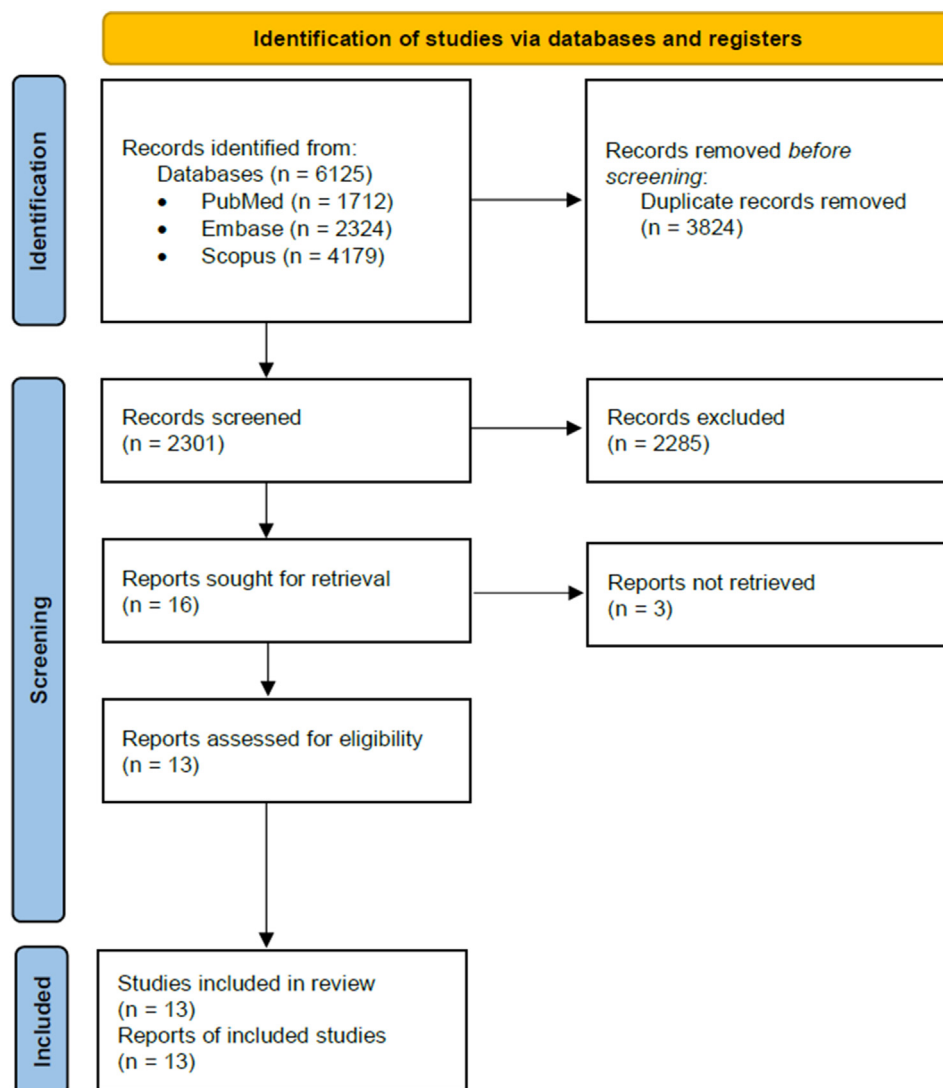
Figure 1: PRISMA 2020 flow diagram.

3.4.2. Effects of metformin on diversity of human gut microbiota

The effects of metformin on the diversity of human gut microbiota have been investigated through various studies, as presented in Table 2. Among the studies conducted on healthy individuals, Elbere et al. [28] reported a significant reduction in gut microbiota diversity 24 h after metformin administration using 16S rRNA V3 region sequencing and Shannon index. Conversely, Bryrup et al. [29]found no significant changes in gut microbial richness, evenness, or diversity in response to metformin treatment.

In obese individuals, Ejtahed et al. [25] observed no significant changes in alpha or beta diversity but reported a negative correlation of Simpson index with BMI, waist, insulin, and HOMA, indicating potential metabolic associations.

Regarding patients with newly diagnosed T2D, Tong et al. [13] reported increased diversity, as indicated by Chao1 richness estimates based on 16S rRNA V3—V4 region sequencing, while Sun et al. [20] observed a slight decrease in alpha diversity using DNA metagenomics.

Barengolts et al. [22] showed a trend towards higher diversity with metformin treatment, and De La Cuesta-Zuluaga et al. [23] found no

significant differences in diversity indices between metformin users and nonusers.

In other populations, Noel T Mueller et al. [26] reported no change in Shannon diversity but observed increased metagenomic pathway richness with metformin treatment. María Molina-Vega et al. [30] found lower phylogenetic diversity in the metformin group compared to the control group, and Belén Pastor-Villaescusa et al. [27] reported no significant differences in diversity indices or beta diversity.

4. DISCUSSION

Metformin is a widely used medication for the treatment of T2D, and its effects on the gut microbiota have been a topic of interest in recent years [9,15]. Our systematic review of 13 studies found that metformin treatment was associated with changes in the abundance of several bacterial genera across different phyla.

In the Bacteroidetes phylum, *Bacteroides* showed inconsistent results, with one study reporting an increase and two studies reporting a decrease in its abundance. *Parabacteroides* showed an increase in one study, while *Alistipes* and *Prevotella* both showed decreases in one

Table 1 — Characteristics of included studies.

| Author, year	Study design	The country of origin of the population	Participants	Number of participants	Metformin dose	Duration	Analysis method	Comparison
Ejtahed et al., 2019 [25]	Randomized trials	Iran	Obese	20/16	1000 mg	2 months	16S rRNA	Post vs. pre
Tong et al., 2018 [13]	Randomized trials	China	Newly T2D	100/100	750 mg	12 weeks	16S rRNA V3—V4 region	Post vs. pre
Wu et al., 2017 [19]	Randomized trials	EU	Newly T2D	22/18	425—1700 mg	4 months	DNA shotgun metagenomics	Post vs. pre
Bryrup et al., 2019 [29]	Quasi-experimental studies	EU	Healthy	25	500—2000 mg	6 weeks	16S rRNA V4 region	Post vs. pre
Sun et al., 2018 [20]	Quasi-experimental studies	China	Newly T2D	22	2000 mg	3 days	DNA metagenomics	Post vs. pre
Elbere et al., 2018 [28]	Quasi-experimental studies	EU	Healthy	18	1700 mg	7 days	16S rRNA V3 region	Post vs. pre
Napolitano et al., 2014 [21]	Quasi-experimental studies	UK	Prevalent T2D	14/14	As usual	NA	16S rRNA V1, V2, V3 regions	On vs. off
Barengolts et al., 2018 [22]	Cross-sectional studies	USA	Prevalent T2D	25/16	As usual	—	16S rRNA V3—V4 region	With vs. without
De La Cuesta-Zuluaga et al., 2017 [23]	Cross-sectional studies	Columbia	Prevalent T2D	14/14	As usual	—	16S rRNA V4 region	With vs. without
Forslund et al., 2015 [24]	Cross-sectional studies	EU	Prevalent T2D	58/17	As usual	—	16S rDNA shotgun metagenomics	With vs. without
Noel T Mueller et al., 2021 [26]	Randomized trials	USA	Overweight or obese adults with a history of a malignant solid tumor diagnosis	42/39/40	2000 mg	1 year	DNA metagenomics	With vs. without
María Molina-Vega et al., 2021 [30]	Randomized trials	EU	Pregnant women with GDM	30/28	850 mg	During pregnancy	16S rRNA	With vs. without
Belén Pastor-Villaescusa et al., 2021 [27]	Randomized trials	EU	Children with obesity	15/18	1000 mg	6 months	Metagenomic analysis	With vs. without
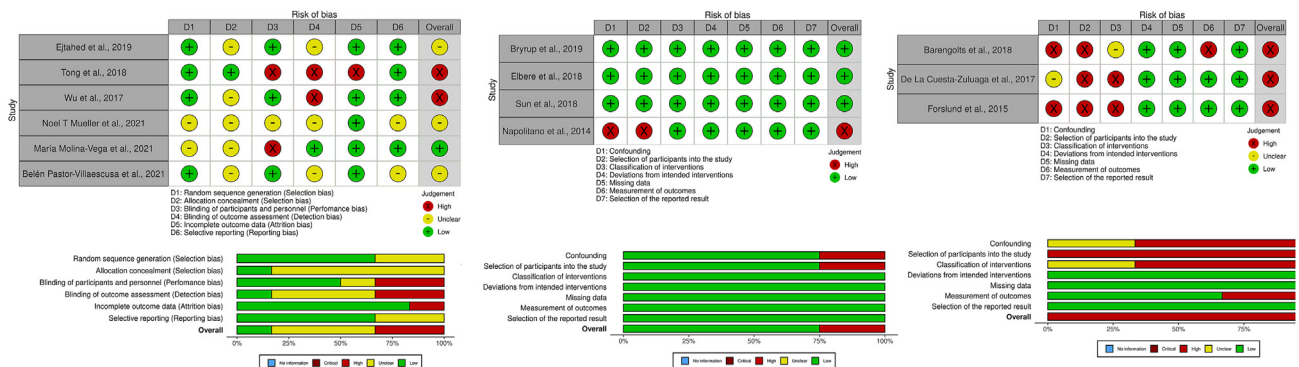
Figure 2: Risk of bias.

study and increases in another. In the Firmicutes phylum, *Blautia* and *Butyrivibrio* increased in two studies each, while *Bacillus* and *Faecalibacterium* decreased in one study each. *Streptococcus* increased in one study, while *Lactobacillus* and *Oscillibacter* decreased in another study. In the Proteobacteria phylum, *Escherichia* increased in two studies. In the Actinobacteria phylum, *Bifidobacterium* increased in one study, while *Adlercreutzia* decreased in one study. Finally, in the Verrucomicrobia phylum, *Akkermansia* showed inconsistent results, with two studies reporting an increase and two studies reporting a decrease in its abundance.

Our findings are consistent with previous studies that have reported changes in gut microbiota composition following metformin treatment. For example, Wu et al. [19] reported an increase in *Akkermansia* in individuals with T2D treated with metformin. However, Tong et al. [13]

found a decrease in *Akkermansia* and no significant changes in *Escherichia* abundance in newly diagnosed T2D patients treated with metformin. These discrepancies may be due to differences in study design, sample size, metformin dosage, or duration of treatment.

Furthermore, it is important to highlight the necessity of future multicenter microbiome studies, standardization of protocols among multicenter studies, as well as in vitro microbiome-drug assays. These initiatives are crucial for advancing our understanding of metformin's impact on the gut microbiota and its implications for T2D.

The role of specific bacterial genera in the pathogenesis of T2D has been a subject of investigation, with some studies suggesting that alterations in gut microbiota composition may contribute to the development of insulin resistance and inflammation [31—33]. For instance, a decrease in butyrate-producing bacteria, such as
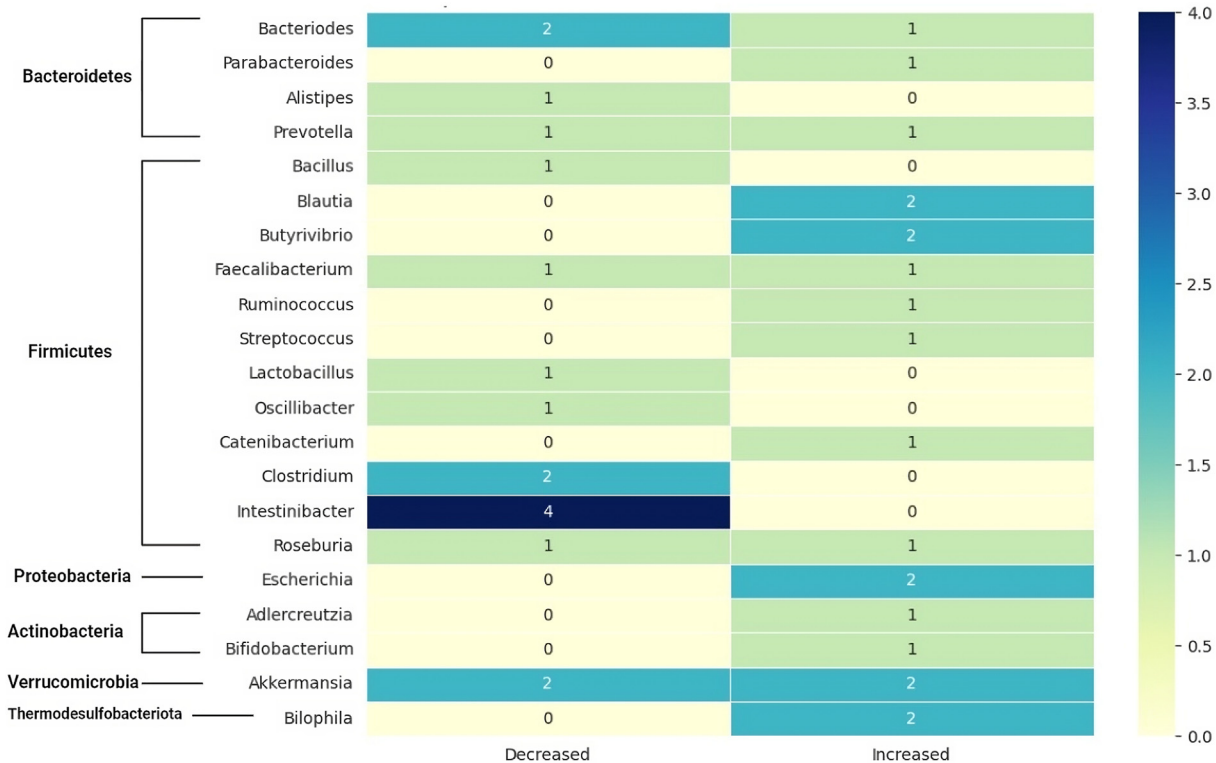
		Decreased	Increased
Bacteroidetes	Bacteriodes	2	1
	Parabacteroides	0	1
	Alistipes	1	0
	Prevotella	1	1
Firmicutes	Bacillus	1	0
	Blautia	0	2
	Butyrivibrio	0	2
	Faecalibacterium	1	1
	Ruminococcus	0	1
	Streptococcus	0	1
	Lactobacillus	1	0
	Oscillibacter	1	0
	Catenibacterium	0	1
	Clostridium	2	0
	Intestinibacter	4	0
	Roseburia	1	1
Proteobacteria	Escherichia	0	2
Actinobacteria	Adlercreutzia	0	1
	Bifidobacterium	0	1
Verrucomicrobia	Akkermansia	2	2
Thermodesulfobacteriota	Bilophila	0	2

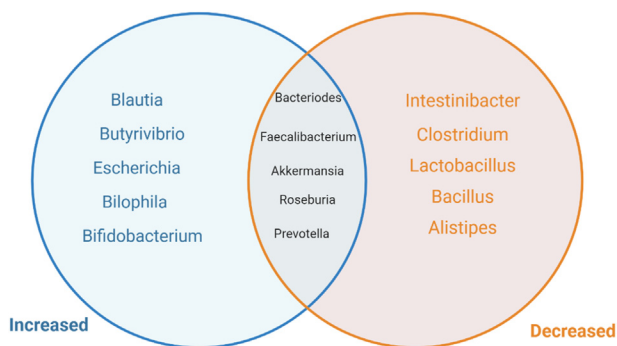**Figure 3:** Effects of metformin on specific taxa in human gut microbiota.

Figure 4: Venn diagram illustrating changes in gut microbiota abundance with metformin treatment.

Faecalibacterium, has been associated with T2D and metabolic syndrome [34]. Similarly, an increase in *Escherichia coli* has been linked to inflammation and insulin resistance in individuals with T2D [35]. On the other hand, *Akkermansia muciniphila* has been shown to have beneficial effects on glucose metabolism and gut barrier function [36—38]. Thus, the changes in gut microbiota composition associated with metformin treatment may have implications for the pathogenesis and management of T2D.

In our previous study, we investigated the gut microbiome composition of patients with T2D and COVID-19 who received metformin treatment, with or without antibiotic treatment. Our findings indicated that metformin-treated patients with T2D and COVID-19 who did not receive antibiotics had a significantly different gut microbiome composition compared to those who did receive antibiotics. Specifically, we observed a higher abundance of the genera *Bacteroides*,

E. coli, and *Lactobacillus*, and a lower abundance of the genera *Clostridium* and *Enterococcus* in the group that did not receive antibiotics [39].

In conclusion, our systematic review provides further evidence of the effects of metformin on gut microbiota composition. The observed changes in bacterial genera may have implications for the pathogenesis and management of T2D, and further research is warranted to elucidate the underlying mechanisms and potential therapeutic targets.

5. CONFOUNDING FACTORS AND INTERPRETATION OF BACTERIAL TAXA CHANGES

The observed variability in the effects of metformin on gut microbiota composition may be attributed to several confounding factors inherent in the included studies. These factors, including study design, disease type, metformin treatment duration, and sequencing methods, played a crucial role in shaping the reported changes in bacterial taxa.

When comparing the results across studies, it becomes evident that different factors contributed to the specific outcomes observed in each study. For instance:

1. **Disease type**: Tong et al. and Sun et al., both focusing on newly diagnosed T2D patients, reported contrasting changes in bacterial taxa. While Tong et al. found decreases in Alistipes and Prevotella, Sun et al. observed a decrease in Bacillus and an increase in Escherichia. These discrepancies highlight how disease-specific characteristics might influence the response of gut microbiota to metformin treatment.

2. **Study duration**: The duration of metformin treatment varied widely across the included studies. Elbere et al. reported reduced gut

Table 2 — Effects of metformin on diversity of human gut microbiota.			
Author, year	Analysis method	Diversity indices or measures	Findings
Ejtahed et al., 2019 [25]	16S rRNA	Richness, Simpson indices	Negative correlation of Simpson index with BMI, waist, insulin, and HOMA. No effect on global gut microbial diversity.
Tong et al., 2018 [13]	16S rRNA V3—V4 region	Simpson's diversity index	Metformin increased diversity (Chao1 richness estimates).
Wu et al., 2017 [19]	DNA shotgun metagenomics	N/A	Not specified.
Bryrup et al., 2019 [29]	16S rRNA V4 region	Richness, evenness, diversity	No effect of metformin on gut microbiota richness, evenness, or diversity.
Sun et al., 2018 [20]	DNA metagenomics	Shannon diversity index	Slight decrease in alpha diversity after metformin treatment.
Elbere et al., 2018 [28]	16S rRNA V3 region	Shannon index, NMDS	Significant reduction in gut microbiota diversity 24 h after metformin.
Napolitano et al., 2014 [21]	16S rRNA V1—V3 regions	Beta-diversity analysis	Gut communities are patient-specific. No specific metformin effect mentioned.
Barengolts et al., 2018 [22]	16S rRNA V3—V4 region	Shannon index	Trend towards higher diversity. No beta-diversity differences.
De La Cuesta-Zuluaga et al., 2017 [23]	16S rRNA V4 region	Beta-diversity estimates	No significant differences except for metformin users vs. nonusers.
Forslund et al., 2015 [24]	16S rDNA shotgun metagenomics	N/A	Not specified.
Noel T Mueller et al., 2021 [26]	DNA metagenomics	Shannon diversity, metagenomic functional pathway richness	No change in Shannon diversity, but increased metagenomic pathway richness with metformin.
María Molina-Vega et al., 2021 [30]	16S rRNA	Phylogenetic diversity	MET group had lower phylogenetic diversity compared to INS group.
Belén Pastor-Villaescusa et al., 2021 [27]	Metagenomic analysis	Alpha indexes and beta diversity in studied children at the phylum level.	No significant differences in diversity, Simpson index, inverse Simpson index, evenness, or beta diversity between placebo and metformin groups. A trend towards higher alpha index and species richness in the metformin group (not statistically significant).

microbiota diversity within 24 h of metformin administration. In contrast, other studies, such as those by Ejtahed et al. and Barengolts et al., did not find significant changes in diversity despite longer-term treatment. These findings suggest that the impact of metformin on gut microbiota might be more pronounced in the short term, while long-term administration may require extended periods to induce noticeable changes.

3. **Sequencing methods**: Variation in sequencing methods might have contributed to the differences in observed changes. For example, Elbere et al. used 16S rRNA V3 region sequencing and found reduced diversity, while Bryrup et al. did not observe significant changes using 16S rRNA V4 region sequencing. This highlights the importance of standardized methodologies to accurately compare results across studies.

4. **Participant characteristics**: Variation in participant characteristics, such as healthy individuals (Bryrup et al., 2019), obese individuals (Ejtahed et al., 2019; Bryrup et al., 2019), and specific disease populations (Noel T Mueller et al., 2021; María Molina-Vega et al., 2021; Belén Pastor-Villaescusa et al., 2021), further underscores the potential influence of baseline microbiota composition on the response to metformin.

6. LIMITATIONS

While this systematic review aims to provide a comprehensive assessment of the impact of metformin on the gut microbiota in humans, several limitations must be acknowledged.

1. **Heterogeneity of included studies:** The studies included in this review exhibited substantial heterogeneity in terms of study design, participant characteristics, metformin dosage, treatment duration, and sequencing methods. This heterogeneity could introduce variability in the observed effects of metformin on the gut microbiota. The diversity of the included populations and methodologies limits the ability to draw definitive conclusions across all studies.

2. **Risk of bias**: The assessment of risk of bias revealed varying levels of methodological quality among the included studies. While efforts were made to minimize bias through the use of robust systematic review methods, the presence of studies with high risk of bias may have influenced the overall findings.

3. **Taxonomic resolution:** Our analysis focused on taxonomic changes at the genus level, which may not fully capture the diversity and complexity of the gut microbiota. Within a single genus, there can be substantial variation at the species or strain level, leading to different responses to metformin. Future studies employing higher taxonomic resolution or metagenomic/metatranscriptomic approaches could provide more detailed insights into the specific changes within microbial communities.

4. **Confounding factors:** The included studies varied in terms of confounding factors such as disease type, metformin treatment duration, and co-administration of other medications. These factors could influence the observed effects of metformin on the gut microbiota. While subgroup analyses were conducted to account for some of these factors, residual confounding remains a potential limitation.

5. **Translation to clinical implications:** While the observed changes in gut microbiota composition are of interest, the clinical implications of these changes remain to be fully elucidated. The complex interplay between gut microbiota, metformin treatment, and human health requires further investigation to understand the functional consequences of these alterations.

6. **Temporal considerations:** Most of the included studies were published in recent years, and the duration of metformin treatment varied across the studies. Longer-term effects of metformin on the gut microbiota may not be fully captured in studies with shorter treatment durations.

AUTHOR CONTRIBUTIONS

P.P. and A.K. conceptualized and designed the study. I.K. conducted the literature search and data extraction. P.P. and A.K. analyzed and interpreted the data. P.P. drafted the manuscript, and all authors provided critical feedback and revisions. All authors have read and approved the final version of the manuscript.

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DECLARATION OF COMPETING INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY

Data will be made available on request.

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