International Journal of Community Medicine and Public Health
*Alsharef AS et al. Int J Community Med Public Health. 2026 Jan;13(1):394-401*
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20254453

**Systematic Review**

# Impact of proton pump inhibitor use on microbiota and diversity

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**Received:** 05 December 2025
**Revised:** 22 December 2025
**Accepted:** 29 December 2025

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## ABSTRACT

Proton pump inhibitors are a class of drugs specifically administered to alleviate stomach acid. In cases of GERD, general GI disturbances and other medication-related GI symptoms, PPIs are widely prescribed globally. Typically, patients taking PPIS have a history of long-term use, which can lead to various health issues. Gut health primarily depends on gut microbiota and dysbiosis of the microbiota can result in numerous metabolic and infectious disorders. Recent research has focused on the impact of PPI usage on the diversity and composition of microbiota. This systematic review aimed to summarize the key findings from studies conducted from January 2015 to June 2025, including only interventional, cohort and case-control studies. After screening 1861 articles sourced from PubMed, Scopus, Clinical trials and other databases, only 12 studies were included in this review. Data revealed that both alpha and beta diversity are significantly increased in individuals after PPI use and there is a significant increase in the colonies of *Streptococcus, Staphylococcus* and pathogenic microbes such as E. coli. It has also been summarized that PPI intake can result in IBS and autoimmune disorders. Therefore, the unregulated use of PPIs should be restricted and research should be conducted to provide better alternatives.

**Keywords:** Gut, Human, Microbiome, Microbiota, Proton pump inhibitors, PPI

## INTRODUCTION

Proton pump inhibitors (PPIs) were developed in the late 1980s and are commonly used by doctors to treat excess gastric acid production. Being in an acidic environment helps PPI prodrugs to become active and permanently stop the H+-K+ ATPase activity in parietal cells. This step inhibits the release of stomach acid and makes the stomach more alkaline, which helps the healing of tissues.[1] On the other hand, taking PPIs seems to raise the possibility of inflammatory bowel disease (IBD), some gut cancers and infections, especially Clostridioides difficile infection (CDI).[2,3] Besides acid suppression, PPIs may change the balance of bacteria in the gut and the body's immune responses.[4] People taking PPIs may change the populations of bacteria in their gut, which can

result in serious gut health issues. Oral bacteria entering the gut may help cause the changes in gut microbiota linked with PPIs, mainly when both stomach acid reduction and reduced oral-gut barrier function exist. It is now recognised that oral-gut microbial translocation has an important role in health as well as health problems.[5] A Swedish pharmaceutical firm named Astra AB, now known as AstraZeneca, developed the first PPI, omeprazole and it was first approved for use in Sweden in 1988. Once omeprazole was launched, medical professionals developed many more PPIs, including lansoprazole, dexlansoprazole, pantoprazole, rabeprazole and esomeprazole. They are currently some of the most common medicines prescribed all over the world.[6]

While most people believe PPIs are safe, high use of these medications in children can increase their chance of contracting infections such as those caused by Clostridium difficile. It has been found in adults that PPIs may increase the chance of small intestinal bacterial overgrowth.[7] Gut imbalance caused by PPIs has been linked to several side effects such as vitamin and mineral deficiencies, bone fractures and osteoporosis, chronic liver disease and more, which may influence users' general health. Compared to others, the risk of infections may be higher for patients with liver cirrhosis from long-term Hepatitis C Virus who take PPIs, either straight away or by influencing the types of bacteria present in the body.[8] Effects of PPIs on the intestinal microbiota are divided into mechanisms that depend on pH and those that do not.

Initial alterations in pH within the digestive system can damage bacteria that have precise pH requirements, for example, H. pylori.[9] Because of these changes, harmful microbes outside the body can make their way into the digestive system more easily. Other than the impact of pH, some PPIs affect the intestinal microbiota in ways unrelated to their acid content. The presence of PPIs causes hormonal changes in the body, which may change the circulation of calcium and phosphorus in the gut. Moreover, PPIs may interfere with digestion and thus can affect the makeup and the distribution of items passing through the digestive tract.[10] The result may be that nutrients are not well absorbed and that the location or form of the bacterial food matter is interrupted, which disrupts the microbiota in the intestines. PPIs can also affect the non-gastric transporters of microbes in the body, affecting their functions and limiting their numbers; the microbes affected are fungi, *Helicobacter pylori* and *Streptococcus pneumoniae*.[11]

Gastric acid works mainly to neutralize the germs so they are not passed into the small intestine. It helps cause both esophagitis and peptic ulcer disease, so being able to control the amount of gastric acid emitted is essential when treating these illnesses. Yet, PPIs are now prescribed for a variety of problems and since the proof for their effectiveness is sometimes weak, a large portion of people in Western countries rely on them. These medications, which aim to control stomach acid, may also change the balance of intestinal bacteria.[12] More uses for PPIs have been revealed in medical research. They are often recommended by doctors in outpatient clinics for issues connected to GERD and in hospitals for people who need to prevent stress ulcers. After obtaining PPIs from pharmacies without a prescription, a lot of people used them for any digestive issue. A lot of patients stay on PPI treatment (for longer than 8 weeks) after beginning it in a clinic or using it on their own without a prescription. Some concerns arise from the constant use of PPIs, such as type 2 diabetes, problems with gut bacteria, diarrhoea related to infection, infections in the digestive tract, more occurrences of pneumonia in the community, vitamin and mineral insufficiencies, bone diseases, fractures and risk of dementia.[13] Many times, PPIs are combined with cancer therapies and may result in shifts in the bacteria found in the gut. It seems likely that gut dysbiosis can reduce the success of ICIs. Still, there is not much information available about how PPIs impact the effects of ICIs, especially when these treatments are given together.[14]

PPIs prevent gastric acid secretion by stopping the H+, K+-ATPase that is located in the lining of stomach cells. PPIs work by being taken up in the small intestine and being distributed by the blood. Consequently, the substances build up in the ducts known as secretory canaliculi that release acid in the parietal cells. Here, the acidic environment changes the PPI prodrugs into metabolites that will block the action of the gastric H+, K+-ATPase. PPIs attach to the gastric H+, K+-ATPase with specificity and limit the blocking of H+, K+-ATPases in other parts of the body. Using PPIs can keep acid levels down for a full 24 hours and ensure the pH stays greater than 4. Since they are more effective than other medicines, many patients prefer PPIs even when H2RAs do not fully help their symptoms.[15]

### *Objective*

The purpose of this systematic study is to thoroughly compare the impacts of Proton Pump inhibitors on the diversity, composition of the Gut microbiota.

## METHODS

The PRISMA framework provides a set of standards for conducting systematic reviews and meta-analyses,16 which were used when conducting this review. The protocol that included the planned objectives, search approach, list of studies to include or exclude, data gathering methods and approaches to analysis was inserted into PROSPERO before the research team started the review (Registration number: CRD420251067633).

### *Eligibility criteria*

Research was deemed suitable for inclusion in this systematic review if it fulfilled the following

requirements: Various study designs utilized include Randomized Controlled Trials (RCTs), observational studies (such as cohort and case-control studies), mixed-methods research and meta-analyses.

*Participants*

The Human population around the globe, from infancy to adulthood, was considered

*Intervention*

Patients who were taking proton pump inhibitors for at least 6 months.

*Comparator*

Intestinal microbiota was compared.

*Language*

English-language publications only.

*Timeframe*

Studies published between January 1, 2015 and June 8, 2025.

***Exclusion criteria***

In the current study, editorials, opinion pieces or review articles were excluded. Studies conducted on animal models only and studies which did not report relevant outcomes or were incomplete were also excluded.

***Search strategy***

The researcher developed search strategies from three electronic databases PubMed, Scopus and Google Scholar. The researcher searched from January 2015 to June 2025, including articles published in English only. Two reviewers conducted an initial screening of the publications. Each reviewer's categorisation of the studies followed an independent approach regarding the eligibility assessment. The list of studies was finalized after everyone agreed on it. The articles' references were checked as well. Moreover, the researcher made use of the clinical trials.gov website (last searched on 8 June 2025).

The search string used for PubMed was ((PPI) OR (PPI)) AND (Microbio Filters: in the last 10 years, free full text, case reports, clinical trial, comparative study, controlled clinical trial, observational study, randomized controlled trial, English, humans, in the last 10 years, free full text, case reports, clinical trial, comparative study, controlled clinical trial, observational study, randomized controlled trial, English, humans–PubMed.

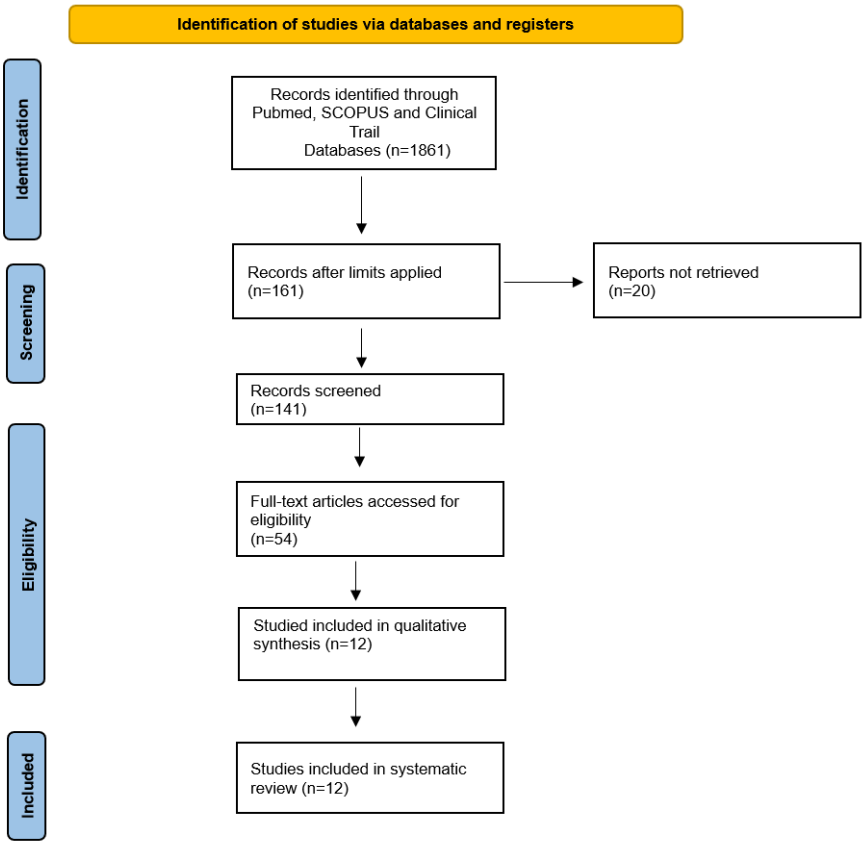


**Figure 1: PRISMA flow diagram.**

### *Study selection*

The results from every database were transferred to a CSV file and the duplicates were deleted. The titles and abstracts that remained were looked at separately by two reviewers according to the set criteria. After that, the full texts of all potentially eligible articles were pulled and both researchers looked at them independently. Full-text articles not included in the review were noted down and shown in the PRISMA flow diagram (Figure 1).

### *Data extraction*

Each reviewer used a pre-prepared, common data extraction form to pick out details from the main studies. Information about the following elements was taken from every study in the analysis.

Check the study authors, when the study was published, the study site, study design, sample size, main health problems studied, how the intervention was applied and Alternative therapies used, together with the main findings of the study.

### *Evaluation of bias risk*

Two reviewers employed the Cochrane Risk of Bias Tool for Randomised Controlled Trials (RoB 2.0) to evaluate the quality of each study and its associated risk of bias. Each domain was classified as having a "low risk," "some concerns," or "high risk" of bias (Figure 2).

## RESULTS

There were 1861 study titles found related to the current study using databases. Only 161 titles were shortlisted after reviewing the titles of studies. After eliminating the papers that did not meet the initial search criteria, researchers selected 141 abstracts for screening; only 54 were eligible after the abstract screening. After the final screening, only 12 studies were shortlisted. Twelve studies that met the inclusion criteria were included in this analysis. The patient populations in each study vary greatly. Populations in different studies included healthy individuals and GI disease patients ranging from childhood to adulthood. Mainly, the studies focused on the microbiota diversity and quality of GI health. Data is summarized in Table 1.

**Table 1: Characteristics of studies added in this systematic review.**

| Reference | Study type | Condition | Number of participants (N) | Intervention | Outcomes | Significant |
|---|---|---|---|---|---|---|
| **(21)** | Cohort study | GI diseases | 1815 | Proton pump inhibitors | PPIs alter the gut microbiota by directly affecting stomach acid. | Yes |
| **(24)** | Cohort study | Healthy twins | 1827 | Proton pump inhibitors | Lower gut microbiota diversity | Yes |
| **(25)** | Cross over trail | Healthy | 12 | Proton pump inhibitors | Increased Enterococcaceae, Micrococcaceae, Staphylococcaceae and Streptococcaceae, decreased Clostridiales | Yes |
| **(20)** | Case control study | GI diseases and healthy individuals | 72 | Proton pump inhibitors | Streptococci were abundant and Fecalibacterium were decreased in PPI users. | Yes |
| **(17)** | Interventional study | GERD | 12 | Proton pump inhibitors | decrease of Lactobacillus and Stenotrophomonas and an increase of Haemophilus | Yes |
| **(19)** | Interventional study | GERD | 20 | Proton pump inhibitors | *Lactobacillus spp.,* counts of the *L. gasseri* subgroup, *L. fermentum,* the *L. reuteri* subgroup and the *L. ruminis* subgroup were significantly increased. | Yes |
| **(18)** | Comparative interventional study | Healthy | 34 | Proton pump inhibitors | There were significant increases in the relative abundance of *Streptococcus* vestibularis and Veillonella dispar | Yes |
| **(26)** | Interventional study | acute gastroenteritis | 20 | Proton pump inhibitors | Increase in the proportion of the phylum Firmicutes | Yes |
| **(22)** | Prospective cohort | IBD | 1419 | Proton pump inhibitors | Regular use of PPIs consistently showed a significantly positive association with IBD, Crohn's disease and ulcerative colitis risk. | Yes |

Continued.

| Reference | Study type | Condition | Number of participants (N) | Intervention | Outcomes | Significant |
|---|---|---|---|---|---|---|
| **(23)** | Cohort study | Patients with different health problems | 297,099 | Proton pump inhibitors | Prescription of proton pump inhibitors is associated with a higher risk of ADs. | Yes |
| **(27)** | Prospective interventional study | GI health problems | 34 | Proton pump inhibitors | There was an enrichment of *Streptococcus* in the stool after PPI use and a reduction in the relative abundance of Bifidobacterium, Peptostreptococcus and Turicibacter. | Yes |
| **(28)** | Longitudinal study | Healthy volunteer | 23 | Proton pump inhibitors | *Fusobacterium nucleatum* and *Streptococcus anginosus* were increased | Yes |

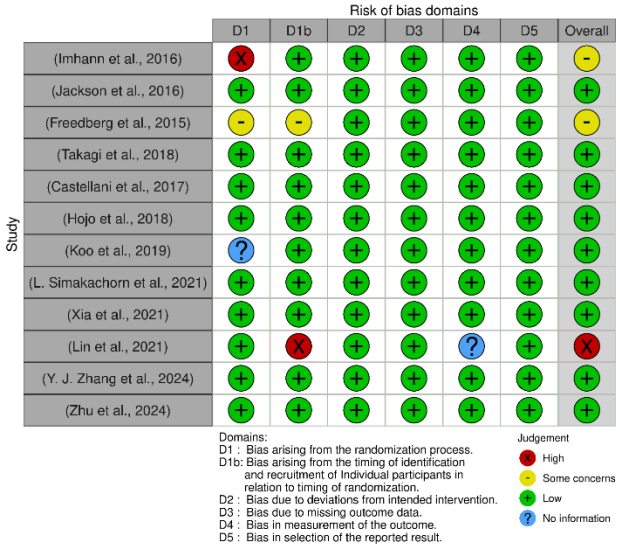


**Figure 2: Risk of bias assessment (COCHRANE).**

### *Microbiome analysis*

For the microbiome diversity and taxa study, mainly NGS-based 16S rDNA sequencing was done of the faecal samples.[17,18] Whereas one of the studies used 16S and 23S rRNA-targeted quantitative reverse transcription-PCR to evaluate the bacterial count (RT-qPCR).[19]

### *Fecal microbiome*

The studies included in this review concluded a significant increase in the counts of the *Lactobacillus spp. Subgroups L. gasseri, L. fermentum, L. reuteri and L. ruminis,* as well as *Streptococcus* species.[18,19] There was an increase in the proportion of the phylum Firmicutes 26 and species like *Fusobacterium nucleatum* and *Streptococcus anginosus*.[25,28] Following PPI use, the relative quantity of *Bifidobacterium*, *Peptostreptococcus*, *Faecalibacterium* and *Turicibacter* decreased.[20,27] A notable rise in harmful species such as *Escherichia coli* and the genera *Enterococcus, Streptococcus* and *Staphylococcus* was also found in PPI users.[21]

### *Microbiota diversity*

Alpha diversity measures the richness and evenness of microbial species within a particular sample. The differences in microbial composition between two or more samples are compared using beta diversity. As per the current review, the α and β diversity in microbiota were significantly increased after the PPI administration.[17,20,21]

### *Effect of microbiome on quality of life*

Frequent PPI use has been linked to a higher risk of developing IBD and its variants.[22] PPIs+ were linked to an increased chance of developing ADs.[23]

## DISCUSSION

The findings of this systematic analysis indicate that PPI medication is consistently linked to measurable changes in gut microbial composition and ecological variety.

The literature review revealed that PPI exposure was associated with a decrease in beneficial commensal organisms, notably *Faecalibacterium prausnitzii* and Bifidobacterium species, while concurrently elevating the relative abundance of taxa such as *Streptococcus, Veillonella* and *Enterococcus*. These alterations indicate that the suppression of gastric acid undermines the stomach's inherent microbial filtration capabilities, thereby fostering eventual microbial dysbiosis. A significant finding in the assessed research was a reduction in butyrate-producing bacteria, specifically *Faecalibacterium prausnitzii*, a primary regulator of gut immunological homeostasis.

Previous research has demonstrated that PPI-induced hypochlorhydria facilitates the survival of oral bacteria during stomach transit and their subsequent colonisation of the lower gastrointestinal tract.[21,24] The rise in

*Streptococcus* and *Veillonella* species observed in PPI users corroborates this notion, as these bacteria are predominantly of oral origin and are typically not present in significant quantities within a healthy gut microbiome. The present findings corroborate this idea, reinforcing the concept that acid suppression promotes microbial translocation and ecological displacement within the gastrointestinal system. Reduced microbial diversity emerged as another persistent effect associated with PPI use.

Numerous studies have shown that people who take PPIs have less diverse microbiota, which means that opportunistic and possibly harmful organisms like *Clostridium* species and Escherichia coli are more likely to grow.[25,29] These alterations have been linked to a compromised gut barrier and increased intestinal permeability. These findings are consistent with the analysed data and provide a valid explanation for the increased incidence of enteric infections and inflammatory conditions noted in long-term PPI users.

The inflammatory consequences of PPI-associated dysbiosis are increasingly acknowledged as a clinical issue. Epidemiological data demonstrate that prolonged exposure to PPIs is associated with a heightened risk of inflammatory bowel disease, with stronger correlations shown at elevated dosages and extended durations of use.[30,31] Much research in this review showed that persons with a major microbial imbalance had greater levels of faecal calprotectin, which could mean that their intestines are inflamed, either without symptoms or with them. This supports the idea that immunological dysregulation caused by microbiota may be involved in gastrointestinal disorders linked to inflammation in people who are on PPIs.

In addition to gastrointestinal outcomes, recent evidence indicates that alterations to the microbiota induced by PPIs may affect the entire body. Reduced levels of bacteria responsible for the production of short-chain fatty acids have been associated with dysfunctions in the epithelial barrier and systemic inflammatory signalling.[32] Consistent with these findings, the analysed studies reported reduced faecal butyrate levels, increased circulating pro-inflammatory cytokines and altered immunological profiles in PPI users. These findings suggest that the impact of PPIs on gut microbiota extends beyond localized intestinal effects, potentially influencing broader metabolic and immunological pathways.

Oncology research has demonstrated the significance of these microbial changes for health. Multiple studies have demonstrated that simultaneous PPI use is associated with reduced efficacy of immune checkpoint inhibitors, particularly in patients with non-small cell lung cancer.[33,34] This effect has been attributed to the reduction of immunomodulatory bacteria, such as *Akkermansia muciniphila* and *Bacteroides fragilis*, known for their role in enhancing anticancer immune responses. The findings of this investigation validate prior observations, emphasizing the role of gut microbiota as a mediator between PPI exposure and therapeutic outcomes. The metabolic effects of dysbiosis associated with PPIs were also evident. Prior studies have identified distinct microbial signatures in individuals with metabolically unhealthy obesity using PPIs, marked by increased insulin resistance and dyslipidemia.[35] Consistent with these findings, the reviewed literature demonstrated increased proportions of Firmicutes and a higher abundance of *Lactobacillus* and *Blautia* species in obese individuals on PPI treatment. These species have been linked to metabolic inflammation and problems with energy control in the past, which suggests that PPIs may play a role in metabolic dysfunction.

It is crucial to take PPIs carefully because they can induce a wide range of symptoms. Previous experimental and clinical studies have shown that prolonged acid suppression can disrupt the host–microbe equilibrium, leading to gastrointestinal, immunological and metabolic complications.[36] This review's findings back up these conclusions and show that changes in the microbiome occur all the time in different groups of people and therapeutic contexts.

PPIs are still helpful for treating acid-related disorders, but they can be harmful if you use them for no reason or for too long. Changes in the microbiota that are connected to PPIs can arise quickly, just like dysbiosis that is produced by antibiotics. Strategies such as limiting treatment duration, employing the minimal therapeutic dose and exploring microbiome-enhancing medicines, including prebiotics or probiotics, may help mitigate side effects. Further longitudinal and interventional studies are necessary to clarify causality, reversibility and individual susceptibility to PPI-induced alterations in gut flora.

## CONCLUSION

All in all, this research shows that using PPIs affects the health of the gut microbes, which can result in dysbiosis that can cause inflammatory, infectious, metabolic and even cancer-related diseases. It is strongly suggested that more steps need to be taken to reduce unwanted PPIs, mainly by keeping the microbiome in mind during decisions about drug use.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

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**Cite this article as:** Alsharef AS, Alsaedi EA, Almohmmadi GT, Alahmadi KM, Alhemshy LZ, Albugami MK, et al. Impact of proton pump inhibitor use on microbiota and diversity. Int J Community Med Public Health 2026;13:394-401.