Microbiota-derived PPAR-γ signaling and risk of bacterial enteric infection: insight from thiazolidinedione users in a US population-based study

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Abstract

The ongoing antimicrobial resistant crisis heralds the need for new therapeutics against enteric infection. In mouse models, colon epithelial peroxisome proliferator-activated receptor-γ (PPAR-γ) signaling limits oxygen and nitrate luminal bioavailability, thereby preventing bacterial pathogen colonization. However, whether this mechanism operates similarly in humans remains uncertain. To investigate, we used the cloud-based TriNetX Analytics Platform which aggregates health records from 117 million patients across 66 US healthcare organizations, to assess the risk of bacterial enteric infection among diabetic patients prescribed thiazolidinediones, a class of PPAR-γ agonists. Among 85,117 thiazolidinedione users, we observed a 22-49% lower risk of bacterial enteric infections compared to users of other anti-diabetes medications. This reduction in risk was consistent across high-risk individuals, regardless of sex or age. Similar results were replicated in high-risk patients when thiazolidinedione users were directly compared to those on DPP-4 inhibitors. These findings support the potential protective role of PPAR-γ signaling against bacterial enteric infection and call for further clinical investigation.

Introduction

The body's primary defense against bacterial enteric infection relies heavily on the abundant and diverse intestinal microbiota [1,2]. These gut commensal microbes confer protection by direct bacteria-to-bacteria interactions and activating host immune defenses—a phenomenon known as colonization resistance [1,2]. Amid the ongoing antimicrobial resistant crisis, understanding the mechanisms of colonization resistance has gained increasing importance. Identifying microbial metabolites, proteins, or host receptors involved in preventing infection can lead to new anti-infective strategies and potentially reduce the 1.6-2.1 million annual diarrheal deaths worldwide [3].

Recent mechanistic studies have highlighted a central role of the host nuclear hormone receptor peroxisome proliferator-activated receptor (PPAR-γ) in colonization resistance [4.5]. Commensal colonic microbes, predominantly obligate anaerobes, thrive in an oxygen- and nitrate- deprived environment, limiting the expansion of facultative anaerobic organisms such as *Salmonella* and Enterobacteriaceae. These microbes maintain the low-oxygen environment by producing metabolites such as butyrate, which activates PPAR-γ in colonocytes [4,5]. This activation enhances oxygen consumption by the host, sustaining the protective anaerobic state. In mouse models, depletion of PPAR-γ signaling—triggered by antibiotics or a high-fat diet—has been associated with increased bacterial pathogenesis, aligning with well-known patient risk factors [4-9]. Pharmacological PPAR-γ agonists have also shown promising results in restoring this protective effect [10]. However, it remains unclear whether PPAR-γ offers similar protection against enteric infection in humans.

Thiazolidinediones, a class of PPAR-γ agonists, are commonly used in the management of type 2 diabetes mellitus (T2DM) [11,12]. Assessing the risk of bacterial enteric infection in thiazolidinediones users compared to those receiving other anti-diabetes medications could provide insights into the viability of targeting PPAR-γ for anti-infective purposes. In this study, we conducted a population-based analysis in the US to assess the risk of bacterial enteric infection in T2DM patients using thiazolidinediones anti-diabetes medications.

Methods

Data

We used the cloud-based TriNetX Analytics Platform, US Collaborative Network, to obtain web-based real-time secure access to fully deidentified electronic health records of 117 million patients from 66 health care organizations, representing 27% of the US population from all 50

states. Both inpatient and outpatient settings mostly from large academic medical institutions in the US, as well as persons from diverse geographic, age, race and ethnicity, income, and insurance groups are represented. The geographic distribution of patients from the TriNetX platform is 25% in the Northeast, 17% in the Midwest, 41% in the South, and 12% in the West, with 5% unknown.

Ethics Statement

The TriNetX platform aggregates and HIPAA de-identifies data contributed from the electronic health records of participating healthcare organizations. The TriNetX platform also only reports population-level results (no access to individual patient data) and uses statistical blurring, reporting all population-level counts between 1 and 10 as 10. Because this study used only deidentified patient records, it was exempted from review by the MetroHealth System Institutional Review Board.

Study populations

Risk for bacterial enteric infection can often be based on factors that are not well captured by electronic medical records, including consumption of undercooked meat or international travel, and may be a rare occurrence in those without risk factors present. Therefore, the outcome of bacterial enteric infection after prescription of thiazolidinedione or other anti-diabetes medication was determined among a “low-risk” and “high-risk” cohort. Low-risk for bacterial enteric infection was defined as no prior history of bacterial enteric infection. High-risk was defined as persons with a previous diagnosis of bacterial enteric infection, suggesting risk factors for disease such as altered gut microbiota, behavioral and environmental factors, or predisposing chronic diseases are present [13-16].

The study was designed for a 5-year recruitment date, from 3 January 2017 to an end date of 3 January 2022. The start date was chosen to help include the approval of semaglutide for T2DM management (FDA approved Dec 2017) and the end date was chosen to minimize overlap of GLP1 agonist approval for weight loss in those without diabetes (FDA approved June 2021). The index events for each were time of anti-diabetes medication prescription

The study population at low-risk for bacterial enteric infection

Two thiazolidinediones are available in the United States, pioglitazone and rosiglitazone. Accordingly, all persons ≥18 years of age between January 2017 and January 2022 who within 1 month after a medical encounter for the diagnosis of type 2 diabetes mellitus were prescribed thiazolidinediones (pioglitazone or rosiglitazone) or non-thiazolidinediones anti-diabetes medications (Glucagon-like peptide-1 (GLP-1) analogues, insulin, metformin, sulfonylureas, alpha glucosidase inhibitors, DPP-4 inhibitors, SGLT2 inhibitors), and had no prior history of bacterial enteric infection before index event (prescription of anti-diabetes medication) were included. The study population was then divided into two cohorts: (1) thiazolidinedione-users at low risk and (2) non-thiazolidinedione users at low risk. Troglitazone users were excluded from the study as the medication is not available in the US due to its hepatoxicity. In the non-thiazolidinedione cohort, persons with thiazolidinedione prescription were excluded from the non-thiazolidinedione cohort.

The study population at high-risk for bacterial enteric infection

Two thiazolidinediones are available in the United States, pioglitazone and rosiglitazone. Accordingly, all persons ≥18 years of age between January 2017 and January 2022 who within 1 month after a medical encounter for the diagnosis of type 2 diabetes mellitus were prescribed thiazolidinediones (pioglitazone or rosiglitazone) or non-thiazolidinediones anti-diabetes medications, and had prior history of bacterial enteric infection before index event (prescription

of anti-diabetes medication) were included. The study population was then divided into two cohorts: (1) thiazolidinedione-users at high risk and (2) non-thiazolidinedione users at high risk. Troglitazone users were excluded from the study as the medication is not available in the US due to its hepatoxicity. In the non-thiazolidinedione cohort, persons with thiazolidinedione prescription were excluded from the non-thiazolidinedione cohort.

Statistical analysis

For each study cohort, the thiazolidinedione users and non-thiazolidinedione users were propensity score matched (1:1 using nearest neighbor greedy matching with a caliper of 0.25 times the standard deviation) on covariates that are potential risk factors for bacterial enteric infection including diabetes severity, such as age, sex, race, ethnicity, overweight and obesity, lifestyle problems, ischemic heart disease, liver disease, kidney disease, lung disease**,** hypertension, hyperlipidemia, cerebrovascular disease, atherosclerosis, other peripheral vascular disease, tobacco use, alcohol use, human immunodeficiency virus (HIV), organ transplant, use of immunosuppressants, use of chemotherapeutics, and Hemoglobin A1C levels.

The outcome bacterial enteric infection that occurred in the 6-month time window after the index event (prescription of medication) were compared between the matched medication groups. The status of bacterial enteric infection was defined by ICD-10 A00-A05 (A00: Cholera, A01: Typhoid and paratyphoid fevers, A02: Other salmonella infections, A03: Shigellosis, A04: Other bacterial intestinal infections, A05: Other bacterial foodborne intoxications, not elsewhere classified). As counts of bacterial enteric infection were low in the cohort, risk for an individual bacterial species (i.e. *Salmonella sp*, *Enterohemorrhagic E coli*) precluded statistical analysis (most counts were less than 10, therefore were rounded to 10 by TriNetX) and was not performed. Only a composite outcome was investigated.

Several subgroup analyses were performed to assess the robustness of our results and possible bias. First, outcomes were examined when stratified by sex and age. Second, given diabetes medications are often prescribed in combination, it was necessary to evaluate whether other medications commonly administered alongside thiazolidinediones could confound observed effects. However, thiazolidinediones are rarely used for the management of T2DM because of weight gain, pedal edema, and heart failure exacerbation, leading to their classification as a third line option. Accordingly, thiazolidinediones were compared with another third-line anti-diabetes medication, dipeptidyl peptidase-4 inhibit0rs (DPP-4) inhibitors. Age and sex stratified analysis were not performed between thiazolidinediones and DPP-4 inhibitors as subgroups often had less than 10 persons with the desired outcome. TriNetX to maintain deidentification does not provide actual counts when below 10, which precludes accurate statistical analysis. All statistical analysis were performed with the TriNetX Advanced Analytics Platform. The TriNetX platform calculates RRs and associated confidence interval (CI) using R's Survival package, version 3.2-3, with proportional hazard assumption tested using the generalized Schoenfeld approach. Statistical significance was set a 2-sided P value of <0.05.

Results:

Association of thiazolidinedione with risk of bacterial enteric infection in patients at low risk

The study population consisted of 85,917 and 2,154,426 persons with T2DM who between 1/2017-1/2022 were prescribed thiazolidinedione or non-thiazolidinedione anti-diabetes medications, respectively, and had no prior history of bacterial enteric infection. Persons on thiazolidinediones compared to non-thiazolidinedione were more likely to be older, male, white, and had higher prevalence of overweight and obesity, chronic kidney disease, and Hgb A1C levels greater than 9 (**Table 1**).

After 1:1 propensity matching, demographic and clinical characteristics were balanced (85,916 in each cohort, 63.2 years of age, 42.9% Female, 12.8% Black, 67.7% White, 14.3% Hispanic) (**Table 1**). Matched cohorts were followed for 6 months after the index event. Compared to anti-diabetes non-thiazolidinedione medications, thiazolidinedione was associated with a lower risk of incident bacterial enteric infection among those at low-risk (0.03% vs 0.06%; RR 0.51, 95% CI 0.32, 0.82). An association of lower risk for bacterial enteric infection was observed across age and sex, however only among those >65 years were findings statistically significant (0.02% vs 0.05%; RR 0.44, 95% CI 0.23,0.88) (**Figure 1**).

Association of thiazolidinedione with risk of bacterial enteric infection in patients at high risk

The study population consisted of 1,975 and 57,963 persons with T2DM who between 1/2017-1/2022 were prescribed thiazolidinedione or non-thiazolidinedione anti-diabetes medications, respectively, and had prior history of bacterial enteric infection. Persons on thiazolidinediones were more likely to be Hispanic and White, and had higher prevalence of overweight and obesity, hypertension, hyperlipidemia, and Hb1C levels greater than 9.

After 1:1 propensity matching, demographic and clinical characteristics were balanced (1,974 in each cohort, 63.0 years of age, 44.1% Female, 16.9% Black, 65.4% White, 20.8% Hispanic) (**Table 1**). Matched cohorts were followed for 6 months after the index event. Compared to anti-diabetes non-thiazolidinedione medications, thiazolidinedione was associated with a lower risk of incident bacterial enteric infection among those at high risk (17.6% vs 22.5%; RR 0.78, 95% CI 0.69,0.88). An association of lower risk for bacterial enteric infection was observed across all sex and age subgroups (**Figure 2).**

Association of thiazolidinedione compared to DPP-4 inhibitors with risk of bacterial enteric infection in patients at low and high risk (sensitivity analysis)

In the matched cohorts, thiazolidinedione use compared to those on DPP-4 inhibitors in patients with T2DM was associated with a lower risk of bacterial enteric infection in those at high-risk (RR 0.82, 95% CI 0.72,0.93) and not those at low-risk (RR 0.96, 95% CI 0.56, 1.65) (**Figure 3**).

Discussion

Our analysis identified a significant association between thiazolidinedione use and a reduced risk of bacterial enteric infections in T2DM patients, consistent with findings from animal models. This protective effect was observed in both low- and high-risk populations, with notable reductions in infection across various age and sex subgroups, particularly in high-risk individuals with a history of prior infections. The reduced risk seen when comparing thiazolidinediones to third-line diabetes medications (DPP-4 inhibitors) further supports the hypothesis that modulating PPAR-γ signaling mitigate bacterial enteric infections, especially in high-risk situations—for example, protracted antibiotic use during hospitalization, international travel to high incidence locales, or outbreaks in nursing homes and chronic care facilities.

Thiazolidinediones are typically used as a third-line medications when other anti-diabetes medications have proven ineffective or when insurance limitations restrict alternative options [12]. Consequently, thiazolidinedione users often represent a population with more severe or poorly controlled diabetes, characterized by frequent healthcare encounters and lower socioeconomic status [17-18]. These factors are associated with an increased risk of bacterial enteric infection, suggesting the protective effect of thiazolidinediones may be greater than what this analysis indicates [19-21].

Repurposing thiazolidinediones is not a novel concept. Initially, PPAR-γ was believed to primarily function on adipose tissue, regulating insulin resistance, which led to the development

of thiazolidinediones for diabetes management [22]. However, investigators soon appreciated the abundance of PPAR-γ in colonic epithelial cells and its involvement in colon cancer [23,24]. Subsequently, PPAR-γ signaling was shown to reduce colonic inflammation, prompting the exploration of thiazolidinediones for inflammatory bowel disease [25]. Promising results were observed in mouse models and clinical trials [25-27]. Despite these benefits, concerns over toxicities, such as weight gain, fluid retention, and heart failure, have overshadowed the benefits of thiazolidinediones. Therefore, while this study suggests thiazolidinediones may protect against bacterial enteric infection, their repurposing for this indication is likely limited by their associated risks.

Fortunately, there are alternative ways to increase PPAR-γ signaling. For instance, mesalamine (5-ASA), a PPAR-γ agonist widely used for treating mild to moderate ulcerative colitis, may offer a safer alternative. Studies suggest that 5-ASA prevents the expansion of colitogenic bacteria such as *Escherichia coli* [10], indicating its potential role in preventing bacterial enteric infection in high-risk individuals.

Dietary modifications may also enhance PPAR-y signaling. A high-fiber diet can increase butyrate levels, which, in turn, activate PPAR-y. However, this depends on the presence of a gut microbiota capable of butyrate production. Unsaturated fatty acids, found in dairy and meat products, are natural PPAR-y ligands and may also promote colonic health, although achieving sufficient intraluminal concentrations *in vivo* remains controversial. Small animal studies have demonstrated possible benefits from such dietary interventions [28,29].

One hypothesis behind the protective effects of PPAR-γ activation is its ability to maintain an anaerobic environment in the gut, which helps prevent bacterial enteric infections. However, this mechanism does not directly explain why thiazolidinediones may also protect against

Clostridioides difficile, an obligate anaerobe. It is possible that PPAR-γ signaling supports the growth of beneficial anaerobes such as *Clostridium scindens* or *Blautia producta*, which inhibit *C. difficile* through the production of secondary bile acids and lantibiotics, respectively [30,31]. Further, PPAR-γ activity in macrophages, which has been shown to ameliorate colonic inflammation, may also contribute to this protective effect. Given that thiazolidinediones are primarily absorbed in the small intestine and may not directly reach the colon, this macrophage-mediated mechanism merits further investigation [10].

Limitations

There are limitations that bear consideration when interpreting the results of this study. Residual confounding, particularly diabetes severity, may impact the findings. Although we controlled for factors like ischemic heart disease, peripheral vascular disease, chronic kidney disease, and HbA1C levels, fully characterizing the severity of diabetes remains a challenge. Further, medication adherence cannot be confirmed based on electronic health records. However, our inclusion of individuals with thiazolidinedione or other anti-diabetes prescriptions following a healthcare encounter for T2DM suggests active management of the disease. Limited sample sizes precluded an analysis of dose-dependent effects and we could not assess the duration of thiazolidinedione use required for a protective effect. Further, since T2DM is often managed with a combination of medications, it is possible that other medications commonly used alongside thiazolidinediones contributed to the observed protective effect. To address this, we conducted a direct comparison with DPP-4 inhibitors, which showed a decreased risk of bacterial enteric infection in high-risk individuals. Lastly, the severity of enteric infections was not captured in this study, so it remains unknown whether thiazolidinediones can reduce disease severity.

Conclusion

Bacterial enteric infections remain a significant public health concern, with acute gastroenteritis causing an estimated 179 million outpatient visits and nearly 500,000 hospitalizations annually [32-34]. Current antimicrobial treatments are often inadequate, as antibiotics can prolong symptoms, increase bacterial shedding, and lead to recurrence [14-16]. Given the limitations of existing treatments, preserving beneficial intestinal microbes with alternative therapies that minimize collateral damage to the microbiome is a key consideration. In this context PPAR-γ agonists may offer a promising alternative.

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AUTHOR CONTRIBUTIONS

MB conceptualized the project, designed the analysis, processed the data, and analyzed the results. DCK assisted with data acquisition. MB wrote the manuscript, DCK, VN, and AZ provided critical intellectual input. AZ supervised the study and is ultimately responsible for its content.

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CONFLICT OF INTEREST

AZ is a co-founder and acting CMO of Endure Biotherapeutics. He holds equity in the company.

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513 Table 1: Characteristics of the thiazolidinedione cohort and the non-thiazolidinedione anti-
514 diabetes medication cohort for the study population at low risk for bacterial enteric infection

	Before matching			After matching		
Characteristics	TZD users	Non-TZD users	Std diff	TZD users	Non-TZD users	Std diff.
Total No.	85,917	2,154,436		85,916	85.916	
Age, mean, y	63.2 ± 12.3	61.4 ± 14.5	0.13	63.2 ± 12.3	63.4 ±12.8	0.014
Sex, %						
Male	54.9	49.0	0.117	54.9	55,5	0.013
Female	42.9	46.9	0.082	42.9	42,3	0.012
Ethnicity, %						
Hispanic/Latino	14.3	9.3	0.156	14.3	13.6	0.021
Not Hispanic/Latino	64.2	62.3	0.040	64.2	65.1	0.019
Unknown	21.5	28.4	0.161	21.5	21.3	0.005
Race,%						
African American/Black	12.8	18.0	0.144	12.8	12.8	0.001
Asian	5.1	4.4	0.034	5.1	5.1	0.001
White	67.7	59.9	0.164	67.7	68.1	0.008
American Indian or Alaska Native	0.3	0.3	0.002	0.3	0.3	0.002
Native Hawaiian or other Pacific Islander	0.4	0.6	0.033	0.4	0.3	0.007
Other Race	3.4	3.4	0.002	3.4	3.3	0.009
Unknown	10.3	13.5	0.100	10.3	10.1	0.005
Problems related to lifestyle	4.5	4.0	0.023	4.5	4.1	0.024
Tobacco Use	10.0	10.7	0.022	10.0	9.1	0.030
Alcohol Use Disorder	2.1	2.8	0.049	2.1	1.8	0.017
Comorbidities, %						
Overweight & Obesity	31.0	25.0	0.134	31.0	30.1	0.019
BMI 19.9 or less	0.3	0.5	0.027	0.3	0.3	0.008
BMI 20-29	4.8	4.0	0.042	4.8	4.4	0.019
BMI 30-39	12.3	9,2	0.100	12.3	11.9	0.013
BMI 40 or greater	7.2	6.3	0.037	7.2	7.0	0.011
Hypertension	64.0	51.6	0.254	64.0	63.5	0.011
Hyperlipidemia	48.4	35.5	0.264	48.4	47.7	0.015
Chronic respiratory disease	17.0	17.1	0.004	17.0	16.3	0.018
Liver Disease	10.2	8.6	0.057	10.2	9.5	0.025
Chronic Kidney Disease	14.0	12.6	0.040	14.0	13.2	0.023
CKD Stage 1	0.8	0.5	0.031	0.8	0.7	0.012
CKD Stage 2 (mild)	2.5	1.8	0.048	2.5	2.2	0.018
CKD Stage 3 (moderate)	12.3	9.2	0.083	9.1	8.7	0.016
CKD Stage 4 (severe)	1.9	2.2	0.016	1.9	1.8	0.011
CKD Stage 5	0.5	1.0	0.054	0.5	0.5	0.003
End stage renal disease	1.2	2.7	0.106	1.2	1.2	0.006
Ischemic heart disease	17.0	18.4	0.035	17.0	16.3	0.019
Cerebrovascular Disease	8.7	9.1	0.011	8.7	8.1	0.023
Atherosclerosis	4.5	4.1	0.001	4.5	4.1	0.020
Other peripheral vascular disease	5.7	5.2	0.022	5.7	5.1	0.026

HIV	0.6	0.5	0.012	0.6	0.5	0.009
Organ Transplant	0.9	1.6	0.060	0.9	0.9	0.006
Medications, %						
Immunosuppressants	3.2	3.5	0.017	3.2	3.0	0.012
Chemotherapy	12.4	11.4	0.030	12.4	12.0	0.014
Labs, %						
Hemoglobin A1C						
<9%	54.3	43.2	0.225	54.3	54.0	0.006
≥9%	30.6	16.5	0.338	30.6	30.1	0.011

Abbreviations: TZD; thiazolidinedione, non-TZD; non-thiazolidinedione, std diff; Standard mean difference, y; years, CKD; chronic kidney disease, HIV; Human Immunodeficiency Virus; BMI; body mass index

Population	Thiazolidinedione Cohort	Non-thiazolidinedione Cohort	RR (95% CI)
Overall (n=85,916/cohort)	0.03% (26)	0.06% (51)	0.51 (0.32, 0.82)
Female (n=36,832/cohort)	0.03% (12)	0.06% (23)	0.53 (0.26,1.05)
Male (n=47,124/cohort)	0.03% (14)	0.05% (22)	0.64 (0.33, 1.23)
18-64 years (n=30,039/cohort)	0.05% (14)	0.08% (24)	0.58 (0.30,1.13)
>65 years (n=55,874/cohort)	0.02% (12)	0.05% (27)	0.44 (0.23,0.88)

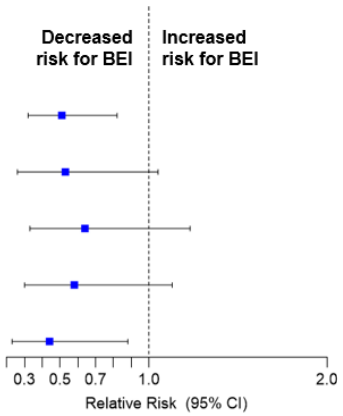

Figure 1: Risk of bacterial enteric infection in low-risk individuals (no prior history of bacterial enteric infection); BEI, Bacterial Enteric Infection

559 Table 2: Characteristics of the thiazolidinedione cohort and the non-thiazolidinedione anti-
560 diabetes medication cohort for the study population at high-risk for bacterial enteric infection

Characteristics	Before matching			After matching		
	TZD users	Non-TZD users	Std diff.	TZD users	Non-TZD users	Std diff.
Total No.	1,975	57,963		1,974	1,974	
Age, mean, y	63.0 ± 12.7	62.6 ± 14.1	0.029	63.0 ± 12.7	63.1 ± 13.3	0.007
Sex, %						
Male	44.1	43.3	0.017	44.1	42.8	0.027
Female	54.3	52.9	0.029	54.3	55.1	0.017
Ethnicity, %						
Hispanic/Latino	20.9	12.3	0.233	20.8	20.8	0.001
Not Hispanic/Latino	65.7	66.3	0.013	65.7	64.5	0.026
Unknown	13.5	21.4	0.211	13.5	14.7	0.036
Race,%						
African American/Black	16.9	20.8	0.099	16.9	16.3	0.016
Asian	4.4	4.1	0.014	4.4	4.4	<0.001
White	65.4	57.7	0.158	65.4	65.8	0.009
American Indian or Alaska Native	0.5	0.4	0.020	0.5	0.5	<0.001
Native Hawaiian or other Pacific Islander	0.6	1.0	0.053	0.6	0.5	0.007
Other Race	3.4	3.3	0.011	3.4	3.2	0.011
Unknown	9.0	12.7	0.120	9.0	9.4	0.014
Lifestyle problem	8.6	7.6	0.036	8.6	7.4	0.041
Tobacco Use	16.2	18.2	0.053	16.2	14.4	0.049
Alcohol Use Disorder	5.3	6.9	0.067	5.3	4.4	0.040
Comorbidities, %						
Overweight & Obesity	45.9	38.6	0.147	45.8	43.4	0.049
BMI 19.9 or less	1.8	2.0	0.011	1.8	1.6	0.020
BMI 20-29	8.4	8.4	0.001	8.4	7.0	0.049
BMI 30-39	17.5	15.2	0.061	17.5	16.0	0.039
BMI 40 or greater	12.7	10.5	0.067	12.6	11.6	0.031
Hypertension	79.8	71.5	0.195	79.8	77.1	0.067
Hyperlipidemia	67.4	54.7	0.263	67.4	64.9	0.051
Chronic respiratory disease	29.6	31.9	0.050	29.6	27.7	0.043
Liver Disease	24.4	21.8	0.061	24.2	22.2	0.052
Chronic Kidney Disease	28.7	32.5	0.084	28.6	27.4	0.027
CKD Stage 1	2.0	1.5	0.036	1.9	2.3	0.028
CKD Stage 2 (mild)	5.7	5.1	0.026	5.7	6.3	0.026
CKD Stage 3 (moderate)	19.3	18.2	0.029	19.3	18.2	0.027
CKD Stage 4 (severe)	5.4	8.6	0.125	5.4	5.1	0.014
CKD Stage 5	1.7	5.0	0.184	1.7	1.6	0.012
End stage renal disease	4.4	10.9	0.248	4.4	4.0	0.020
Ischemic heart disease	28.7	33.9	0.113	28.7	26.2	0.055
Cerebrovascular Disease	17.0	18.9	0.050	16.9	14.6	0.064
Atherosclerosis	10.9	12.2	0.043	10.9	9.2	0.056
Other peripheral vascular disease	11.6	12.8	0.037	11.6	10.0	0.051
HIV	1.4	1.3	0.007	1.4	1.3	0.009
Organ Transplant	3.7	8.0	0.184	3.7	4.0	0.013
Medications						
Immunosuppressants	8.2	11.7	0.116	8.2	7.0	0.044
Chemotherapy	24.8	25.6	0.020	24.8	22.7	0.049
Labs						
Hemoglobin A1C						

	<9%	69.8	61.6	0.173	69.8	69.1	0.014
	≥9%	43.0	24.5	0.400	43.0	43.2	0.003

Abbreviations: TZD; thiazolidinedione, non-TZD; non-thiazolidinedione, std diff; Standard mean difference, y; years, CKD; chronic kidney disease, HIV; Human Immunodeficiency Virus; BMI; body mass index

Population	Thiazolidinedione Cohort	Non-thiazolidinedione Cohort	RR (95% CI)
Overall (n=1,974/cohort)	17.6% (347)	22.5% (445)	0.78 (0.69,0.88)
Female (n=1,071/cohort)	16.4% (176)	21.9% (235)	0.75 (0.63,0.89)
Male (n=871/cohort)	18.7% (163)	24.1% (210)	0.78 (0.65,0.93)
18-64 years (n=714/cohort)	16.9% (121)	21.3% (152)	0.80 (0.64,0.99)
>65 years (n=1,215/cohort)	18.0% (219)	24.3%(295)	0.74 (0.64,0.87)

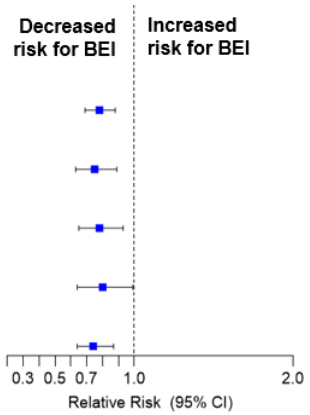

Figure 2: Risk of bacterial enteric infection in high-risk individuals (prior history of bacterial enteric infection); BEI, Bacterial Enteric Infection

Population	Thiazolidinedione Cohort	DPP4-I cohort Cohort	RR (95% CI)
Low-risk (n=84,801/cohort)	0.03% (26)	0.03% (27)	0.96 (0.56,1.65)
High-risk (n=1,986/cohort)	17.7% (353)	21.6% (429)	0.82 (0.73,0.93)

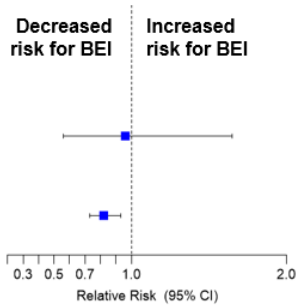

Figure 3: Risk of bacterial enteric infection in thiazolidine users compared to DPP-4 inhibitors with T2DM in low-risk (no prior history of bacterial enteric infection) and high-risk (prior history of bacterial enteric infection); BEI, Bacterial Enteric Infection, T2DM, Type 2 Diabetes Mellitus

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631 Supplementary Table 1: Definition of variables

Variable	Definition
Thiazolidinediones	ATC: 84108,33738
Non-thiazolidinedione	ATC: A10A, A10BA, A10VV, A10VF, A10BH, A10BH, A10BJ, A10BK, A10BX
DPP-4 inhibitors	A10BH
Type 2 Diabetes Mellitus	ICD 10: E11
Age	Time of index
Sex	male or female
Race	Black or African American (2054-5), White (2106-3), Asian (2028-9), American Indian or Alaska native (1002-5), Native Hawaiian or Other Pacific Islander (2076-81), Other Race, Unknown
Ethnicity	Hispanic or Latino (2135-2), Not Hispanic or Latino (2186-5), Unknown
Lifestyle Problems	ICD10: Z72
Tobacco Use	ICD 10: F17
Alcohol Use	ICD 10: F10
Overweight & Obesity	ICD 10: E66
BMI	ICD: Z68.1 - Z68.4
Hypertension	ICD 10: I10
Hyperlipidemia	ICD10: E78.5
Chronic respiratory disease	ICD 10: J40-J4A
Chronic Kidney Disease	ICD 10: N18, N18.1-N18.6
Ischemic Heart Disease	ICD10: I20-I25
Cerebrovascular Disease	ICD 10: I60-I69
Atherosclerosis	ICD 10: I70
Other peripheral vascular disease	ICD 10: I73
Human immunodeficiency virus	ICD10: B20
Organ Transplant	ICD 10: Z94
Immunosuppressants	ATC: L04
Chemotherapy	ATC: L
HgbA1C	TNX Curated: 9037

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