

Search strategy

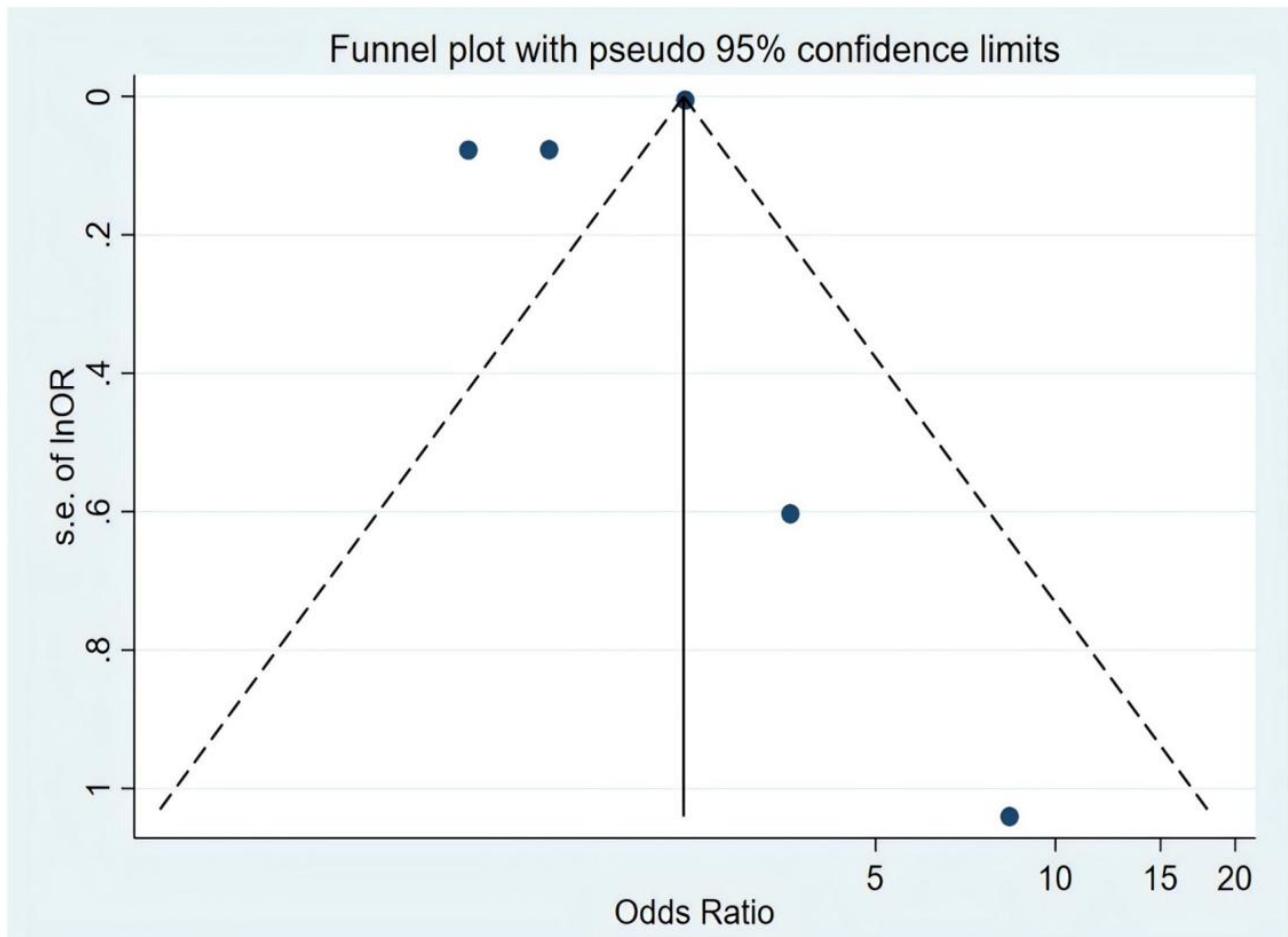
IBD: 'Inflammatory Bowel Disease' OR 'Bowel Diseases, Inflammatory' OR 'Ulcerative Colitis' OR 'Colitis Gravis' OR 'Inflammatory Bowel Disease, Ulcerative Colitis Type' OR 'Crohn's Enteritis' OR 'Regional Enteritis' OR 'Crohn's Disease' OR 'Crohns Disease' OR 'Inflammatory Bowel Disease' OR 'Enteritis, Granulomatous' OR 'Granulomatous Enteritis' OR 'Enteritis' OR 'Regional Ileocolitis' OR 'Colitis, Granulomatous' OR 'Granulomatous Colitis' OR 'Ileitis, Terminal' OR 'Terminal Ileitis' OR 'Ileitis, Regional' OR 'Regional Ileitides' OR 'Regional Ileitis'

PPI:

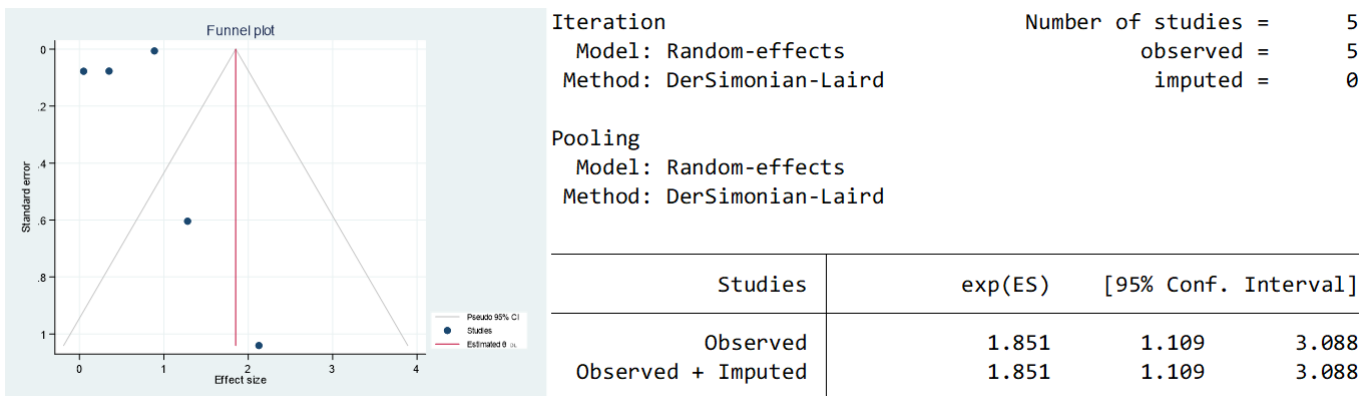
1. 'Proton pump inhibitor' OR 'Inhibitors, Proton Pump' OR 'PPI'
2. 'Omeprazole' OR 'Prilosec' OR 'H 168-68' OR 'H 16868' OR 'H 168 68' OR 'Omeprazole Sodium' OR 'Sodium, Omeprazole' OR 'Omeprazole Magnesium' OR 'Magnesium, Omeprazole'
3. 'lansoprazole' OR 'Lansoprazoles' OR 'Lansoprazol' OR 'Prevacid' OR 'Takepron' OR 'Agopton' OR 'Bamalite' OR 'Promeco' OR 'Lanzor' OR 'Monolitim' OR 'Opiren' OR 'Pro Ulco' OR 'Ulpax' OR 'Zoton' OR 'Lansol' OR 'Lansoprazole Sodium' OR 'Sodium, Lansoprazole' OR 'Ogast' OR 'Prezal' OR 'AG 1749' OR 'AG-1749' OR 'AG1749' OR 'Ogastro'
4. 'Esomeprazole' OR 'Nexium' OR 'Esomeprazole Sodium' OR 'Esomeprazole Magnesium' OR 'Esomeprazole Potassium' OR 'Esomeprazole Strontium' OR 'Strontium, Esomeprazole' OR 'Esomeprazole Strontium Anhydrous'
5. 'Pantoprazole' OR 'BY 1023' OR 'BY-1023' OR 'BY1023' OR 'SK and F 96022' OR 'SK and F-96022' OR 'SK and F96022' OR 'SKF-96022' OR 'SKF96022' OR 'SKF 96022' OR 'Protonix' OR 'Pantoprazole Sodium'
6. 'Dexlansoprazole' OR 'R-Lansoprazole' OR 'R Lansoprazole' OR 'Lansoprazole, R-Isomer' OR 'Lansoprazole, R Isomer' OR 'R-Isomer Lansoprazole' OR '2-((R)-((3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole' OR 'TAK 390MR' OR 'TAK-390MR' OR 'TAK390MR' OR 'Dexilant' OR 'TAK-390' OR 'TAK390' OR 'TAK 390' OR 'T-168390' OR 'T168390' OR 'T 168390' OR 'Dexlansoprazole Sesquihydrate'
7. 'ilaprazole' OR 'IY 81149' OR 'IY-81149' OR 'IY81149'

8. 'Rabeprazole' OR '2-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methylsulfinyl)-1H-benzimidazole' OR 'E 3810' OR 'E3810' OR 'Rabeprazole Sodium' OR 'Sodium, Rabeprazole' OR '1H-Benzimidazole, 2-(((4-(3-methoxypropoxy)-3-methyl-2-pyridinyl)methyl)sulfinyl)-, Sodium Salt' OR 'LY-307640' OR 'LY 307640' OR 'LY307640' OR 'Pariet' OR 'Dexrabeprazole' OR 'Aciphex'

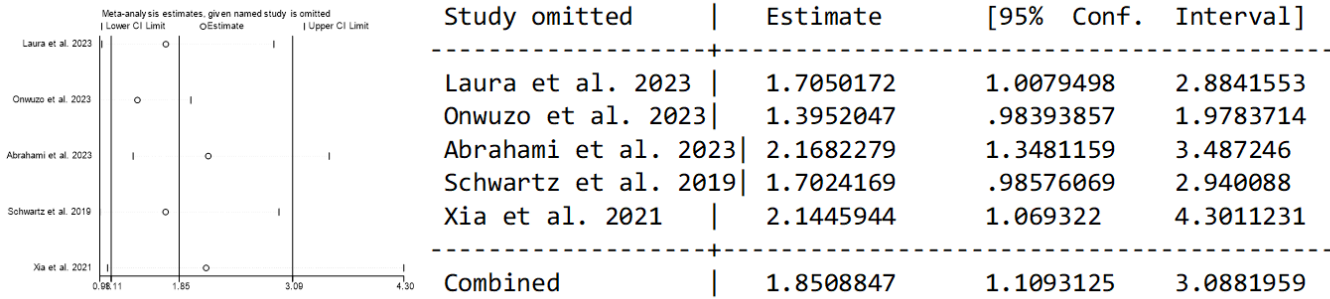
eg. **Pubmed: IBD AND PPI**



Supplementary Figure 1 Funnel plot for publication bias analysis of PPI use and IBD risk.



Supplementary Figure 2 Funnel plot assessing publication bias (trim-and-fill method).



Supplementary Figure 3 Sensitivity analysis evaluating PPI use and IBD risk.

Data merging method: The method implemented to merge the separate odd ratios for Crohn’s disease and ulcerative colitis is available for downloading from <http://www.pnlee.co.uk/software.htm>.

Supplementary Table 1 Risk of bias assessment (using the Newcastle-Ottawa Scale and Agency for Healthcare Research and Quality scale)

Study	Selection				Comparability		Exposure			Quality score
	Is the definition adequate	the cases	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or the analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Laura(2023)	*		-	*	*	-	*	*	-	5
Abrahami(2023)	*		*	*	*	**	*	*	-	8
Schwartz(2019)	*		-	*	*	**_	*	*	-	6
Xia(2021)	*		*	*	*	*	*	*	*	8
Items				Assessment	Explanation					
1. Define the source of information (survey, record review).				YES	IBM® Explorys platform					
2. List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications.				YES	A cohort of patients with a SNOMED-CT diagnosis of ulcerative colitis (UC) and Crohn’s disease (CD) between 1999 and May 2022 was identified. Patients aged 18 to 65 years were included. We excluded any individual who has had a diagnosis of chronic liver disease, autoimmune disease (excluding IBD), or cancer.					
3. Indicate time period used for identifying patients.				YES	A cohort of patients with a SNOMED-CT diagnosis of ulcerative colitis (UC) and Crohn’s disease (CD) between 1999 and May 2022 was identified.					
4. Indicate whether or not subjects were consecutive if not population-based.				YES						
5. Indicate if evaluators of subjective components of study were masked to other aspects of the participants.				Unclear						
6. Describe any assessments undertaken for quality assurance purposes (e.g.,test/ retest of primary outcome measurements).				NO	Furthermore, given that this database is HIPAA-compliant and anonymous, it is not possible to verify the accuracy of the diagnoses made due to the lack of information regarding the diagnostic tests, diagnostic imaging, diagnostic criteria, and duration of medication intake.					
7. Explain any patient exclusions from analysis.				YES	We excluded any individual who had a diagnosis of chronic liver disease, autoimmune disease (excluding IBD), or cancer					
8. Describe how confounding was assessed and/or controlled.				YES	Confounding factors associated with UC and CD were identified and collected if SNOMED-CT diagnoses were available. These were non-steroidal anti-inflammatory drug (NSAID) use, smoking, alcoholism, GERD, irritable bowel syndrome (IBS), and metabolic syndrome.					

9. If applicable, explain how missing data were handled in the analysis. NO

Furthermore, given that this database is HIPAA-compliant and anonymous, it is not possible to verify the accuracy of the diagnoses made due to the lack of information regarding the diagnostic tests, diagnostic imaging, diagnostic criteria, and duration of medication intake. Hence, further in-depth analysis is not feasible.

10. Summarize patient response rates and completeness of data collection. YES

11. Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained. YES
