

Original Article

Association between Inflammatory Bowel Disease and Age-related Macular Degeneration from the TriNetX Global Electronic Health Records Database

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Purpose. This study aims to investigate the association between inflammatory bowel disease (IBD) and age-related macular degeneration (AMD) among the elderly population aged 65 and above, emphasizing the necessity of regular eye examinations for this demographic.

Methods. Utilizing the TriNetX database, a retrospective cohort study was conducted, comparing IBD patients to a non-IBD control group from January 1, 2012, to October 31, 2023. Propensity score matching (PSM) was employed to adjust for variables such as age, gender, race, BMI, hypertension, hyperlipidemia, and diabetes to calculate the adjusted risk ratios and 95% confidence intervals.

Results. Compared to the non-IBD group, individuals aged 65 and over with IBD exhibited a significantly higher risk of AMD. Specifically, the adjusted risk ratio (aHR) for macular and posterior pole degeneration was 2.367 (95% CI: 2.015-2.782), for unspecified AMD was 2.665 (95% CI: 1.983-3.582), for dry AMD was 2.627 (95% CI: 1.904-3.623), and for wet AMD was 2.614 (95% CI: 1.635-4.179). Additionally, risks of blindness and low vision significantly increased in this age group.

Conclusions. IBD patients, particularly those aged 65 and above, face a higher risk of AMD, underscoring the importance of regular eye examinations for this population. Future research should further explore the mechanisms linking IBD to AMD to develop effective prevention strategies.

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Key Words

Inflammatory bowel disease;

Age-related macular degeneration;

Elderly health;

TriNetX database

IBD is a group of chronic digestive system diseases that includes Crohn's disease (CD) and ulcerative colitis (UC), characterized by recurrent chronic in-

flammation of the digestive system. Recent studies have shown that the incidence of IBD is related to various factors, including genetic susceptibility, imbal-

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ance of intestinal microbial communities, environmental factors, and abnormalities in the immune system.^{1,3} It is noteworthy that the prevalence and incidence of IBD globally are on the rise.^{5,6}

AMD is the leading cause of visual impairment affecting people over the age of 55. AMD is characterized by damage to the macula leading to loss of central vision, which affects the quality of life of patients. Research indicates that the development of AMD is related to genetics, environmental factors, and chronic inflammation,¹⁶ and the global prevalence is also increasing.

Preliminary studies have found a significant association between IBD and ocular diseases, especially AMD-related symptoms, such as vitreous warts seem to be more common among IBD patients, further highlighting the interaction between the two diseases.^{25,28} Imbalance of the intestinal microbiota is considered a potential mechanism linking these two diseases. Therefore, further exploring the association between IBD and AMD is crucial for improving the quality of life of patients.

The purpose of this study is to explore the risk of newly developed AMD and its impact on blindness or low vision in patients over 65 years old with IBD.

Methods

Study design

This retrospective cohort study utilized the TriNetX Global Health Research Network database, spanning from January 1, 2012, to October 31, 2023. The study population was established by excluding cases with a history of eye removal surgery or cancer and requiring at least three visits to healthcare facilities. Within this framework, two main groups were compared: individuals diagnosed with IBD and treated with IBD-specific medications, and a non-IBD group who underwent related diagnostic tests but were not diagnosed with IBD. Cases diagnosed with AMD, blindness, or low vision prior to the index date were excluded. After applying these criteria, participants aged 65 and over were selected for further analysis. The study aimed to determine the incidence of newly diagnosed AMD among IBD pa-

tients compared to the non-IBD population, specifically focusing on this elderly cohort.

Data source and population

The study leveraged data from the TriNetX Global Health Research Network, which integrates de-identified electronic health records (EHRs) from over 120 healthcare organizations (HCOs), covering approximately 250 million individuals. The database adheres to HIPAA and GDPR regulations for de-identification. IBD patients were identified through ICD-10 codes for Crohn's disease (K50) and ulcerative colitis (K51), along with records of specific IBD medication use. The non-IBD group included individuals who underwent relevant diagnostic tests but lacked an IBD diagnosis. Both groups were matched 1:1 on various factors including age, gender, ethnicity, BMI, and comorbidities, using propensity score matching (PSM) to ensure comparability.

Inclusion and exclusion criteria

The inclusion criteria for the IBD group required a diagnosis based on ICD-10 codes and evidence of IBD medication use. The non-IBD group required undergoing related diagnostic tests without an IBD diagnosis. Participants were excluded if they had a diagnosis of AMD, blindness, or low vision before the index date, had undergone eye removal surgery, or had a cancer diagnosis at any time.

Outcome measures

The primary outcome was the incidence of AMD (ICD-10 code H35.3) among participants aged over 65. Secondary outcomes included various subtypes of macular degeneration and vision problems, such as unspecified macular degeneration (H35.30), non-exudative AMD (H35.31), and exudative AMD (H35.32), along with blindness and low vision (H54).

Statistical analysis

Statistical analysis was conducted using the real-

time analytics software TriNetX. PSM was employed for 1:1 matching of study subjects based on multiple covariates. The standardized mean difference (SMD) was used to compare matched cohorts. Kaplan-Meier analysis estimated the incidence rates of the study objectives. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were calculated using survival analysis modules in R, with significance determined by a p-value less than 0.05.

Ethical considerations

Given the use of de-identified data, the study was exempt from Institutional Review Board (IRB) review under HIPAA and GDPR regulations. However, formal approval was obtained from the IRB of Chung

Shan Medical University Hospital, with case number CS2-23174, to ensure ethical compliance.

Results

This study is a retrospective cohort analysis conducted from January 1, 2012, to October 31, 2023, aimed at examining the association between IBD and AMD in individuals aged 65 and above. Utilizing the TriNetX Global Health Research Network platform, data from approximately 59,634,784 participants were initially included (Fig. 1). After applying precise inclusion and exclusion criteria, propensity score matching was employed to form two comparison groups for the final analysis: 26,908 IBD patients versus

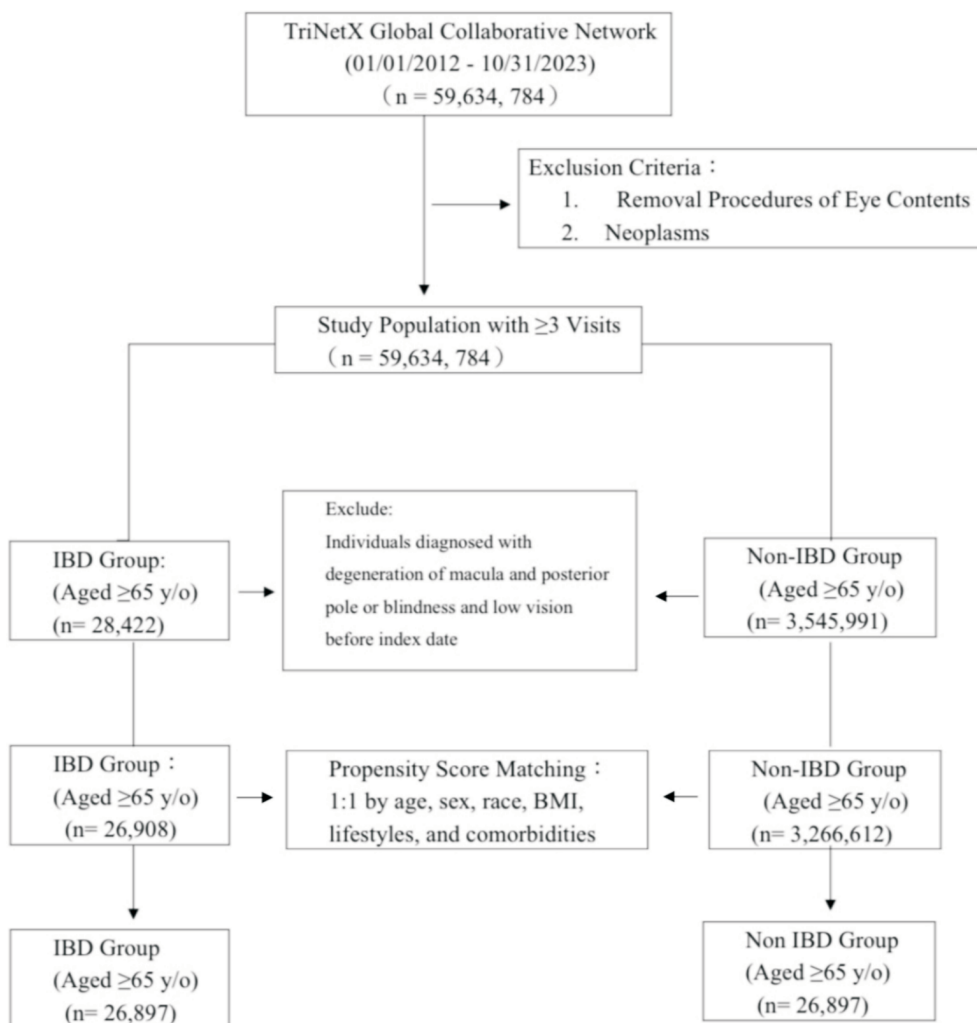


Fig. 1. Flow chart 65 y/o.

3,266,612 non-IBD individuals (Table 1). This matching aimed to provide a fair basis for comparison to accurately assess the risk of AMD.

The study design featured a longitudinal follow-up approach, where “after completing the matching, we began longitudinal tracking 30 days after each participant’s index date,” to evaluate the incidence of newly developed AMD (Fig. 2). This means that although the study spanned over 11 years, the observation for each participant started 30 days after their baseline date, followed by long-term tracking, rather than having only a 30-day observation period for the entire study duration. This design allowed for the assessment of the risk of newly developed AMD after a specified starting point and to track this risk over time.

The analysis revealed that individuals aged 65 and above with IBD faced a significantly higher risk of developing all forms of AMD compared to non-IBD individuals. Specifically, for macular and posterior pole lesions, IBD patients’ risk more than doubled, with an adjusted hazard ratio (aHR) of 2.367 (95% CI: 2.015-2.782) (Fig. 3). In cases of unspecified AMD, the risk further increased, with an aHR reaching 2.665 (95% CI: 1.983-3.582) (Fig. 4). Additionally, both

nonexudative and exudative forms of AMD were associated with increased risks, with aHRs of 2.627 (95% CI: 1.904-3.623) and 2.614 (95% CI: 1.635-4.179), respectively, confirming the IBD cohort’s heightened susceptibility to both major forms of AMD

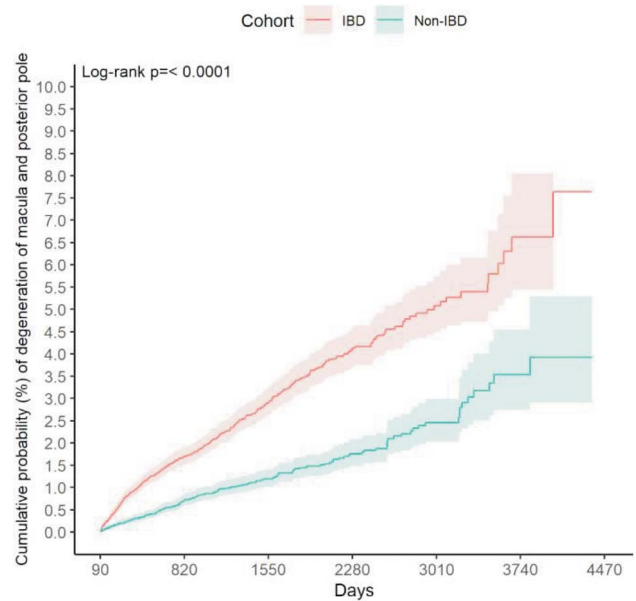


Fig. 2. Kaplan-Meier curve of degeneration of macula and posterior pole (≥ 65 y/o).

Table 1. Propensity score matching (PSM) criteria

No.	Matching criteria	Code type	Code
1	Age at index	NA	AI
2	Female	NA	F
3	Male	NA	M
4	BMI	TNX Curated	9083
5	White	NA	2106-3
6	Black or African American	NA	2054-5
7	Unknown race	NA	UNK
8	Chronic ischemic heart disease	ICD-10-CM	I25
9	Diabetes mellitus	ICD-10-CM	E08-E13
10	Chronic kidney disease (CKD)	ICD-10-CM	N18
11	Other chronic obstructive pulmonary disease	ICD-10-CM	J44
12	Cerebral infarction	ICD-10-CM	I63
13	Generalized anxiety disorder	ICD-10-CM	F41.1
14	Other and unspecified intestinal obstruction	ICD-10-CM	K56.6
15	Fistula of intestine	ICD-10-CM	K63.2
16	Hypertensive diseases	ICD-10-CM	I10-I1A
17	Disorders of lipoprotein metabolism and other lipidemias	ICD-10-CM	E78
18	Nicotine dependence	ICD-10-CM	F17
19	Tobacco use	ICD-10-CM	Z72.0
20	Overweight and obesity	ICD-10-CM	E66

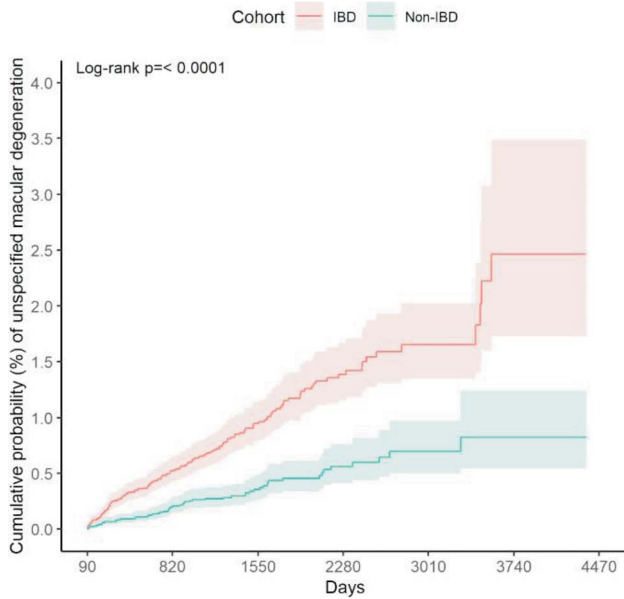


Fig. 3. Kaplan-Meier curve of unspecified macular degeneration (≥ 65 y/o).

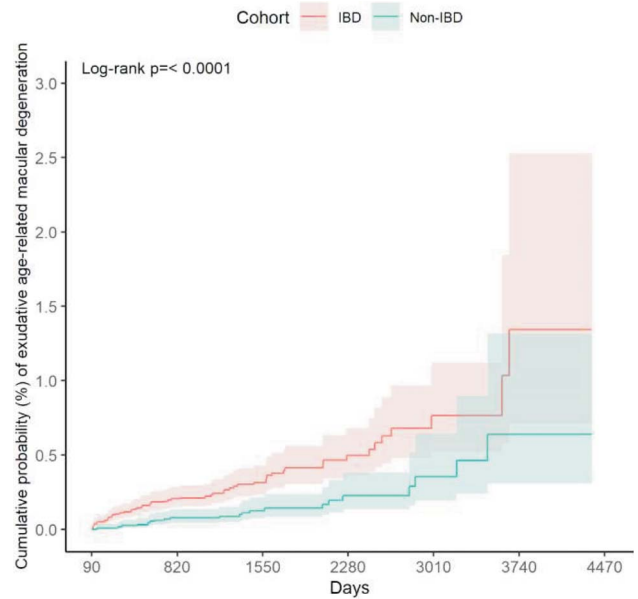


Fig. 5. Kaplan-Meier curve of exudative age-related macular degeneration (≥ 65 y/o).

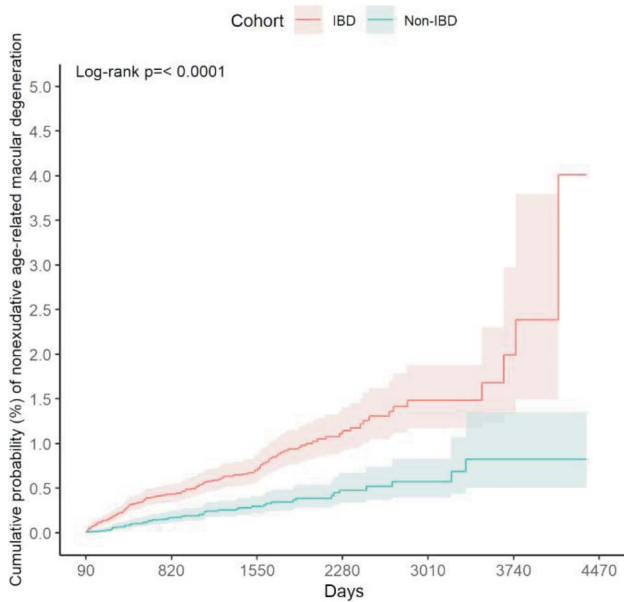


Fig. 4. Kaplan-Meier curve of nonexudative age-related macular degeneration (≥ 65 y/o).

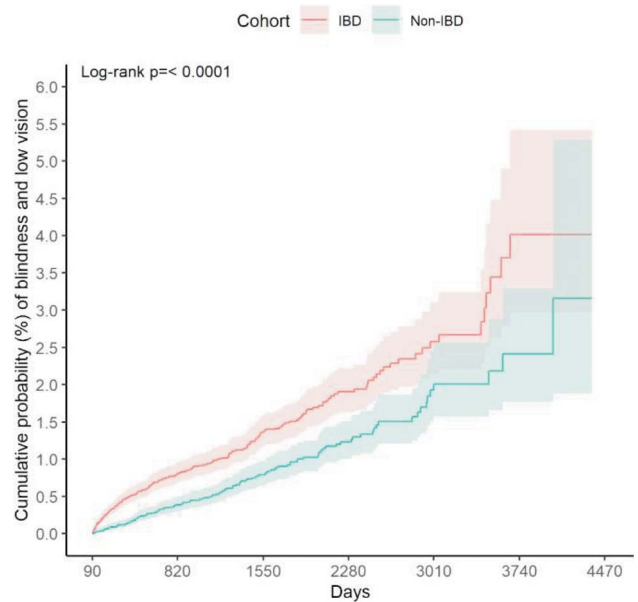


Fig. 6. Kaplan-Meier curve of blindness and low vision (≥ 65 y/o).

(Figs. 5 and 6). The risk for blindness and visual impairment was also significantly higher in the IBD group, with an aHR of 1.742 (95% CI: 1.412-2.150), emphasizing the severe potential impact of IBD on the visual health of the elderly population. These findings underscore the importance of regular and comprehensive eye examinations for older IBD patients to pro-

actively detect and manage the increased risk of AMD and its complications (Table 2).

Discussion

Our retrospective cohort study illuminates a sig-

Table 2. Comparative risk of AMD and vision outcomes in CD and UC patients aged ≥ 65 versus non-IBD controls

	CD vs. non-IBD	UC vs. non-IBD
Degeneration of macula and posterior pole	2.112 (1.654-2.697)	2.299 (1.868-2.830)
Unspecified macular degeneration	2.769 (1.757-4.365)	2.356 (1.625-3.416)
Nonexudative age-related macular degeneration	2.957 (1.806-4.841)	3.050 (1.902-4.891)
Exudative age-related macular degeneration	2.983 (1.340-6.644)	2.962 (1.573-5.575)
Blindness and low vision	1.691 (1.224-2.336)	1.921 (1.424-2.590)

nificant association between IBD and increased risk of AMD in the elderly population. The findings align with previous literature suggesting a systemic inflammatory link between IBD and ocular diseases, most notably AMD, which adds to the mounting evidence of extra-intestinal manifestations of IBD.

The doubling of the risk for macular and posterior pole lesions in IBD patients aged 65 and above (aHR of 2.367) cannot be understated, given the profound impact such conditions have on the central vision and, consequently, the quality of life. This study's hazard ratios clearly illustrate the stark contrast in the risk profiles between IBD and non-IBD individuals, further supporting the hypothesis of an inflammatory pathway shared by both IBD and AMD.

The significant increase in risk for both nonexudative and exudative forms of AMD among the IBD cohort highlights the need for heightened surveillance for AMD in these patients. It is imperative that health-care providers are cognizant of the potential for these ocular complications and incorporate regular eye screenings into the management plan for elderly patients with IBD.

Moreover, the escalated risk for blindness and visual impairment in the IBD group (aHR of 1.742) underscores the potential for these visual conditions to compound the morbidity associated with IBD. These data provide a compelling argument for the integration of ophthalmological evaluations in the standard care protocol for IBD, especially given the aging population.

It is pertinent to note that while the TriNetX Global Health Research Network offered a large, diverse population for analysis, limitations inherent to retrospective studies, such as the potential for unmeasured confounders, must be considered. Nevertheless, our application of propensity score matching and rigorous inclusion criteria aimed to mitigate such biases, pro-

viding a robust analysis of the risks associated with IBD and AMD.

Future research should focus on unraveling the mechanistic links between chronic systemic inflammation and ocular pathology, particularly the role of the gut microbiota, which may offer novel therapeutic targets. Longitudinal studies with a focus on intervention outcomes would also be invaluable in shaping comprehensive care strategies for IBD patients at risk of AMD.

In conclusion, our study presents strong evidence for the association between IBD and AMD, emphasizing the need for a multidisciplinary approach to patient care that includes regular ophthalmological assessment. The elevated risk of ocular complications in IBD patients over 65 calls for a paradigm shift in management, recognizing the interplay between systemic disease and ocular health.

Conclusion

The study reveals that patients over the age of 65 with IBD have a significantly increased risk of developing AMD. These findings underscore the importance of regular eye examinations for this specific population, especially considering their significantly heightened risk of developing AMD. Future research should delve deeper into the mechanisms of interaction between IBD and AMD, particularly focusing on how inflammatory pathways in IBD may affect the pathogenesis of AMD.

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原 著

以 TriNetX 全球電子病歷資料庫探索發炎性腸道疾病和年齡相關性黃斑部病變的相關性

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目的 本研究旨在調查 65 歲及以上老年人群中發炎性腸道疾病 (IBD) 與年齡相關性黃斑部病變 (AMD) 之間的關聯，強調對此人群進行定期眼科檢查的必要性。

方法 利用 TriNetX 資料庫，進行了一項回溯性世代研究，比較了 2012 年 1 月 1 日至 2023 年 10 月 31 日期間的 IBD 患者與非 IBD 對照組。採用傾向評分配對 (PSM) 調整年齡、性別、種族、BMI、高血壓、高血脂和糖尿病等變量，計算調整後的風險比率及 95% 信賴區間。

結果 與非 IBD 組相比，65 歲及以上的 IBD 患者顯示出 AMD 風險顯著增高。具體來說，黃斑部和後極部退化的調整風險比 (aHR) 為 2.367 (95% CI: 2.015-2.782)，未明確的 AMD 為 2.665 (95% CI: 1.983-3.582)，乾性 AMD 為 2.627 (95% CI: 1.904-3.623)，濕性 AMD 為 2.614 (95% CI: 1.635-4.179)。此外，該年齡組失明和視力低下的風險顯著增加。

結論 IBD 患者，特別是 65 歲以上的老年人，面臨較高的 AMD 風險，凸顯了定期眼科檢查對這一人群的重要性。未來研究應進一步探究 IBD 與 AMD 之間的聯繫機制，以發展有效的預防策略。

關鍵詞 發炎性腸道疾病、年齡相關性黃斑部病變、老年健康、TriNetX 資料庫。