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Association Between Autoimmune Diseases and Colorectal Cancer Risk: A Structured Narrative Review with Focused Meta-Analysis of Ulcerative Colitis and an Evidence-Gap Assessment of Psychological Stress and Anxiety

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ABSTRACT:

Background: Autoimmune diseases may influence colorectal cancer (CRC) risk through chronic inflammation, treatment, surveillance, and disease-specific mechanisms. Psychological stress and anxiety may also affect cancer-related pathways through behavioral, neuroendocrine, immune, or health-care mechanisms.

Methods: A structured narrative-review framework, informed by PRISMA 2020 reporting conventions but based on backward and forward citation chasing rather than a complete multi-database export, assessed 31 source-linked records. Eight records were excluded (most often for an ineligible exposure, outcome, or study design), 23 reports underwent primary-evidence assessment, and 18 provided numeric data. Only exchangeable ulcerative colitis (UC) outcomes were pooled. Log standardized incidence ratios (SIRs) and incidence rates were analyzed using restricted maximum likelihood

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random-effects models with modified Hartung-Knapp confidence intervals. Heterogeneity, prediction intervals, and leave-one-out analyses were evaluated. Other autoimmune diseases and psychological evidence were synthesized narratively.

Results: Nine UC cohorts reported 1,848 CRC cases over 1,411,909.5 person-years; pooled incidence was 1.41 per 1,000 person-years (95% CI, 1.16-1.72; I^2 = 58.4%), the more stable and interpretable contemporary benchmark. Four UC cohorts contributed comparative SIRs. The pooled SIR was 2.86 (95% CI, 0.51–16.00; 95% prediction interval, 0.02–462.99; I^2 = 95.6%), an elevated point estimates whose prediction interval spans three orders of magnitude and therefore does not support a stable estimate of true effect in a new setting. Evidence for other autoimmune conditions varies by population, direction, and endpoint. Five psychological records were identified, but no eligible study jointly modeled autoimmune disease, psychological stress or anxiety, and incident CRC; mediation or effect modification could not be estimated.

Conclusions: Current evidence supports UC-focused meta-analysis and disease-specific interpretation of other autoimmune conditions. Psychological stress and anxiety cannot yet be established as mediators or modifiers of autoimmune-associated CRC risk, and their role remains unresolved rather than confirmed or excluded. Interpretation is limited by incomplete database searching, risk-of-bias assessment, and primary-source verification.

INTRODUCTION

Colorectal cancer is a significant malignancy whose risk involves the interactions of age, inherited susceptibility, environmental exposures and acquired inflammatory conditions. The duration of disease and the extent of anatomic involvement are key clinical risk markers in inflammatory bowel disease (IBD) and are biologically plausible factors for colitis-associated carcinogenesis, since repetitive injury and repair of the intestinal epithelium may lead to oxidative stress, genomic instability, dysplasia and cancer (Ullman & Itzkowitz, 2011; Wijnands et al., 2021).

The most direct links between CRC and autoimmune or immune-mediated disorders are for ulcerative colitis (UC) and colonic Crohn disease. The level of risk is not static, but varies depending on the extent of the disease, on how much the disease is inflamed, at what age the disease first presents, whether the patient has primary sclerosing cholangitis, family history, geography, time of treatment and access to colonoscopic surveillance (Krugliak Cleveland et al., 2022; Wijnands et al., 2021). The variation is partly responsible for the different relative estimates that have been provided in population-based studies published in various countries and calendar periods (Zhang, Zhang, et al., 2025).

Previous syntheses found an increased population level risk in UC; however, they also indicated a decrease in absolute incidence over time. Jess et al. (2012) reported a pooled population-based SIR of ~2.4 and Lutgens et al. (2013) reported a lower pooled SIR of ~1.7; Castaño-Milla et al. (2014) estimated an incidence of ~1.58 per 1000 person-years with a long-term downtrend. In a 2025 update of 13 population-based cohorts of UC, the pooled SIR was 2.48 and pooled incidence 1.47 per 1,000 person-years, with a strong emphasis on the important difference in heterogeneity and limited representation outside of Europe and North America (Zhang, Zhang, et al., 2025).

The literature outside IBD is more fragmented. A recent review of 47 studies and 237 estimates found that celiac disease, systemic lupus erythematosus, multiple sclerosis, and type 1 diabetes showed disease- and site-specific patterns, but most contributing studies had important risks of bias and results often changed after bias-oriented sensitivity analyses (Reizner et al., 2025). A Mendelian-randomization analysis likewise produced modest and nonuniform associations across autoimmune phenotypes, supporting the view that autoimmune disease should not be treated as one interchangeable exposure (Chen et al., 2024).

Psychological stress, anxiety, and depression are common concerns in chronic disease, and plausible neuroendocrine, immune, behavioral, and health-care pathways have been proposed. In this review, the term 'role' refers to whether psychological stress or anxiety is associated with CRC risk directly, modifies the strength of the autoimmune disease-CRC association, or mediates part of that association; it does not presuppose that any of these pathways is causal. The strongest recent individual-participant-

data synthesis found no association between depression or anxiety and incident CRC, while broader cancer-wide meta-analyses have been vulnerable to residual confounding by smoking, alcohol, adiposity, and other behaviors (van Tuijl et al., 2023; Wang et al., 2020).

Accordingly, this study had three objectives: first, to quantify contemporary comparative CRC risk in UC using SIRs; second, to estimate contemporary CRC incidence in UC; and third, to evaluate the potential role of psychological stress and anxiety by identifying evidence for direct CRC associations, effect modification, or mediation within autoimmune populations. Where direct autoimmune-specific evidence was unavailable, the review characterized the strength and limits of the relevant contextual psychological literature rather than inferring a causal pathway. This outcome-specific strategy was chosen to preserve clinical and statistical exchangeability (Page et al., 2021; Stroup et al., 2000).

LITERATURE REVIEW

Ulcerative Colitis and Colorectal Cancer

The canonical UC literature links cumulative inflammatory exposure to cancer risk. Population-based cohorts are particularly valuable because referral-center series may overrepresent severe or extensive disease. Contemporary cohorts nevertheless differ in diagnostic era, duration of follow-up, surveillance intensity, age structure, and definition of CRC, which can generate real between-study heterogeneity even when study quality is acceptable (Jess et al., 2012; Zhang, Zhang, et al., 2025).

Recent cohort findings illustrate this spread. A Hungarian population cohort reported stable incidence over long follow-up, a Chinese cohort reported a high SIR, a Utah cohort reported elevated familial risk, and a Dutch cohort reported an SIR below one with a confidence interval crossing the null (Samadder et al., 2019; van den Heuvel et al., 2016; Wetwittayakhlang et al., 2024; Zhang, Zhang, et al., 2022). Large Scandinavian and UK cohorts contributed most person-time to contemporary absolute-incidence estimates and are consistent with lower absolute incidence than early historical series (King et al., 2020; Olen et al., 2020).

Age at Onset, Disease Phenotype, and Surveillance

Age at IBD onset changes both the duration of inflammatory exposure and the competing-risk structure. Scandinavian data suggest very high relative CRC risks after childhood-onset UC or Crohn disease, whereas analyses restricted to elderly-onset disease and excluding the first year after diagnosis can produce estimates at or below the general-population rate (Everhov, Ludvigsson, et al., 2022; Everhov, Erichsen, et al., 2022). These results are not contradictory in a statistical sense because the underlying populations, time scales, surveillance processes, and baseline CRC rates are different.

An early-onset CRC study from Sweden also found a strong association with IBD, reinforcing that age-specific endpoints can produce larger relative effects than all-age CRC analyses (Lundqvist et al., 2023). Such subgroup estimates should not be mixed with all-age SIRs unless a model explicitly addresses effect modification and baseline-risk differences (Wijnands et al., 2021).

Other Autoimmune Diseases

For multiple sclerosis, a French nationwide cohort reported a modestly reduced CRC hazard, and a 2025 disease-spanning review reported a similar inverse pooled association after outlier handling (Pierret et al., 2024; Reizner et al., 2025). These findings may reflect surveillance patterns, competing risks, treatment selection, or residual confounding as well as biology; they should not be interpreted as proof of protection.

For type 1 diabetes, a Korean cohort reported increased colon-cancer risk, while the 2025 review reported a modestly elevated pooled CRC risk. Celiac-disease evidence was imprecise for CRC despite strong associations with some other gastrointestinal malignancies, and psoriasis findings were inconsistent across datasets (Reizner et al., 2025; Shin et al., 2024). A large case-control analysis similarly confirmed the expected IBD-CRC association but found no clear association for psoriasis or celiac disease (Loosen et al., 2025).

A substantially larger pooled analysis has since become available. Cheng et al. (2025) pooled 523 observational studies and more than 91 million participants across a broad set of autoimmune diseases, including primary sclerosing cholangitis, inflammatory myopathies, IBD, autoimmune hepatitis, ANCA-associated vasculitis, sarcoidosis, scleroderma, type 1 diabetes, psoriasis,

membranous nephropathy, hidradenitis suppurativa, and immune thrombocytopenic purpura, and reported an elevated overall CRC risk ratio (1.24, $p < .001$), with rheumatoid arthritis as a notable protective exception. This demonstrates that quantitative pooling across non-UC autoimmune diseases is feasible when studies are combined at the level of a single overall risk ratio rather than disease-specific, CRC-only SIRs with extractable person-time. Cheng et al. (2025) was assessed for the present review and was not entered into the quantitative synthesis because it does not report the disease-stratified, CRC-specific SIRs with extractable person-time that this review's eligibility criteria require; its pooled risk ratio combines disease categories, endpoints, and comparator populations that are not exchangeable with the UC-focused SIR and incidence models reported here. It is nonetheless the most comprehensive available benchmark for non-UC autoimmune-CRC risk and is retained as a point of comparison for the narrative synthesis in Table 4.

Psychological Stress and Anxiety

Cancer-wide observational studies have sometimes reported small positive associations for depression or anxiety, but site-specific estimates are inconsistent and can attenuate after behavioral adjustment (Wang et al., 2020). In contrast, the PSY-CA individual-participant-data meta-analysis combined 18 cohorts and found no association between depression or anxiety and incident CRC (van Tuijl et al., 2023).

Evidence concerning psychological stress or anxiety must be interpreted at more than one level. General-population studies can inform whether these exposures are associated with incident CRC, but they cannot by themselves establish that psychological factors mediate or modify CRC risk among people with autoimmune disease. Demonstrating such a role would require, at minimum, measurement of the autoimmune exposure, a temporally ordered psychological exposure, incident CRC, and adequate control of exposure-outcome, exposure-mediator, and mediator-outcome confounding. No eligible record identified in this review satisfied those requirements; therefore, the psychological evidence was synthesized to determine what is known about the proposed role and where direct evidence remains absent (van Tuijl et al., 2023).

METHODS

Design and Reporting Framework

This systematic review and meta-analysis used an outcome-specific evidence-synthesis framework with two UC meta-analyses and structured narrative syntheses for non-UC autoimmune diseases and psychological factors. The psychological question was treated as an integral review objective and was evaluated separately to avoid combining mechanistically distinct evidence. The structure of study-selection reporting was informed by PRISMA 2020, while the quantitative synthesis and reporting followed the MOOSE recommendations for observational evidence (Page et al., 2021; Stroup et al., 2000). The review protocol was not prospectively registered.

The review question, eligibility criteria, extraction fields, and synthesis rules were specified systematically; however, evidence identification relied primarily on citation-based searching rather than on a complete set of de-duplicated exports from multiple bibliographic databases. Accordingly, the study-selection counts refer to the records evaluated in the present review process, and the quantitative analyses are restricted to studies with extractable, outcome-compatible numerical data. This distinction is retained transparently because it limits the completeness expected from a fully database-derived systematic search (Page et al., 2021).

Eligibility Criteria

Eligible primary studies were observational cohort, case-control, or registry studies published from January 1, 2011, through August 20, 2026. Studies had to evaluate a defined autoimmune or immune-mediated disease and report incident CRC, colon cancer, rectal cancer, or an extractable comparative or incidence estimate. Eligible quantitative measures included SIRs, hazard ratios, risk ratios, odds ratios, and event counts with person-time. Reviews were retained only for citation chasing, methodological context, or benchmark comparisons.

The primary comparative meta-analysis was restricted to overall CRC SIRs in UC. The secondary incidence meta-analysis was restricted to UC cohorts reporting CRC events and person-years. Studies of Crohn disease, childhood-onset or elderly-onset IBD, multiple sclerosis, celiac disease, type 1 diabetes, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, or mixed autoimmune groups were not combined because fewer than three independent, exchangeable estimates were available within

any common effect/outcome definition compatible with disease-stratified, CRC-specific SIRs. A much larger pooled analysis across non-UC autoimmune diseases exists (Cheng et al., 2025); it was considered and excluded from quantitative synthesis because it reports a single combined risk ratio across heterogeneous disease categories rather than the disease-specific, exchangeable estimates this review's models require, and is instead used as a narrative benchmark (see Literature Review and Discussion).

For the psychological objective, evidence was classified into two levels. Direct autoimmune-specific evidence required an autoimmune exposure, a measure of stress, anxiety, distress, or depression occurring before CRC, incident CRC, and a mediation or interaction estimate. General-population psychological studies that examined incident CRC were retained as contextual evidence for the direct psychological-CRC component of the review, whereas studies of psychological outcomes occurring after CRC were not considered informative for the proposed role.

Information Sources and Search Strategy

Studies included in the present synthesis were identified through backward and forward citation chasing of recent disease-specific reviews and relevant primary cohorts. To support reproducibility and future verification, database search strategies were also drafted for PubMed/MEDLINE, Embase, Web of Science Core Collection, and Scopus; only the PubMed strings were finalized and are reproduced in Appendix A, and the Embase, Web of Science, and Scopus strings were not developed to the same level of detail. The search vocabulary combined controlled terms and free text for autoimmune diseases, CRC, and observational effect measures, a separate string targeted stress, anxiety, distress, and depression. The intended date window was January 1, 2011, through August 20, 2026. These strategies were not used to generate complete database hit counts for the present analysis.

Study Selection and Data Extraction

Each identified record was assessed at title/abstract and report level for eligibility, quantitative suitability, exclusion reason, potential cohort overlap, and evidence stream. Screening and data extraction were performed by a single reviewer without independent duplicate screening or a formal conflict-resolution procedure, which is noted here as a limitation of the review process itself. In total, 31 records were assessed; 23 reports were retained for primary-evidence assessment, and 18 provided numerical information suitable for extraction.

Extracted variables included author, year, country, design, cohort period, autoimmune disease, exposed and comparator sample sizes, CRC cases, person-years, outcome definition, effect measure, point estimate, 95% confidence limits, adjustment status, potential cohort overlap, and intended synthesis role. When cohorts overlapped, the most recent or most informative estimate was preferred for a given model. Review-level pooled estimates were never entered as independent studies in the primary meta-analysis.

One overall SIR confidence interval for Wetwittayakhlang et al. (2024) was reconstructed during data extraction because a secondary review table contained an implausible typographical interval. The model used SIR 2.02 with an estimated 95% CI of 1.46-2.72. This reconstructed interval adds uncertainty and requires confirmation against the primary report; direct verification with the original authors or the primary published report is recommended before submission, although sensitivity analysis did not remove the broader problem of extreme heterogeneity.

Outcomes

The primary outcome was the SIR for incident CRC among people with UC relative to the reference population. The secondary outcome was the crude incidence rate of CRC per 1,000 person-years among people with UC. Narrative outcomes included age- or phenotype-specific CRC hazard ratios and disease-specific comparative estimates for other autoimmune conditions. Colon-only and early-onset CRC outcomes were labeled separately and were not treated as interchangeable with all-age combined CRC.

Risk of Bias and Certainty of Evidence

ROBINS-E was selected because it provides a structured seven-domain assessment for nonrandomized exposure studies, including confounding, selection, exposure measurement, post-exposure interventions, missing data, outcome measurement, and selective reporting (Higgins et al., 2024). However, item-level ROBINS-E judgments were not completed for all included

studies. Published secondary ratings indicated acceptable Newcastle-Ottawa scores for the UC cohorts (Zhang, Zhang, et al., 2025), while a broader autoimmune review judged most contributing studies to have serious or high risk of bias; these external ratings were used only as contextual evidence and were not substituted for an independent assessment (Reizner et al., 2025; Zhang, Zhang, et al., 2025).

Because item-level risk-of-bias assessment was incomplete, formal GRADE certainty ratings were not assigned. The comparative SIR result was interpreted as very uncertain because of few studies, extreme inconsistency, wide modified Hartung-Knapp and prediction intervals, and the unverified reconstructed interval. The incidence result was interpreted as more stable descriptively but remained observational, single-arm, and moderately heterogeneous.

Statistical Analysis

Ratio measures were transformed to the natural-log scale. Standard errors were derived from 95% confidence limits as [ln(upper) - ln(lower)]/(2 x 1.96). For incidence, the effect was ln(events/person-years), with sampling variance approximated by 1/events; exact Poisson intervals were used for study-level display. Analyses were conducted in Python using double-precision numerical routines. For comparison, a conventional DerSimonian-Laird random-effects model was also fitted as a sensitivity analysis.

Random-effects models used restricted maximum likelihood to estimate between-study variance (tau2). Confidence intervals for the pooled mean used a modified Hartung-Knapp adjustment, which prevents the small-sample scale factor from producing an interval narrower than the conventional random-effects interval. This approach was selected because conventional normal-theory DerSimonian-Laird inference can have poor error control when the number of studies is small and heterogeneity is present (IntHout et al., 2014; Partlett & Riley, 2017).

Statistical heterogeneity was summarized with Cochran's Q, I2, tau2, and a 95% prediction interval. The prediction interval used a t distribution and incorporates estimated between-study dispersion; it therefore reflects the uncertainty expected for the true effect in a new comparable setting rather than only the mean effect (Nagashima et al., 2019). Leave-one-out analysis was performed for the four-study SIR model. Funnel-plot asymmetry and small-study tests were not used because both models included fewer than 10 studies and such tests would be underpowered and potentially misleading (Sterne et al., 2011).

No pooled model fits across SIRs, hazard ratios, odds ratios, incidence rates, age-specific endpoints, or overlapping national databases. Statistical significance was assessed at two-sided alpha = .05, but interpretation emphasized magnitude, confidence intervals, prediction intervals, consistency, and data quality rather than a binary threshold.

RESULTS

Evidence Selection and Study Coverage

The review process identified 31 records for assessment. All 31 underwent title/abstract and report-level evaluation; 8 reports were excluded, 23 were retained for primary-evidence assessment, 5 remained pending quantitative verification, and 18 had extracted numerical data. Figure 1 presents the study-selection flow and shows the quantitative and narrative synthesis streams; it is structured for readability with reference to PRISMA 2020 flow-diagram conventions but does not represent a complete, database-derived PRISMA search (see Methods and Limitations).

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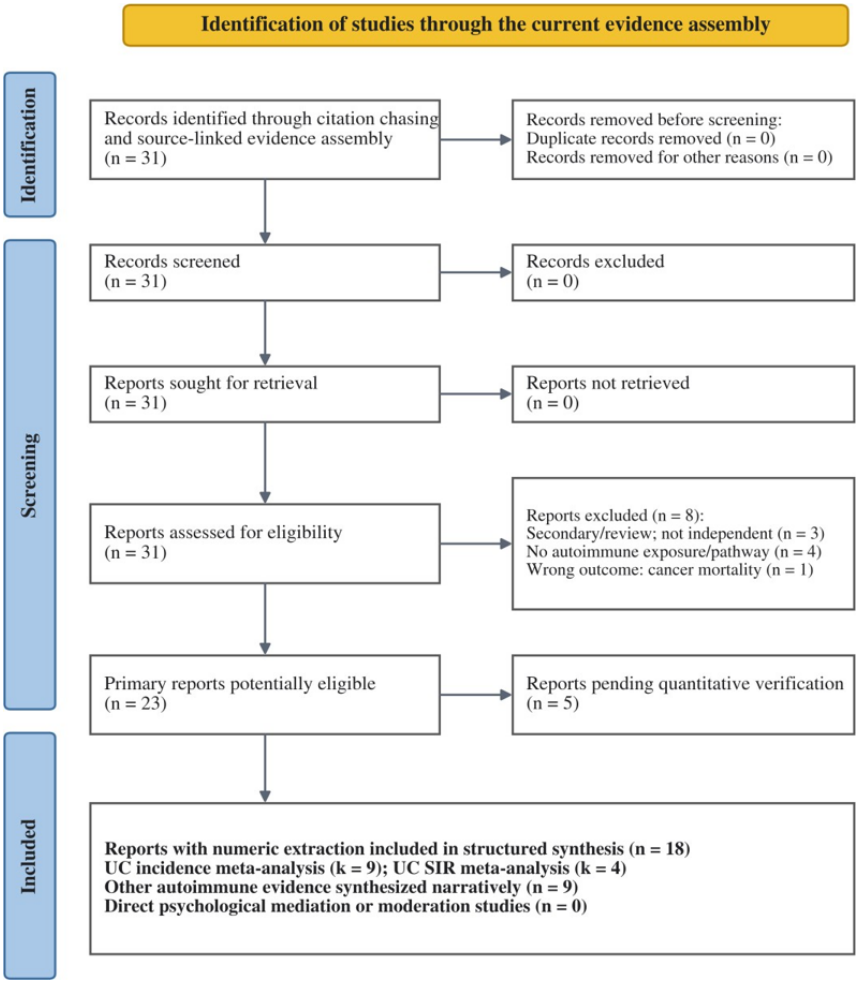
Figure 1 Study Selection Flow Diagram



The 18 numerically extracted reports represented UC, age-defined IBD, mixed IBD, multiple sclerosis, celiac disease, type 1 diabetes, and psoriasis evidence from Europe, Asia, and North America. Their design, setting, sample information, outcome, effect estimate, and synthesis role are summarized in Table 1.

The quantitative UC incidence evidence comprised nine cohorts published from 2011 to 2024 and conducted in Hungary, China, Denmark/Sweden, the United Kingdom, the United States,

South Korea, Norway, the Netherlands, and a multicounty European collaboration. Together, the cohorts reported 1,848 CRC cases during 1,411,909.5 person-years (the half-year value reflects legitimate partial-year follow-up contributed by the van den Heuvel et al. (2016) cohort rather than a rounding or unit-conversion artifact); their study-level data are presented in Table 2 (Hovde et al., 2017; Jung et al., 2017; Katsanos et al., 2011; King et al., 2020; Olen et al., 2020; Samadder et al., 2019; van den Heuvel et al., 2016; Wetwittayakhlang et al., 2024; Zhang, Zhang, et al., 2022).

Comparative CRC Risk in Ulcerative Colitis

Four cohorts contributed overall SIRs. Individual estimates ranged from 0.71 to 8.38. The REML pooled SIR was 2.86 (95% modified Hartung-Knapp CI 0.51-16.00; Q = 67.69, df = 3; I2

= 95.6%; tau2 = 1.105). The 95% prediction interval was 0.02-462.99. The point estimate was above one, but the confidence interval included the null and the prediction interval was extremely broad (Figure 2).

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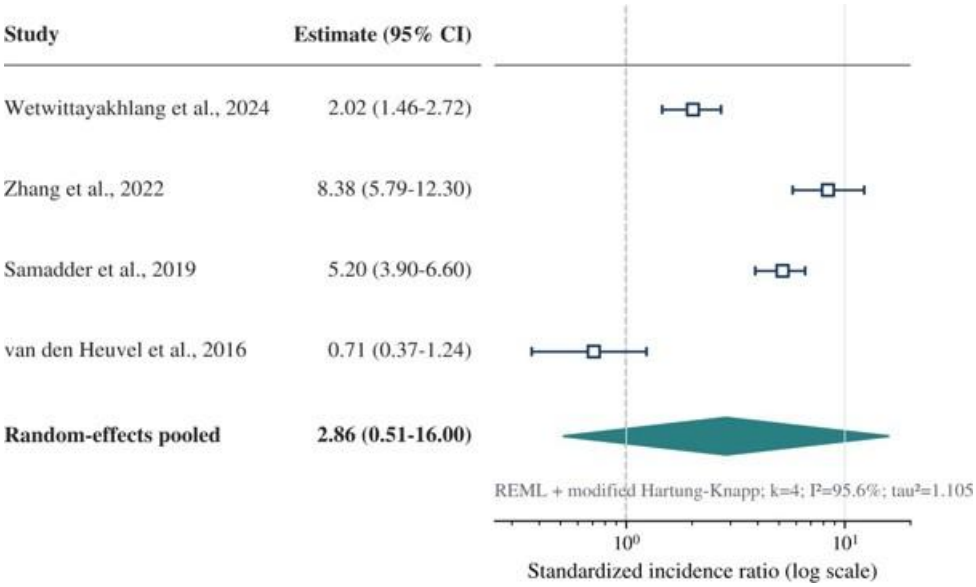

Figure 2 Forest Plot of Colorectal Cancer Standardized Incidence Ratios in Ulcerative Colitis

Note. Squares and horizontal lines show study SIRs and 95% confidence intervals. The diamond shows the REML pooled estimate with modified Hartung-Knapp confidence interval. The dashed line marks SIR = 1.

The conventional DerSimonian-Laird sensitivity model produced a pooled SIR of 2.89 (95% normal-theory CI 1.24-6.76), demonstrating that the apparent statistical significance depended on the inferential method. Modified Hartung-Knapp inference was retained as primary because only four heterogeneous studies were available (IntHout et al., 2014).

CRC Incidence in Ulcerative Colitis

Across nine cohorts, individual crude incidence estimates ranged from 0.74 to 2.79 per 1,000 person-years. The REML pooled incidence was 1.41 per 1,000 person-years (95% modified

Hartung-Knapp CI 1.16-1.72; Q = 19.25, df = 8; I2 = 58.4%; tau2 = 0.018). The 95% prediction

interval was 0.97-2.06 per 1,000 person-years (Figure 3).

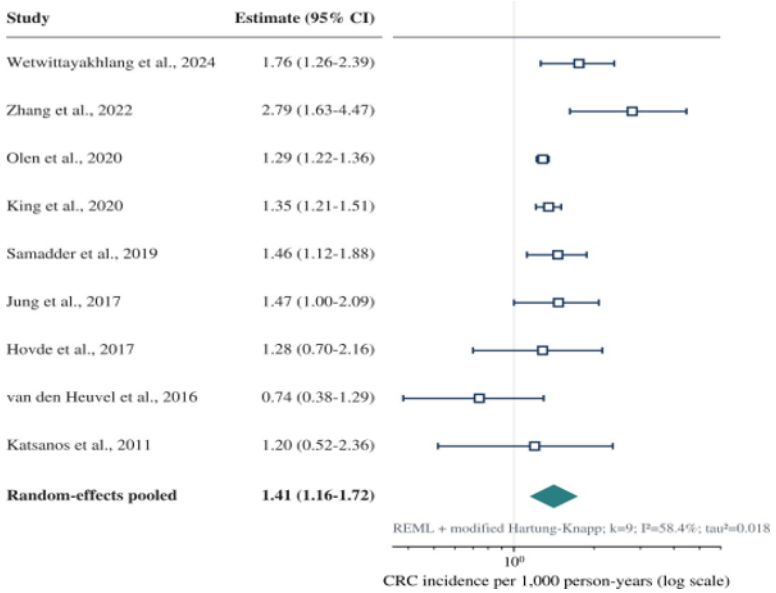

Figure 3 *Forest Plot of Colorectal Cancer Incidence in Ulcerative Colitis*

Note. Study-level intervals are exact Poisson intervals. The diamond shows the REML pooled incidence and modified Hartung-Knapp confidence interval.

The pooled incidence was close to the 1.47 per 1,000 person-years reported by a broader 2025 population-based review, despite the present restriction to studies published in the recent 2011-2024 window (Zhang, Zhang, et al., 2025). Moderate heterogeneity indicates that the average remains a benchmark rather than a universal patient-level risk. The comparative SIR and incidence model summaries are presented together in Table 3.

Sensitivity Analysis

Leave-one-out SIR estimates ranged from 2.01 to 4.43, but every modified Hartung-Knapp confidence interval crossed one and remained very wide. I2 remained between 94.5% and 96.5%, indicating that no single study explained the heterogeneity (Figure 4). The sensitivity analysis therefore supported the stability of an elevated point estimate but not precise inference.

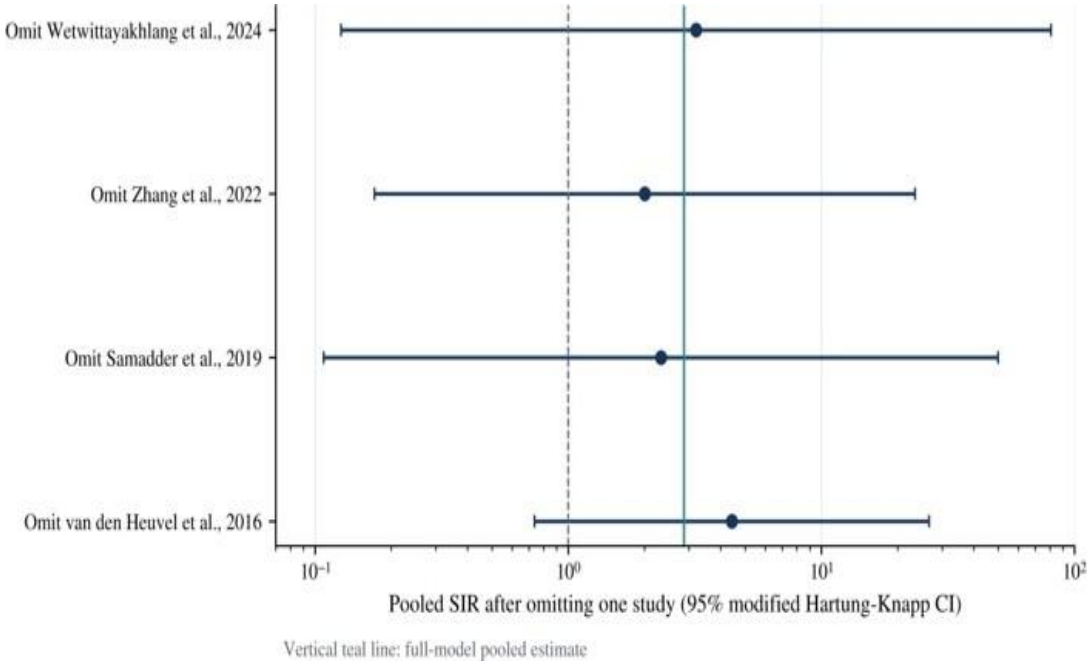

Figure 4 Leave-One-Out Sensitivity Analysis for the Ulcerative Colitis SIR Model

Note. Each row refits the REML model after removing one study. All modified Hartung-Knapp intervals cross the null.

Other Autoimmune Diseases

The non-UC evidence was clinically heterogeneous. In elderly-onset Scandinavian IBD, estimates more than one year after diagnosis were below one for Crohn disease and UC, whereas childhood-onset IBD showed large relative hazards for both diseases. Swedish early-onset CRC data showed a strong IBD association, and a German case-control study reported a more modest all-age IBD odds ratio (Everhov, Erichsen, et al., 2022; Everhov, Ludvigsson, et al., 2022; Loosen et al., 2025; Lundqvist et al., 2023).

Multiple sclerosis was associated with a modestly lower CRC hazard in one French nationwide cohort, consistent with a recent pooled review. Type 1 diabetes was associated with increased colon-cancer hazard in one Korean cohort and modestly increased pooled CRC risk in the broader review. Celiac and psoriasis estimates were too sparse or inconsistent for new pooling, and no verified primary comparative estimate was available among the included reports for rheumatoid arthritis or systemic lupus erythematosus (Pierret et al., 2024; Reizner et al., 2025; Shin et al., 2024). Figure 5 summarizes model readiness, and Table 4 presents the study-specific non-UC estimates retained for structured narrative synthesis.

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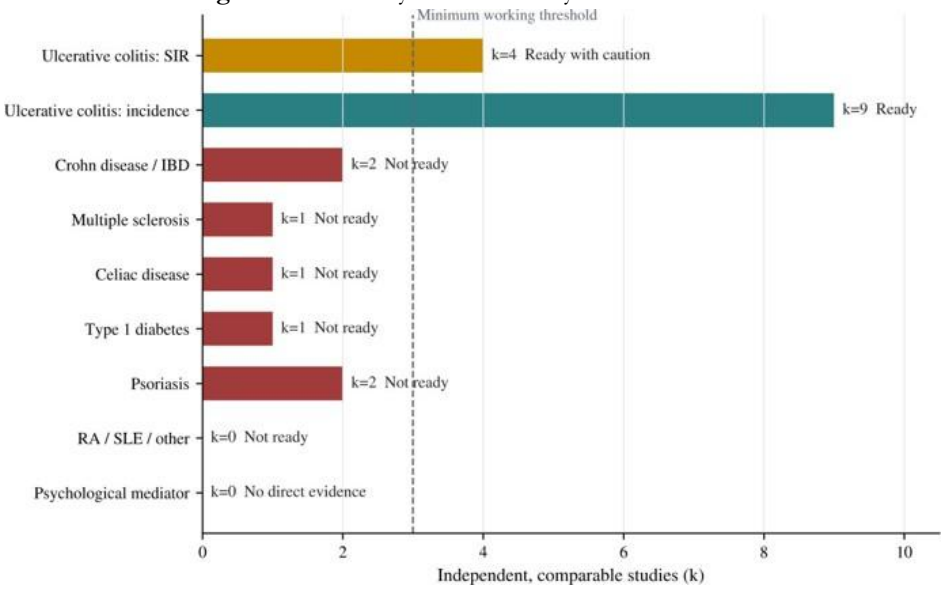
Figure 5 Meta-Analysis Readiness by Evidence Stream

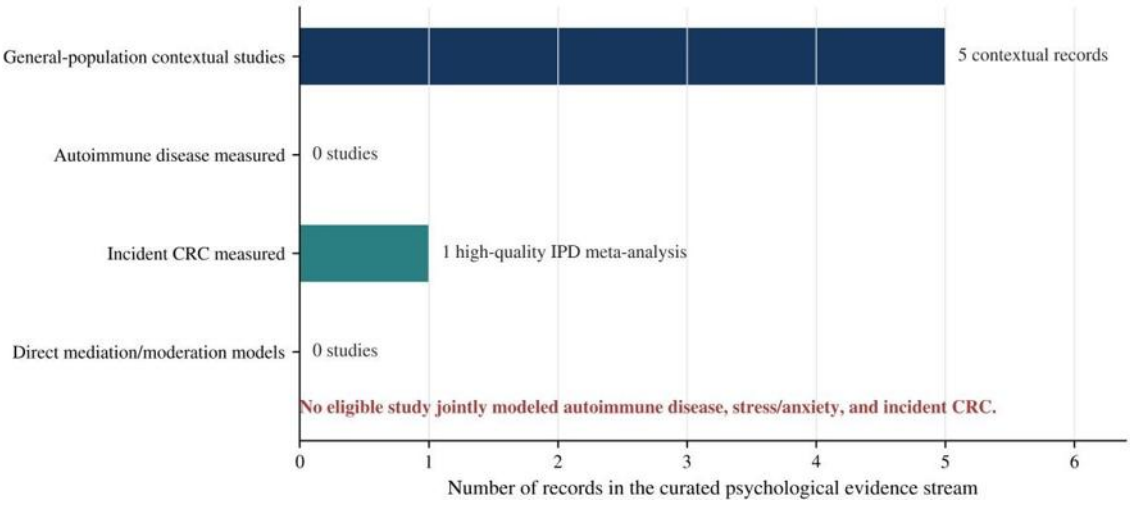


Note. A working minimum of three independent and comparable studies was required before quantitative pooling was considered. Readiness also depended on compatible populations, endpoints, and effect measures.

Role of Psychological Stress and Anxiety

The potential role of psychological stress and anxiety was evaluated across three evidence levels: a direct association between psychological exposures and incident CRC, effect modification of the autoimmune disease-CRC association, and mediation of that association. Five contextual psychological records addressed the first level, including individual-participant-data and cohort meta-analytic evidence, but none evaluated effect modification or mediation within an autoimmune cohort. The strongest CRC-incidence evidence came from the PSY-CA individual-participant-data meta-analysis, which found no association of depression or anxiety with incident CRC in the general population (van Tuijl et al., 2023). Thus, the available literature does not demonstrate a direct CRC effect large enough to support a psychological explanation of the autoimmune association, while autoimmune-specific mediation and moderation remain untested. Figure 6 summarizes the distribution of available and missing evidence, and Table 5 details the contextual studies.

Figure 6 Evidence Concerning the Role of Psychological Stress and Anxiety



Note. Contextual psychological studies provide evidence about direct psychological-CRC associations but did not jointly model autoimmune disease, a psychological mediator, and incident CRC; autoimmune-specific mediation and moderation therefore could not be estimated.

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Risk of Bias and Certainty

Item-level ROBINS-E judgments were not completed for all included studies. This is an important limitation because exposure misclassification, differential surveillance, residual confounding, overlapping registries, and detection bias may influence observational CRC estimates. Published evidence also suggests that risk-of-bias concerns are common across non-IBD autoimmune cancer studies (Higgins et al., 2024; Reizner et al., 2025).

Study and Model Summaries

Table 1 provides a consolidated study-level description of all 18 reports with numerical information retained for structured synthesis, including their design, disease exposure, sample information, extracted result, and role in the analysis.

Table 1 *Characteristics of the 18 Reports With Numeric Extraction Included in the Structured Synthesis*

Study	Region/design	Disease	Period/follow-up	Sample and CRC data	Extracted result / synthesis role
Wetwittayakhlang et al. (2024)	Hungary; population cohort	UC	1997-2020; 17 y	N=1,370; 41 CRC; 23,290 PY	SIR 2.02 (1.46-2.72); incidence 1.76/1,000 PY; both UC models
Zhang et al. (2022)	China; population cohort	UC	1998-2018; 7 y	N=869; 17 CRC; 6,083 PY	SIR 8.38 (5.79-12.30); incidence 2.79/1,000 PY; both UC models
Olen et al. (2020)	Denmark/Sweden; population cohort	UC	1969-2017; 13 y	N=96,447; 1,336 CRC; 1,039,672 PY	Incidence 1.29/1,000 PY; UC incidence model
King et al. (2020)	United Kingdom; population cohort	UC	2000-2017; 6.4 y	N=37,793; 328 CRC; 242,407 PY	Incidence 1.35/1,000 PY; UC incidence model
Samadder et al. (2019)	Utah, USA; population cohort	UC	1996-2011; 9.4 y	N=4,421; 61 CRC; 41,642 PY	SIR 5.20 (3.90-6.60); incidence 1.46/1,000 PY; both UC models
Jung et al. (2017)	South Korea; nationwide cohort	UC	2011-2014; 2.2 y	N=9,785; 31 CRC; 21,048 PY	Incidence 1.47/1,000 PY; UC incidence model; overall SIR unavailable
Hovde et al. (2017)	Norway; population cohort	UC	1990-2013; 21 y	N=519; 14 CRC; 10,899 PY	Incidence 1.28/1,000 PY; UC incidence model
van den Heuvel et al. (2016)	Netherlands; population cohort	UC	1991-2011; 8.8 y	N=1,644; 12 CRC; 16,193.5 PY	SIR 0.71 (0.37-1.24); incidence 0.74/1,000 PY; both UC models
Katsanos et al. (2011)	Europe; population cohort	UC	1993-2009; 15 y	N=445; 8 CRC; 6,675 PY	Incidence 1.20/1,000 PY; UC incidence model
Everhov, Erichsen, et al. (2022)	Denmark/Sweden; population cohort	Elderly-onset CD and UC	1969-2017; 6-7 y	CD: N=7,869/165 CRC; UC: N=21,224/403 CRC	Lagged HR 0.69 (0.56-0.86) for CD and 0.78 (0.69-0.88) for UC; narrative
Everhov, Ludvigsson, et al. (2022)	Denmark/Sweden; population cohort	Childhood-onset CD and UC	1969-2017	25 CRC in CD; 113 CRC in UC	HR 6.46 (3.95-10.60) for CD and 32.50 (23.00-45.90) for UC; narrative
Lundqvist et al. (2023)	Sweden; nested case-control	IBD	2007-2016	2,626 early-onset CRC cases; 15,756 controls	HR 5.98 (4.78-7.48); age-specific narrative evidence

Loosen et al. (2025)	Germany; retrospective case-control	IBD	2005-2024	N=120,876; 20,146 CRC cases	OR 1.53 (1.33-1.75); narrative; OR kept separate
Pierret et al. (2024)	France; nationwide cohort	Multiple sclerosis	2012-2021; 10 y	N=140,649; comparator N=562,596	HR 0.90 (0.84-0.97); disease-specific narrative evidence

Study	Region/design	Disease	Period/follow-up	Sample and CRC data	Extracted result / synthesis role
Ilus et al. (2014)	Finland; population cohort	Celiac disease	Not available for extraction	CRC count and person-time not available for extraction	SIR 1.17 (0.43-2.54); narrative
Shin et al. (2024)	South Korea; nationwide cohort	Type 1 diabetes	Not available for extraction	Sample and CRC count not available for extraction	aHR 1.37 (1.11-1.68) for colon cancer; narrative
Fu et al. (2021)	Multinational; systematic review/meta-analysis	Psoriasis	Nine cohorts	N=10,544,609	HR 1.16 (1.08-1.24); contextual secondary evidence; not pooled as an independent study
Han et al. (2026)	South Korea; nationwide cohort	Psoriasis	2002-2019	N=16,670; comparator N=66,680	aHR 0.96 (0.83-1.10); disease-specific narrative evidence

Note. aHR = adjusted hazard ratio; CD = Crohn disease; CRC = colorectal cancer; HR = hazard ratio; IBD = inflammatory bowel disease; OR = odds ratio; PY = person-years; SIR = standardized incidence ratio; UC = ulcerative colitis. Fu et al. (2021) is secondary evidence and was not entered as an independent study in a pooled model. The Loosen et al. (2025) "IBD" row combines UC and Crohn disease under a single odds ratio without disease-level disaggregation, unlike every other row in this table.

Across the 18 reports summarized in Table 1, UC contributed the only evidence streams with sufficient numerical compatibility for quantitative pooling. The incidence cohorts covered diverse healthcare systems and calendar periods, while only a subset also reported overall CRC SIRs; the remaining reports addressed age-defined IBD or other autoimmune diseases using different effect measures and endpoints. This pattern explains why the meta-analysis was deliberately confined to clinically exchangeable UC outcomes rather than expanded across heterogeneous autoimmune conditions. The nine cohort-level inputs used to estimate contemporary CRC incidence in UC are detailed in Table 2.

Table 2 Characteristics of Ulcerative Colitis Cohorts Included in the Incidence Meta-Analysis

Study	Region	Period	UC N	CRC	Person-years	Rate/1,000 PY
Wetwittayakhlang et al. (2024)	Hungary	1997-2020	1,370	41	23,290	1.76
Zhang et al. (2022)	China	1998-2018	869	17	6,083	2.79
Olen et al. (2020)	Denmark/Sweden	1969-2017	96,447	1,336	1,039,672	1.29

King et al. (2020)	United Kingdom	2000-2017	37,793	328	242,407	1.35
Samadder et al. (2019)	Utah, USA	1996-2011	4,421	61	41,642	1.46
Jung et al. (2017)	South Korea	2011-2014	9,785	31	21,048	1.47
Hovde et al. (2017)	Norway	1990-2013	519	14	10,899	1.28
van den Heuvel et al. (2016)	Netherlands	1991-2011	1,644	12	16,193.5	0.74
Katsanos et al. (2011)	Europe	1993-2009	445	8	6,675	1.20

Note. CRC = colorectal cancer; PY = person-years; UC = ulcerative colitis. Rates are crude events/person-years and may differ slightly from adjusted measures.

Although there were substantial differences in the numbers of participants as well as follow-up durations across the cohorts listed in Table 2, each cohort had a relatively well constrained crude incidence rate of 0.74-2.79 CRC cases per 1,000 person-years. The incidence rate indicates the absolute number of cases of CRC, while the SIR indicates the number of cases of CRC in the sample compared to the number of cases expected in a reference population. For this reason, an SIR was calculated for each outcome of the incidence rate rather than combined. Estimates, tests of heterogeneity and prediction intervals for the two UC outcomes are reported in Table 3 for the primary random-effects model.

Table 3 Primary Random-Effects Meta-Analysis Results

Outcome	k	Q (df)	Pooled estimate	95% CI	I2	tau2	95% prediction interval
UC CRC SIR	4	67.69 (3)	2.86	0.51-16.00	95.6%	1.105	0.02-462.99
UC CRC incidence/1,000 PY	9	19.25 (8)	1.41	1.16-1.72	58.4%	0.018	0.97-2.06

Note. CI = confidence interval; CRC = colorectal cancer; PY = person-years; SIR = standardized incidence ratio; UC = ulcerative colitis. Models used REML and modified Hartung-Knapp inference.

Table 3 shows a marked difference in precision between the two UC models. The synthesis under SIR resulted in a higher relative point estimate, but a very high heterogeneity and prediction interval than the incidence model did. This contrast helps to justify the use of the incidence result as a contemporary descriptive benchmark and the use of the comparative SIR as exploratory and context dependent. No evidence outside UC was required to go into either pooled model; the non-UC estimates that were used in the structured narrative interpretations are shown in Table 4.

Table 4 Structured Narrative Findings for Other Autoimmune Disease Evidence

Study/evidence	Disease/population	Endpoint	Estimate (95% CI)	Interpretive constraint
Everhov et al. (2022)	Elderly-onset Crohn disease; >1 y	CRC	HR 0.69 (0.56-0.86)	Lagged, older population
Everhov et al. (2022)	Elderly-onset UC; >1 y	CRC	HR 0.78 (0.69-0.88)	Lagged, older population
Everhov et al. (2022)	Childhood-onset Crohn disease	CRC	HR 6.46 (3.95-10.60)	Young-onset, long exposure
Everhov et al. (2022)	Childhood-onset UC	CRC	HR 32.50 (23.00-45.90)	Young-onset, long exposure

Study/evidence	Disease/population	Endpoint	Estimate (95% CI)	Interpretive constraint
Lundqvist et al. (2023)	IBD	Early-onset CRC	HR 5.98 (4.78-7.48)	Age-specific endpoint
Loosen et al. (2025)	IBD	CRC	OR 1.53 (1.33-1.75)	Case-control; OR not HR/SIR
Pierret et al. (2024)	Multiple sclerosis	CRC	HR 0.90 (0.84-0.97)	One primary cohort
Ilus et al. (2014)	Celiac disease	CRC	SIR 1.17 (0.43-2.54)	Secondary extraction; wide CI
Shin et al. (2024)	Type 1 diabetes	Colon cancer	aHR 1.37 (1.11-1.68)	Colon only, not combined CRC
Reizner et al. (2025)	Type 1 diabetes	CRC	RR 1.16 (1.07-1.26)	Review aggregate; benchmark only

Note. aHR = adjusted hazard ratio; CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; IBD = inflammatory bowel disease; OR = odds ratio; RR = risk ratio; SIR = standardized incidence ratio; UC = ulcerative colitis. These estimates were not pooled because of nonexchangeable populations, endpoints, effect measures, or evidence sources.

Estimates in Table 4 are all based on different age groups, auto-immune phenotypes, cancer endpoints, and effect measures, and therefore vary significantly. The colon-only estimate for type 1 diabetes is not necessarily comparable to the lagged estimate in elderly onset disease, and the large relative hazards in childhood onset disease cannot be directly compared to those in elderly onset disease. Likewise, single-cohort findings for multiple sclerosis and celiac disease are insufficient to establish stable pooled disease-specific effects. This heterogeneity is central to interpreting the first part of the review question. The psychological component is addressed separately in Table 5 so that evidence concerning stress and anxiety is not conflated with disease-specific autoimmune effect estimates.

Table 5 Evidence on Psychological Stress and Anxiety in Relation to CRC Risk

Study	Design	Exposure	CRC-relevant finding	Direct autoimmune mediation?
van Tuijl et al. (2023)	IPD meta-analysis; 18 cohorts	Depression/anxiety	No association with incident CRC	No
Wang et al. (2020)	Cohort meta-analysis	Depression/anxiety	Cancer-wide association; site heterogeneity	No
Batty et al. (2017)	Pooled cohorts	Psychological distress	Cancer mortality, not incident CRC	No
Pan et al. (2024)	Prospective mediation study	Depression/anxiety and behaviors	Cancer incidence; no autoimmune pathway	No
Basten et al. (2024)	Prospective cohort	Psychosocial factors	Cancer incidence context	No

Note. CRC = colorectal cancer; IPD = individual participant data. These contextual studies inform the review of the psychological component but cannot establish mediation or effect modification of an autoimmune disease-CRC association.

Taken together, Tables 1-5 distinguish the interconnected but analytically separate components of the review title: autoimmune disease-CRC associations, quantitative CRC risk and incidence in the UC evidence stream, and the potential role of psychological stress and anxiety.

Only the UC comparative-risk and incidence questions had sufficiently compatible quantitative inputs for meta-analysis. Psychological literature contributes to interpretation of the proposed role, but the absence of autoimmune-specific mediation or interaction studies prevents a causal or pooled psychological estimate. Keeping these streams separate reduces the risk of producing a statistically precise but clinically uninterpretable result.

Discussion Principal Findings

This evidence synthesis demonstrates that the included evidence base is adequate for two

narrow UC analyses but not for an all-autoimmune meta-analysis. The pooled UC SIR point estimate was elevated, yet modified Hartung-Knapp inference and the prediction interval exposed profound uncertainty. In contrast, pooled UC incidence was comparatively stable at approximately

1.4 cases per 1,000 person-years. The apparent conflict is informative: a single-arm incidence benchmark can be estimated with reasonable precision even when the relative comparison against heterogeneous reference populations is unstable.

The third review objective concerned the role of psychological stress and anxiety in the autoimmune disease-CRC relationship. The available evidence resolves only part of that question. General-population evidence does not support a large direct association between depression or anxiety and incident CRC, while no eligible autoimmune-specific study tested whether psychological stress or anxiety mediates or modifies CRC risk. The role of these factors should therefore be described as unresolved: a mediating or modifying pathway has not been demonstrated, but the absence of direct studies also means that disease-specific indirect pathways cannot be excluded.

Comparison With Previous Evidence

The incident rate we combined is similar to the reported incident rate of 1.47 per 1,000 person-years by Zhang, Zhang et al. (2025) and 1.58 per 1,000 person-years by Castaño-Milla et al. (2014). The convergence indicates that the incidence of the current period is notably lower than the historical estimate of 3/1,000 person-years used in earlier syntheses (Eaden et al., 2001), but this is not a direct estimate of the change in incidence over time, as the difference in cohort composition and surveillance may also be partly responsible for this convergence (Castaño-Milla et al., 2014; Zhang, Zhang, et al., 2025).

The SIR point estimate of 2.86 is consistent with the prior pooled estimates in the range of 1.7–2.5, but had a large uncertainty range due to the deliberate use of only four recent SIR studies, and conservative small-sample inference (Jess et al., 2012; Lutgens et al., 2013; Zhang, Zhang, et al., 2025). The practical implications of the choice of method when k is small is demonstrated in this example by the significant DerSimonian-Laird model compared to the nonsignificant modified Hartung-Knapp interval (IntHout et al., 2014).

As described by Reizner et al. (2025), outcomes are disease specific and conclusions can change if the data is biased or outliers are removed from the data set. Modest inverse association with the MS should be considered a hypothesis for confirmation only and not a causal effect (Pierret et al., 2024); modest positive association with the type 1 diabetes should be interpreted similarly (Reizner et al., 2025; Shin et al., 2024). The overall pooled risk ratio of 1.24 reported by Cheng et al. (2025) across a broad set of non-UC autoimmune diseases is directionally consistent with the disease-specific elevations summarized in Table 4, but because that analysis combines disease categories, endpoints, and populations that are not exchangeable with the present review's models, it is best read as corroborating context rather than as a pooled estimate this review could have adopted directly.

Clinical and Biological Interpretation

The association of CRC with UC is likely to be attributable to the build-up of inflammatory burden, rather than the diagnosis itself. A longer duration, a larger extent, persistent activity, primary sclerosing cholangitis, and a family history of PSC identify higher-risk groups, while good control of inflammation and surveillance could help decrease the incidence observed or cause the diagnosis to be shifted towards earlier disease (Krugliak Cleveland et al., 2022; Ullman & Itzkowitz, 2011; Wijnands et al., 2021).

Therefore, high heterogeneity should not be considered as just statistical noise. It is likely due to variations in the age at onset, severity of the disease, treatment, colectomy, surveillance, calendar time, background CRC incidence and construction of the reference population. The wide SIR prediction interval highlights the need to take these contextual factors into account when using the pooled mean in an individual health system.

This is supported by the age-specific evidence of the IBDs. Given that childhood-onset disease results in decades of potential inflammatory exposure and may have a low baseline CRC incidence, while elderly-onset analyses have high baseline CRC incidence, competing mortality and robust early diagnosis surveillance, the large relative effects of childhood-onset disease on

CRC incidence should be interpreted with caution (Everhov, Erichsen, et al., 2022; Everhov, Ludvigsson, et al., 2022). These strata should be kept separate for future meta-regression and individual-participant-data.

Role of Psychological Stress and Anxiety

There are two complementary findings in the psychological literature. First, van Tuijl et al. (2023) conducted a PSY-CA (Psychosocial Factors and Cancer Incidence) individual-participant-data meta-analysis that did not reveal an association between depression or anxiety and CRC incidence among the general population, suggesting that the potential direct psychological effect on CRC incidence is likely to be small. Second, broader studies have looked at how psychosocial factors, health behaviors, interaction and mediation relate to cancer incidence, which provides pathways that can be tested analytically without establishing an autoimmune specific pathway of interaction and mediation between these factors and CRC. The present review thus suggests that psychological stress and anxiety are not established mediators of autoimmune-associated CRC, but rather that this is a significant research gap.

Further measurements of the psychological outcome following the diagnosis of the autoimmune disease but prior to the diagnosis of CRC, detailed information on disease activity and treatment, history of surveillance colonoscopy, detailed information on lifestyle factors and formal causal mediation and interaction approaches would be needed for a definitive evaluation of this role. In other autoimmune groups, with a lower prevalence of CRC, such studies would probably necessitate linked national registries, large prospective cohorts and/or pooled individual patient data, instead of a small clinical sample.

LIMITATIONS

The biggest constraint is the lack of a systematic search across multiple databases to put evidence together; the evidence was collated by citation chasing. However, due to the fact that the database-derived hit counts are not complete, de-duplication is not possible between the different exports of the databases, and the independent screening of duplicates is not performed, it is not possible to be certain of the completeness of the eligible study set (Page et al., 2021). Because of this search strategy, together with the absence of prospective registration, this review does not meet full PRISMA 2020 or AMSTAR-2 standards for a database-derived systematic search, and it is reported here as a structured narrative review with a focused meta-analysis of ulcerative colitis rather than as a complete systematic review.

Secondly, judgments were not completed for items. If time constraints require prioritization, the 13 studies feeding the two pooled models (4 SIR and 9 incidence cohorts, noting overlap) should be assessed first, since they anchor the paper's headline quantitative estimates. Until that assessment is completed, the manuscript can thus not be accompanied by a formal risk-of-bias figure, a sensitivity analysis on excluding studies rated as having serious risk of bias, or a GRADE certainty table. Thirdly, one SIR confidence interval was created using secondary data and needs to be validated in the primary article. Fourth, incidence models employed crude events and person-time and were unable to account for age, sex, extent of disease, treatment and surveillance. Fifth, the small SIR model does not allow the testing for publication bias or meta-regression and the prediction interval is quite unstable. Sixth, multiple non-UC estimates were derived from other national registries/review level extraction, which did not allow pooling across the estimates. Seventh, the psychological evidence was largely context and was not combined with an autoimmune cohort of participants, and did not contain temporally ordered stress or anxiety measures and incident CRC, which means that a psychological role (mediation or effect modification) could not be quantified.

CONCLUSION

This systematic review and meta-analysis supports a contemporary quantitative synthesis of CRC incidence in UC and an exploratory comparative SIR synthesis, while other autoimmune diseases require disease-specific interpretation because their evidence is sparse and nonexchangeable. Contemporary UC incidence was 1.41 per 1,000 person-years, whereas the comparative SIR point estimate of 2.86 was highly uncertain under conservative small-study inference. Regarding the role of psychological stress and anxiety, available general-population evidence does not support a large direct association with incident CRC, but no eligible autoimmune-specific study tested mediation or effect modification. Psychological stress and anxiety should therefore be regarded as an unresolved component of the autoimmune disease-CRC relationship rather than as an established causal pathway. The conclusions remain constrained by incomplete database-derived searching, risk-of-bias assessment, and primary-source verification.

Declarations

Protocol and Registration. The review protocol was not prospectively registered.

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Conflicts of Interest. The author reports no conflicts of interest.

Data Availability. All study-level numerical data used in the quantitative syntheses are reported in the manuscript tables. No individual participant data were generated or analyzed for this study. The primary articles remain subject to their publishers' access and copyright terms. The extraction dataset underlying Tables 1–5 will be deposited in a public repository (e.g., OSF) with a citable DOI prior to submission.

Author Contributions. [Author name to be inserted]: conceptualization, methodology, data curation, formal analysis, visualization, interpretation, and writing.

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Appendix A: Database Search Strategies Developed for Verification

PubMed - Autoimmune Disease and CRC

(("Autoimmune Diseases"[Mesh] OR autoimmune*[tiab] OR "immune-mediated"[tiab] OR "inflammatory bowel disease"[tiab] OR "ulcerative colitis"[tiab] OR "Crohn Disease"[Mesh] OR celiac*[tiab] OR "systemic lupus erythematosus"[tiab] OR "multiple sclerosis"[tiab] OR psoriasis[tiab] OR "rheumatoid arthritis"[tiab] OR "type 1 diabetes"[tiab]) AND ("Colorectal Neoplasms"[Mesh] OR colorectal cancer*[tiab] OR colon cancer*[tiab] OR rectal cancer*[tiab]) AND (cohort[tiab] OR "case-control"[tiab] OR "hazard ratio"[tiab] OR "risk ratio"[tiab] OR "standardized incidence ratio"[tiab])) AND ("2011/01/01"[Date - Publication] : "2026/08/20"[Date - Publication])

PubMed - Psychological Stress or Anxiety

(("Stress, Psychological"[Mesh] OR "Anxiety"[Mesh] OR stress*[tiab] OR anxiety[tiab] OR distress[tiab] OR depression[tiab]) AND ("Colorectal Neoplasms"[Mesh] OR colorectal cancer*[tiab]) AND (autoimmune*[tiab] OR "immune-mediated"[tiab] OR "inflammatory bowel disease"[tiab])) AND ("2011/01/01"[Date - Publication] : "2026/08/20"[Date - Publication])