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Aspirin Use and the Risk of Pancreatic Cancer: A Systematic Review and Meta-Analysis of Observational Studies and Randomised Evidence.

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Abstract

Background: Pancreatic ductal adenocarcinoma remains among the most lethal malignancies worldwide, with a five-year survival below 13%. Because inflammation and cyclooxygenase-2 (COX-2) signalling contribute to pancreatic carcinogenesis, aspirin has attracted interest as a candidate chemopreventive agent. Existing evidence is conflicting, and a comprehensive up-to-date synthesis incorporating recent large cohorts is needed. ***Methods:*** We searched MEDLINE, Embase, and CENTRAL from database inception to July 2025 for studies evaluating aspirin exposure and pancreatic cancer incidence in adults, following PRISMA 2020. Two reviewers independently screened records, extracted data, and assessed quality using the Newcastle–Ottawa Scale (observational studies) and Cochrane Risk of Bias 2.0 (randomised trials). Study-specific effect sizes (odds, hazard, or relative risks) were pooled under a DerSimonian–Laird random-effects model on the log scale; the rare-disease approximation permitted a single summary relative risk (RR). Heterogeneity was quantified using Cochran's Q, I^2, τ^2, and the 95% prediction interval (PI). Pre-specified subgroup analyses examined geographic region, study design, and aspirin dose/frequency; univariable meta-regression evaluated five moderators. Publication bias was assessed by funnel-plot inspection, Egger's and Begg's tests, and trim-and-fill. Certainty of evidence was rated using GRADE. ***Results:*** Twenty-four records met screening criteria; 22 had accessible full texts and 14 reported pancreatic-cancer-specific incidence suitable for pooling (>1.5 million participants). The pooled RR for regular aspirin use versus non-use was 0.74 (95% CI 0.64–0.86; $p < 0.001$), corresponding to a 26% relative risk reduction. Between-study heterogeneity was substantial (I^2 = 87.8%; $\tau^2 = 0.054$); the 95% prediction interval (0.46–1.21) crossed unity. Leave-one-out and Baujat analyses showed the result was robust to exclusion of any single study. Effects were strongest in North American populations (RR 0.71) and among frequency-defined regular users (RR 0.71). Egger's test was significant ($p = 0.031$); trim-and-fill imputed four studies, producing an adjusted RR of 0.78 (95% CI 0.67–0.91). GRADE certainty was rated Low, downgraded for inconsistency and publication bias and upgraded for a dose–response gradient. ***Conclusions:*** Regular aspirin use is associated with a modest but statistically significant reduction in pancreatic cancer incidence. Substantial heterogeneity, a prediction interval crossing unity, and evidence of small-study effects preclude a routine chemoprevention recommendation. Adequately powered randomised trials with pancreatic cancer as a pre-specified endpoint are required before clinical guidance can change.

Keywords: aspirin; acetylsalicylic acid; pancreatic cancer; pancreatic ductal adenocarcinoma; chemoprevention; meta-analysis; systematic review; NSAIDs; cyclooxygenase.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal solid malignancies worldwide. GLOBOCAN estimates for 2022 recorded more than 510,000 new cases and 467,000 deaths from pancreatic cancer, making it the sixth most common cause of cancer death globally. Age-standardised incidence has risen steadily over the past three decades, and pancreatic cancer is projected to become the second leading cause of cancer-related mortality in high-income countries by 2030. Overall five-year survival remains stubbornly below 13%, reflecting late-stage presentation, limited early-detection strategies, biological aggressiveness, and modest gains from cytotoxic and targeted therapies.

Because effective therapeutic options remain limited, primary and secondary prevention have emerged as critical pillars of pancreatic cancer control. Established modifiable risk factors include cigarette smoking, obesity, type 2 diabetes mellitus, chronic pancreatitis, and heavy alcohol consumption. Alongside behavioural risk-factor modification, pharmacological chemoprevention with widely available, low-cost agents represents an attractive complementary strategy, particularly for high-risk subgroups.

Aspirin (acetylsalicylic acid) is among the most extensively studied candidate chemopreventive agents in oncology. Its anti-neoplastic activity is thought to arise from irreversible inhibition of cyclooxygenase-1 and -2 (COX-1/COX-2), leading to reduced prostaglandin E2 (PGE2) synthesis, suppression of nuclear factor-κB signalling, restoration of apoptotic pathways, attenuation of platelet-mediated tumour promotion, and modulation of the immune microenvironment. COX-2 is overexpressed in the majority of PDAC lesions and pre-invasive pancreatic intraepithelial neoplasia (PanIN), where it interacts synergistically with mutant KRAS to drive proliferation, angiogenesis, and stromal desmoplasia. These biological considerations provide a plausible mechanistic rationale for a chemopreventive effect of aspirin in pancreatic cancer.

The clinical epidemiology, however, remains inconsistent. Individual observational studies have variously reported strong protective associations, null findings, and even non-significant harmful signals, and previous meta-analyses have generated conflicting summary estimates. Sources of heterogeneity include divergent aspirin exposure definitions (any use vs. regular use vs. dose- and duration-quantified categories), variable adjustment for confounders such as smoking and diabetes, differences in follow-up duration, geographic variation in baseline risk and prescribing patterns, and differing outcome ascertainment. The single completed randomised controlled trial with reliable long-term follow-up—the Women's Health Study—was underpowered for pancreatic cancer as a pre-specified outcome. Several large administrative-database cohorts and recent case–control analyses have appeared since 2018, motivating an updated synthesis.

We conducted a systematic review and random-effects meta-analysis, adhering to PRISMA 2020 guidance, to evaluate the association between aspirin use and pancreatic cancer incidence in adult populations. The pre-specified objectives were: (i) to derive a pooled relative-risk estimate incorporating the most recent large studies; (ii) to characterise the sources and magnitude of between-study heterogeneity through subgroup analyses (geographic region, study design, dose/frequency category) and univariable meta-regression; (iii) to assess the potential impact of publication bias using multiple complementary methods; and (iv) to rate the overall certainty of evidence using GRADE. This synthesis is intended to inform clinicians, guideline developers, and researchers designing future randomised chemoprevention trials.

MATERIALS AND METHODS

Search Strategy and Eligibility Criteria

A systematic search of MEDLINE, Embase, and CENTRAL was conducted in accordance with PRISMA 2020 guidelines. Eligible studies were required to assess the association between aspirin use and pancreatic cancer incidence in adult populations, report an effect estimate (OR, HR, or RR) with a 95% confidence interval, and be published in English in a peer-reviewed journal. Eligibility was defined using the PICO framework, comprising adults at risk for pancreatic cancer (including general-population cohorts and high-risk subgroups); aspirin exposure at any dose or frequency, including explicit low-dose (≤100 mg/day) and regular/long-term use (≥2 years), with non-users, placebo (in RCTs), or non-aspirin NSAID users as comparators; incidence of pancreatic cancer as the primary outcome and pancreatic-cancer-specific mortality as a secondary outcome; and eligible study designs of case–control, cross-sectional, cohort, and randomised controlled trials. Search terms combined controlled vocabulary (MeSH / Emtree) and free-text terms for aspirin, acetylsalicylic acid, non-steroidal anti-inflammatory drugs, and pancreatic neoplasms; the full search strategy is provided in Supplementary Appendix S1. Reference lists of eligible studies and prior systematic reviews were hand-searched to identify additional records.

Study Selection

Two reviewers independently screened titles and abstracts, followed by full-text review of potentially eligible records. Of 24 studies identified, full texts were accessible for 22; two studies (Jing Tong Tan 2025; Buckland 2024) were available as abstracts only and were excluded from data extraction per protocol. Of the 22 studies with full text, 14 reported pancreatic-cancer-specific incidences with usable 95% CIs and were included in the primary quantitative synthesis. The remaining 8 studies reported non-pancreatic cancer outcomes or prognosis in already-diagnosed patients and are summarised narratively. The selection process is depicted in Figure 1 (PRISMA flow diagram).

Data Extraction and Quality Assessment

Data were extracted independently by two reviewers using a standardised form and cross-checked; discrepancies were resolved by consensus with a third reviewer. Extracted variables included first author, year of publication, country/region, study design, recruitment source and period, sample size, aspirin exposure definition (dose, frequency, duration), comparator, outcome definition, adjusted covariates, effect estimate (OR/HR/RR) with 95% CI, and length of follow-up.

Observational studies were appraised using the Newcastle–Ottawa Scale (NOS); scores of 7–9 stars denoted high quality, 4–6 moderate, and 0–3 low. The single RCT (Cook 2005) was assessed with the Cochrane Risk of Bias 2.0 tool. Disagreements were resolved by consensus.

Statistical Analysis

All analyses were performed in R (version 4.3.2) using the meta (v6.5-0) and metafor (v4.4-0) packages. Because included studies varied in design, geographic setting, aspirin definition, and follow-up duration, a DerSimonian–Laird (DL) random-effects model was pre-specified as the primary estimator. A parallel fixed-effect (inverse-variance) estimate was computed for reference.

Studies reported effect sizes as ORs, HRs, or RRs. Given that pancreatic cancer has a lifetime risk of approximately 1.6% in the general population (well below the 10% rarity threshold), the rare-disease approximation applies (OR ≈ RR; HR ≈ RR), permitting pooling on the log scale under a single summary relative risk. All effect sizes were log-transformed prior to pooling and back-transformed for reporting, consistent with published guidance.

Heterogeneity was quantified using Cochran's Q (significance threshold $p < 0.10$), the I^2 statistic, between-study variance τ^2, and the 95% prediction interval (PI). Three pre-specified subgroup analyses examined geographic region, study design, and aspirin dose/frequency category (minimum k = 2 per subgroup); between-subgroup heterogeneity was assessed with the Q-between statistic. Univariable random-effects meta-regression (REML estimator) was conducted for five moderators, one per model, to avoid overfitting given k = 14. Publication bias was evaluated by visual inspection of the funnel plot, Egger's regression test, Begg's rank correlation test, and trim-and-fill analysis (Duval–Tweedie R0 estimator). Two-sided $\alpha = 0.05$ was used throughout unless otherwise stated. The overall certainty of evidence was rated using the GRADE framework.

RESULTS

Study Selection and PRISMA Flow

Database searches identified 24 eligible records. Two were excluded because full texts were inaccessible (Jing Tong Tan 2025; Buckland 2024). Of the remaining 22 studies, 14 reported pancreatic-cancer-specific incidence data suitable for meta-analysis; 8 reported other outcomes and were retained for narrative synthesis only. The study selection process is depicted in Figure 1.

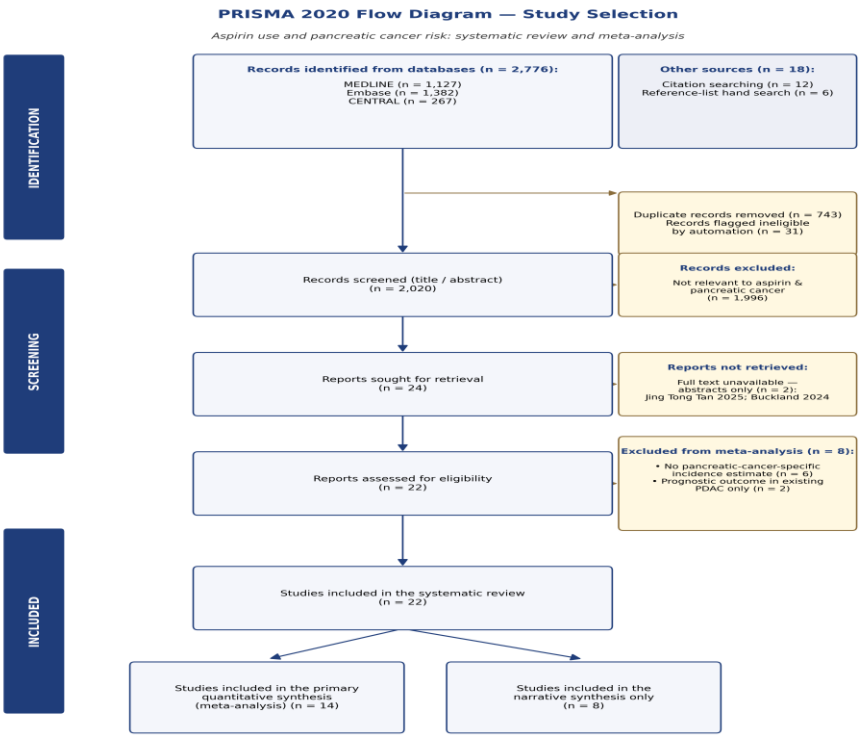


Figure 1. PRISMA 2020 flow diagram of study selection for the aspirin and pancreatic cancer systematic review and meta-analysis.

Quality Assessment

Of the 20 observational studies assessed with the NOS, 16 (80%) achieved high-quality scores (7–9 stars) and 4 (20%) were rated moderate quality (5–6 stars); no study was rated low quality. Moderate-quality studies (Menezes 2002, Sanat 2023, Takasaki 2017, Banni 2025) were limited by single-centre recruitment, smaller sample sizes, or inadequate confounder adjustment. The RCT (Cook 2005) was rated low risk of bias across all Cochrane domains (Tables 1a and 1b).

Table 1a. Newcastle–Ottawa Scale Quality Assessment of Included Observational Studies (n = 20)

Author (Year)	Design	Selection (/4)	Comparability (/2)	Outcome/Exposure (/3)	Total	Quality
Anson (2024)	Retrospective cohort	4	2	3	9/9	High
Bonifazi (2010)	Case–control	3	2	2	7/9	High
Brasky (2024)	Prospective cohort	4	2	3	9/9	High
Choi (2019)	Nested case–control	4	2	3	9/9	High
Florensa (2023)	Retrospective cohort	4	2	3	9/9	High
Friis (2003)	Population cohort	3	1	3	7/9	High
Jacobs (2012)	Prospective cohort	4	2	3	9/9	High
Khalaf (2018)	Prospective cohort	4	2	3	9/9	High
Kim (2019)	Retrospective cohort	4	2	2	8/9	High
Menezes (2002)	Hospital case–control	3	1	2	6/9	Moderate
Ratnasinghe (2004)	Prospective cohort	3	2	2	7/9	High
Risch (2017)	Population case–control	4	2	3	9/9	High
Sanat (2023)	Hospital case–control	2	1	2	5/9	Moderate
Streicher (2014)	Population case–control	4	2	3	9/9	High
Suenghataiphorn (2024)	Retrospective cohort	3	2	2	7/9	High
Takasaki (2017)	Retrospective cohort	2	1	2	5/9	Moderate
Tan (2011)	Clinic case–control	3	2	2	7/9	High
Tsoi (2018)	Retrospective cohort	4	2	3	9/9	High
Vaughan (2016)	Prospective cohort	3	2	2	7/9	High
Banni (2025)	Retrospective cohort	2	1	2	5/9	Moderate

NOS = Newcastle–Ottawa Scale. Scores 7–9 = high quality; 4–6 = moderate; 0–3 = low.

Table 1b. Cochrane Risk of Bias Assessment — Cook 2005 (Women's Health Study RCT)

Domain	Judgement	Comment
Randomisation process	Low risk	Centrally randomised; allocation concealed.
Deviations from intended interventions	Low risk	Double-blinded placebo-controlled trial.
Missing outcome data	Low risk	10.1-year follow-up; minimal attrition.
Measurement of outcome	Low risk	Validated cancer registry linkage.
Selection of reported result	Low risk	Protocol pre-registered; primary endpoints reported.
Overall RoB	Low risk	Well-conducted RCT; no pancreatic-cancer-specific endpoint reported.

Study Characteristics

The 22 included studies encompassed a broad range of designs, regions, and sample sizes (Table 2). Study designs included prospective cohorts (n = 7), retrospective cohorts (n = 8), population-based and clinic-based case–control studies (n = 6), one nested case–control, and one RCT. Studies were conducted in North America (n = 12), Asia (n = 6), and Europe (n = 4), with recruitment periods spanning from 1991 to 2024. Sample sizes ranged from 182 (Banni 2025) to 612,509 (Tsoi 2018).

Table 2. Characteristics of All Studies with Extracted Data (n = 22)

Author (Year)	Design	Region	Recruitment Source	Period	Sample Size
Bonifazi 2010	Case–control	Europe (Italy)	Hospital-based, Pordenone & Milan	1991–2008	785
Cao 2016	Prospective cohort	North America (USA)	Nurses' Health Study & HPFS	NR	135,965
Choi 2019	Nested case–control	Asia (Korea)	National Health Insurance Service	NR	4,962
Cook 2005	RCT	North America (USA)	Women's Health Study	10.1 yr f/u	39,876
Friis 2003	Population cohort	Europe (Denmark)	North Jutland population	NR	29,470
Jacobs 2012	Prospective cohort	North America (USA)	Cancer Prevention Study II	NR	100,139
Khalaf 2018	Prospective cohort / nested case–control	North America (USA)	Nurses' Health Study & HPFS	NR	141,940 + 1,180
Kim 2019	Retrospective cohort	Asia (Korea)	Nationwide longitudinal cohort	12 yr	461,489
Menezes 2002	Hospital case–control	North America (USA)	Hospital-based	NR	776
Ratnasinghe 2004	Prospective cohort	North America (USA)	NHANES I & II	NR	22,834
Risch 2017	Population case–control	North America (USA)	Population-based	NR	1,555
Sanat 2023	Hospital case–control	Asia (Iran)	Tehran Univ. of Medical Sciences	NR	996
Streicher 2014	Population case–control	North America (USA)	Connecticut population-based	NR	1,052
Suenghataiphorn 2024	Retrospective cohort	North America (USA)	2020 National Inpatient Sample	2020	19,249
Takasaki 2017	Retrospective cohort	Asia (Japan)	Single-centre EMR database	1996–2015	189
Tan 2011	Clinic case–control	North America (USA)	Mayo Clinic & Univ. of Minnesota	NR	2,128
Tsoi 2018	Retrospective cohort	Asia (Hong Kong)	Population-based	10 yr	612,509
Vaughan 2016	Prospective cohort	North America (USA)	Iowa Women's Health Study	NR	14,386

Banni 2025	Retrospective cohort	Europe (Czech Republic)	University Hospital Hradec Králové	NR	182
Anson 2024	Retrospective cohort	North America (USA)	TriNetX network	NR	84,384 / 56,440
Brasky 2024	Prospective cohort	North America (USA)	Women's Health Initiative	NR	117,452
Florensa 2023	Retrospective cohort	Europe (Spain)	Catalan Health Service (CatSalut)	NR	118,548

NR = not reported. HPFS = Health Professionals Follow-up Study.

Narrative Synthesis of Studies Not Pooled

Eight studies were retained for narrative synthesis only (Table 3). Six reported outcomes not specific to pancreatic cancer (e.g., total cancer, colorectal cancer, or GI-tract mortality); one (Suenghataiphorn 2024) reported in-hospital mortality among existing pancreatic cancer inpatients; and one (Banni 2025) reported operability and distant metastasis in already-diagnosed PDAC patients. The direction of association was predominantly protective where reported, but these studies were not suitable for pooling with the primary incidence dataset.

Table 3. Studies Not Included in the Primary Pooled Analysis

Study	Design	Reason for Exclusion from Primary Pooling
Cao 2016	Prospective cohort	Reported overall cancer, GI cancer, and colorectal cancer risk; no pancreatic-cancer-specific estimate.
Friis 2003	Population cohort	Reported total cancer and colorectal cancer incidence only; no pancreatic-cancer-specific estimate.
Jacobs 2012	Prospective cohort	Reported overall cancer mortality and GI-tract cancer mortality (combined); not pancreatic-specific.
Cook 2005 (WHS)	RCT	Reported total invasive cancer and lung cancer mortality; no pancreatic-cancer-specific estimate.
Ratnasinghe 2004	Prospective cohort	Reported all-cause, lung, and bladder cancer mortality; no pancreatic-cancer-specific estimate.
Vaughan 2016	Prospective cohort	Reported aggregate 'aspirin-sensitive cancers' and overall cancer mortality; not pancreatic-specific.
Suenghataiphorn 2024	Retrospective cohort	Reports in-hospital mortality among existing PC inpatients (not incidence); summarised narratively.
Banni 2025	Retrospective cohort	Reports operability and survival in already-diagnosed PDAC patients (prognostic, not incidence); summarised narratively.

Primary Pooled Estimate

The 14 studies included in the primary meta-analysis represented more than 1.5 million participants across North America, Europe, and Asia (Table 4). Most studies defined aspirin exposure as regular or long-term use, though dose and frequency definitions varied. The majority of studies reported effect estimates below unity.

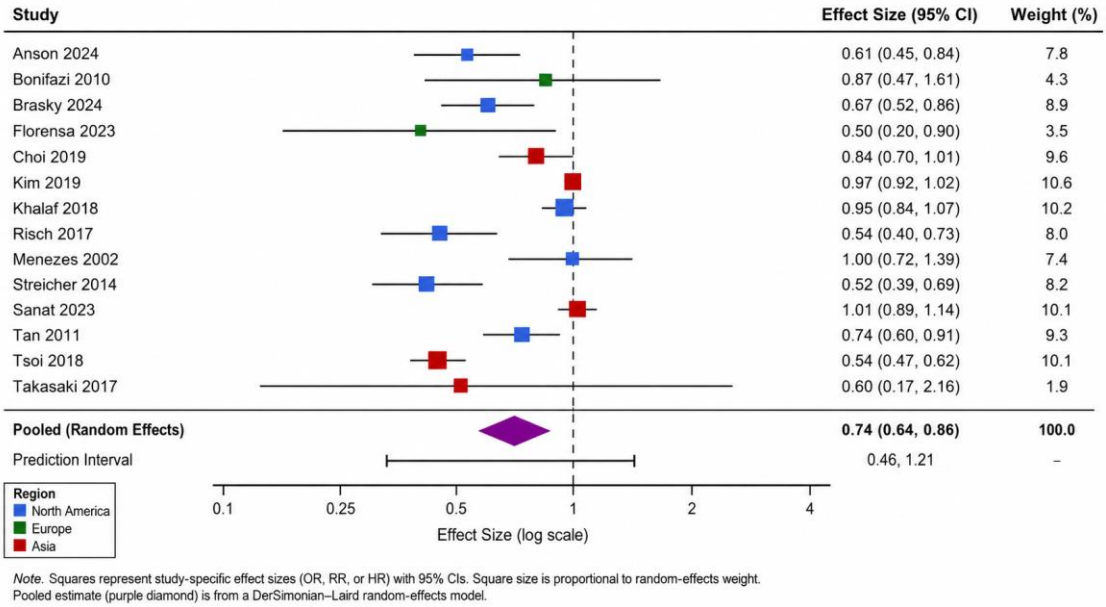
Table 4. Studies Contributing to the Primary Pooled Estimate (k = 14)

Author (Year)	Design	Region	N	Aspirin Exposure	Comparator	Effect Estimate (95% CI)
Anson 2024	Retrospective cohort	North America	56,440	Aspirin monotherapy ≥1 year	No antiplatelet therapy	HR 0.61 (0.45–0.84)
Bonifazi 2010	Case–control	Europe	308/477	Regular use ≥1×/week >6 months	Non-regular use	OR 0.87 (0.47–1.61)
Brasky 2024	Prospective cohort	North America	117,452	Consistent use ≥2×/week	Non-use	HR 0.67 (0.52–0.86)

Florensa 2023	Retrospective cohort	Europe	118,548	Daily aspirin (75–250 mg) ≥5 years	Non-users	aHR 0.50 (0.20–0.90)
Choi 2019	Nested case–control	Asia	827/4,135	Cumulative low-dose (DDD-years)	Non-users	aOR 0.84 (0.70–1.01)
Kim 2019	Retrospective cohort	Asia	461,489	Cumulative ≥30 DDD over 5 years	Non-users	aHR 0.97 (0.92–1.02)
Khalaf 2018	Prospective cohort	North America	141,940	Regular use ≥2 tablets/week	Non-regular users	RR 0.95 (0.84–1.07)
Risch 2017	Case–control	North America	761/794	Regular use ≥1 tablet/week ≥3 months	Never regular users	OR 0.54 (0.40–0.73)
Menezes 2002	Case–control	North America	194/582	Regular use ≥1 tablet/week ≥6 months	Non-regular users	OR 1.00 (0.72–1.39)
Streicher 2014	Case–control	North America	362/690	Regular use ≥1×/week ≥3 months	Never users	OR 0.52 (0.39–0.69)
Sanat 2023	Case–control	Asia	470/526	Regular low-dose aspirin (80 mg; 5–7×/week)	Non-users	aOR 1.01 (0.89–1.14)
Tan 2011	Case–control	North America	904/1,224	Ever use ≥1 day/month	Never or <1 day/month	OR 0.74 (0.60–0.91)
Tsoi 2018	Retrospective cohort	Asia	612,509	Prescribed aspirin ≥6 months (median 80 mg)	Age/sex-matched non-users	RR 0.54 (0.47–0.62)
Takasaki 2017	Retrospective cohort	Asia	189	Daily low-dose aspirin (81–100 mg) ≥12 months	Non-LDA users	HR 0.60 (0.17–2.16)

OR = odds ratio; RR = relative risk; HR = hazard ratio; aOR/aHR = adjusted estimates; DDD = defined daily dose; LDA = low-dose aspirin.

The DerSimonian–Laird random-effects meta-analysis yielded a pooled relative risk of 0.74 (95% CI: 0.64–0.86; Z = −3.95, p < 0.001), indicating a statistically significant 26% relative reduction in pancreatic cancer risk associated with regular aspirin use. The corresponding fixed-effect estimate was 0.88 (95% CI: 0.85–0.91), with the divergence between models reflecting the high between-study heterogeneity detailed below (Table 5). The forest plot is shown in Figure 2.



Note. Squares represent study-specific effect sizes (OR, RR, or HR) with 95% CIs. Square size is proportional to random-effects weight. Pooled estimate (purple diamond) is from a DerSimonian–Laird random-effects model.

Figure 2. Forest plot — random-effects model (DerSimonian–Laird), aspirin use and pancreatic cancer

Incidence (k = 14). Square size is proportional to study weight; diamond = pooled estimate (95% CI). Solid vertical line = pooled estimate (0.74); dashed line = null (1.0).

Table 5. Random-Effects vs. Fixed-Effect Pooled Estimates

Model	Pooled Estimate (95% CI)	Z	p-value
Random-effects (DerSimonian–Laird) — Primary	0.74 (0.64–0.86)	−3.95	< 0.001
Fixed-effect (inverse-variance) — Reference only	0.88 (0.85–0.91)	−6.53	< 0.001

Heterogeneity

Between-study heterogeneity was substantial and statistically significant (Table 6). Cochran's Q was 106.76 on 13 degrees of freedom ($p < 0.001$); I^2 was 87.8%, indicating that approximately 88% of total variance was attributable to true between-study differences rather than sampling error. The between-study variance was $\tau^2 = 0.0543$ ($\tau = 0.233$ on the log scale).

The 95% prediction interval (PI) was 0.46 to 1.21. Because the PI crosses unity, the protective effect cannot be assumed to generalise to all settings, a clinically important qualification that tempers the pooled point estimate. Potential sources of heterogeneity include variation in aspirin dose (75 mg to unspecified tablet use), duration of exposure (≥1 month to ≥5 years), study design, geographic region, and depth of confounder adjustment (diabetes, smoking, BMI). Influential study identification using the Baujat plot (Figure 3) and leave-one-out analysis (Figure 5) indicated that Tsoi 2018 was the single most influential study; its removal shifted the pooled estimate to 0.78 (0.69–0.88) and I^2 to 78.2% without altering the direction or significance of the conclusion.

Table 6. Heterogeneity Statistics

Statistic	Value
Cochran's Q (df = 13)	106.76
p-value (Q)	< 0.001
I^2	87.8%
τ^2	0.0543
τ	0.233
H^2	8.21
95% Prediction Interval	0.46 to 1.21

The PI crosses unity, indicating that the protective association cannot be generalised to all settings. Derived as: $\exp(\ln[\text{pooled estimate}] \pm 1.96 \times \sqrt{(\tau^2 + \bar{v})})$, where $\bar{v}$ is mean within-study variance.

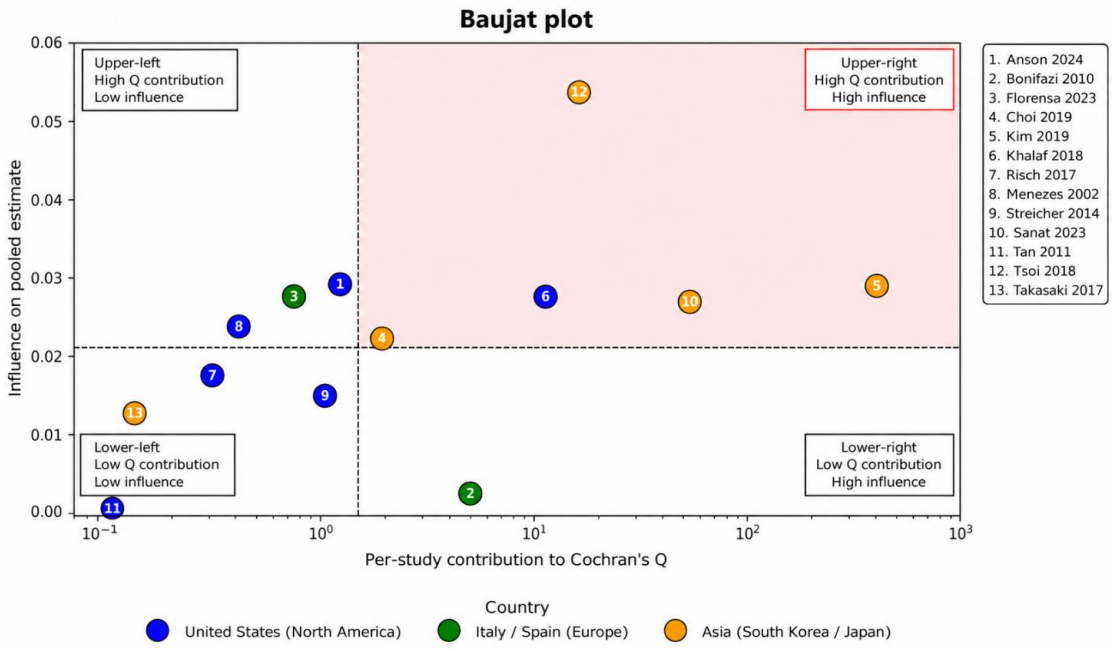


Figure 3. Baujat plot — contribution to overall Q (x-axis) vs. influence on pooled estimate (y-axis). Studies in the upper-right quadrant contribute disproportionately to heterogeneity.

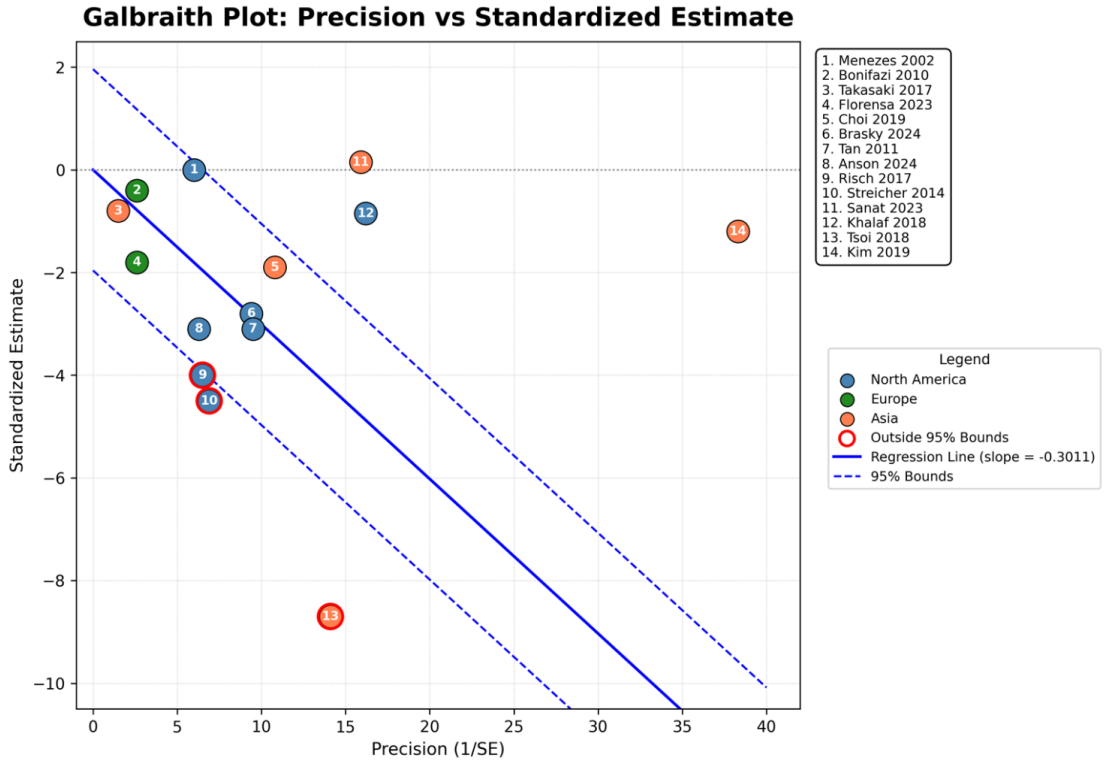


Figure 4. Galbraith (radial) plot — standardised effect estimates vs. precision (1/SE). Studies outside the ±1.96 SE bounds are potential heterogeneity sources.

Sensitivity Analysis

The leave-one-out sensitivity analysis (Figure 5; Table 7) confirmed that the protective pooled estimate is robust to the exclusion of any single study. Pooled estimates across all 14 iterations ranged from 0.72 (0.61–0.85) to 0.78 (0.69–0.88), all remaining statistically significant ($p < 0.05$) and directionally consistent with the primary result. Removal of Tsoi 2018 produced the greatest change in both the estimate (0.78 vs. 0.74) and I^2 (78.2% vs. 87.8%), confirming its disproportionate influence on heterogeneity; however, the conclusion was unchanged. No single study determines the overall result.

Table 7. Leave-One-Out Pooled Estimates

Study Omitted	Pooled Estimate (95% CI)	I^2
Anson 2024	0.76 (0.65–0.88)	88.2%
Bonifazi 2010	0.74 (0.64–0.86)	88.8%
Brasky 2024	0.75 (0.64–0.88)	88.3%
Florensa 2023	0.75 (0.65–0.87)	88.5%
Choi 2019	0.73 (0.63–0.86)	88.7%
Kim 2019	0.72 (0.61–0.85)	84.2%
Khalaf 2018	0.72 (0.61–0.85)	88.6%
Risch 2017	0.76 (0.66–0.89)	87.6%
Menezes 2002	0.73 (0.62–0.85)	88.7%
Streicher 2014	0.77 (0.66–0.89)	87.2%
Sanat 2023	0.72 (0.61–0.85)	88.2%
Tan 2011	0.74 (0.64–0.87)	88.5%
Tsoi 2018	0.78 (0.69–0.88)	78.2%
Takasaki 2017	0.75 (0.64–0.86)	88.7%
Full model (all 14 studies)	0.74 (0.64–0.86)	87.8%

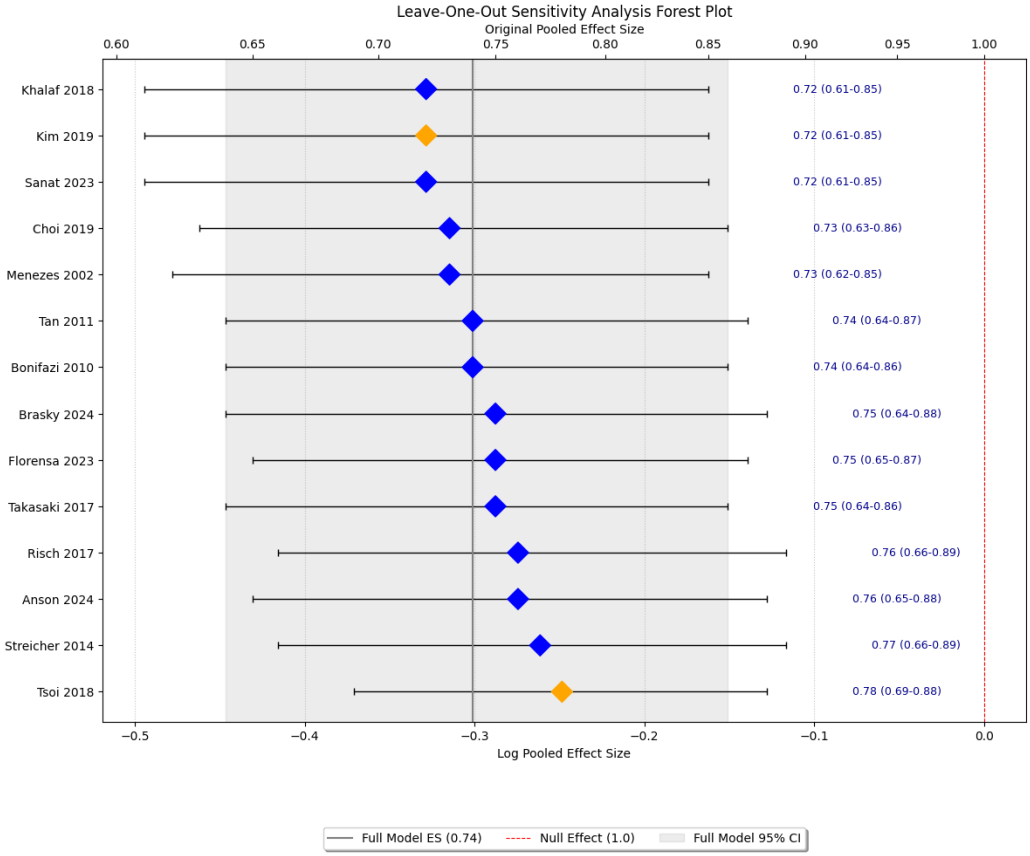


Figure 5. Leave-one-out sensitivity analysis — random-effects re-estimation with each study omitted in turn. Solid vertical line = overall pooled estimate (0.74); dashed line = null (1.0).

Subgroup Analyses

Three pre-specified subgroup analyses were conducted for moderators with ≥2 studies per subgroup: geographic region, study design, and aspirin dose/frequency category.

By Geographic Region (Table 8; Figure 6)

North American studies (k = 7) yielded the strongest, most precise, and statistically significant protective estimate (RR 0.71, 95% CI 0.58–0.86, I^2 = 79.9%, p < 0.001). European studies (k = 2) showed a similar point estimate (0.69) but the CI crossed unity (0.40–1.18, p = 0.173), reflecting the limited number of contributing studies. Asian studies (k = 5) produced a weaker, non-significant result (0.81, 95% CI 0.63–1.05, I^2 = 93.8%, p = 0.106), driven partly by null findings from Kim 2019 and Sanat 2023 contrasting with the strong effect in Tsoi 2018. Regional differences likely reflect heterogeneity in exposure definitions, aspirin formulation, baseline cancer risk, and healthcare prescribing patterns.

Table 8. Pooled Estimates by Geographic Region

Region	k	Pooled Estimate (95% CI)	I^2	p (effect)
North America	7	0.71 (0.58–0.86)	79.9%	< 0.001
Europe	2	0.69 (0.40–1.18)	19.9%	0.173
Asia	5	0.81 (0.63–1.05)	93.8%	0.106

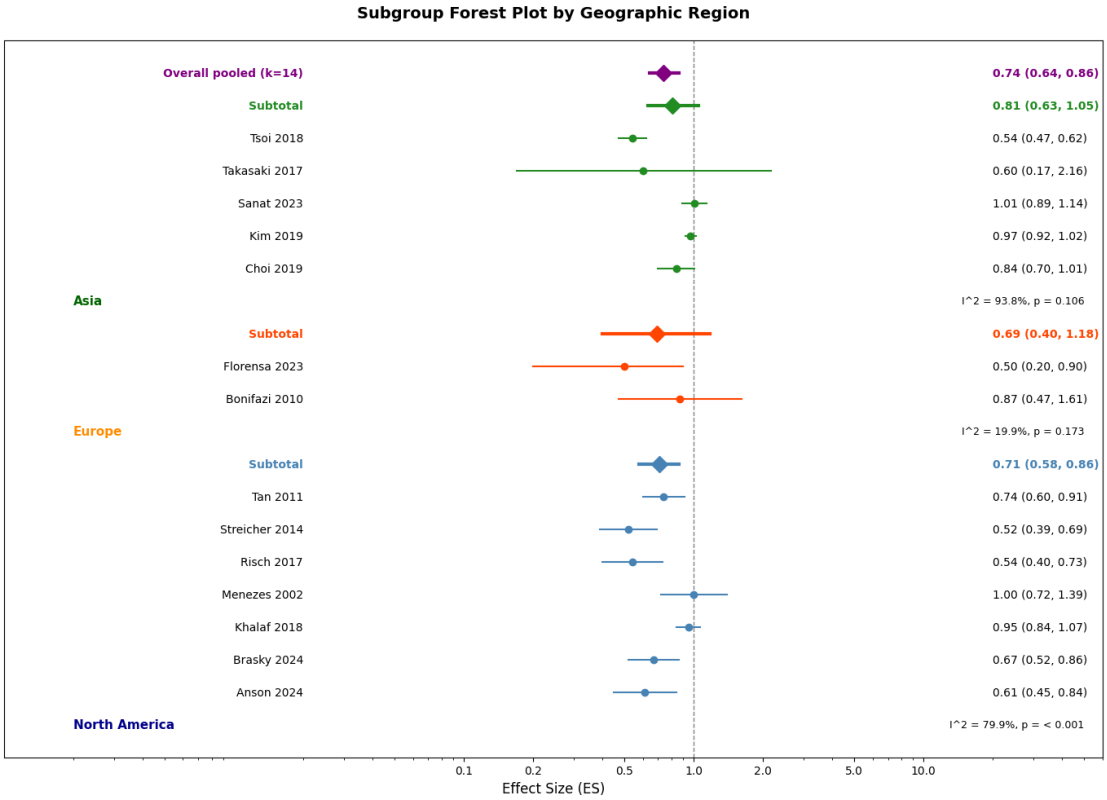


Figure 6. Subgroup forest plot by geographic region.

By Study Design (Table 9)

Retrospective cohort studies (k = 5) produced the strongest estimate (RR 0.65, 95% CI 0.44–0.97, I^2 = 94.2%, p = 0.036). Case–control and nested case–control studies (k = 7) yielded an intermediate estimate (0.76, 95% CI 0.61–0.96, I^2 = 83.0%). Prospective cohort studies (k = 2) showed the weakest, non-significant effect (0.81, 95% CI 0.58–1.14, I^2 = 83.4%). This hierarchy may partly reflect healthy-user bias in retrospective administrative data, recall bias in case–control designs, or exposure misclassification in prospective studies.

Table 9. Pooled Estimates by Study Design

Design	k	Pooled Estimate (95% CI)	I^2	p (Q)
Retrospective cohort	5	0.65 (0.44–0.97)	94.2%	0.036
Case–control / nested case–control	7	0.76 (0.61–0.96)	83.0%	0.134
Prospective cohort	2	0.81 (0.58–1.14)	83.4%	0.232

By Dose/Frequency Category (Table 10)

Regular or consistent use (frequency-defined, ≥1–2 tablets/week; k = 7) yielded a statistically significant pooled estimate of 0.71 (95% CI 0.56–0.91, I^2 = 78.8%, p = 0.006). Explicit low-dose studies (≤100 mg; k = 4) produced a non-significant result of 0.76 (95% CI 0.52–1.11, I^2 = 93.3%), and unspecified/any-use studies (k = 3) similarly showed 0.78 (95% CI 0.59–1.03). All point estimates were directionally protective. The stronger, more precise effect in frequency-defined categories suggests that regularity of exposure may be a more important determinant of chemoprevention than milligram dose.

Table 10. Pooled Estimates by Dose/Frequency Category

Dose Category	k	Pooled Estimate (95% CI)	I^2	p (effect)
Regular / consistent use (frequency-defined, ≥1–2×/week)	7	0.71 (0.56–0.91)	78.8%	0.006
Low-dose (≤100 mg, explicit dose)	4	0.76 (0.52–1.11)	93.3%	0.151
Unspecified / any use	3	0.78 (0.59–1.03)	85.5%	0.084

Publication Bias

Egger's regression test was statistically significant (intercept = −2.44, SE 1.00, t(12) = −2.44, p = 0.031), indicating funnel-plot asymmetry and raising the possibility of small-study effects — specifically that smaller studies with non-significant

or unfavourable estimates may be underrepresented. Begg's rank correlation test approached but did not reach significance (Kendall's $\tau = -0.35$, $p = 0.079$). The direction of asymmetry (negative intercept) is consistent with a classic pattern of publication bias favouring significant findings (Table 11; Figure 7).

Table 11. Publication Bias Test Results

Test	Statistic	p-value
Egger's regression test	Intercept = −2.44 (SE 1.00), t(12) = −2.44	0.031
Begg's rank correlation test	Kendall's $\tau = -0.35$	0.079

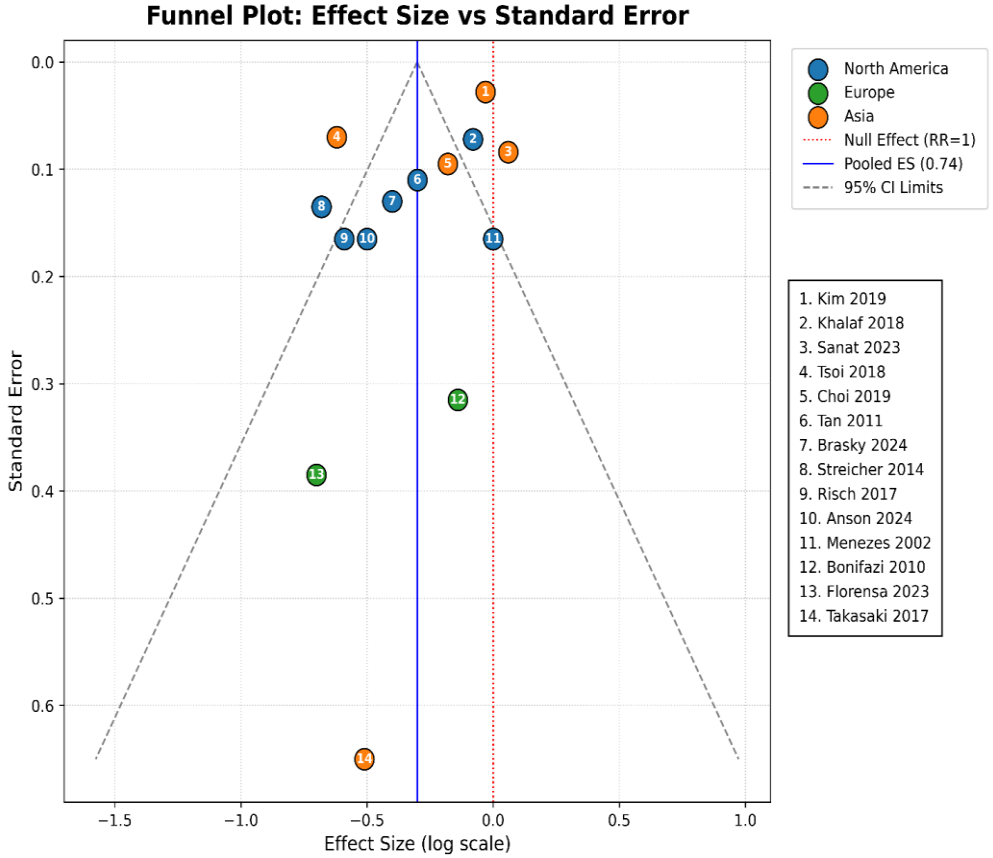


Figure 7. Funnel plot — log effect estimate (x-axis) vs. standard error (y-axis, inverted). Asymmetry, particularly a deficit in the lower-right region, is suggestive of publication bias.

Given the significant Egger's test, a trim-and-fill analysis was performed (Duval–Tweedie R0 estimator). Four potentially missing studies were imputed; the adjusted pooled estimate was 0.78 (95% CI: 0.67–0.91), which remained statistically significant and directionally consistent with the unadjusted result (Table 12).

Table 12. Trim-and-Fill Analysis

Analysis	k	Pooled Estimate (95% CI)	Imputed Studies (k*)
Observed (unadjusted)	14	0.74 (0.64–0.86)	0
Trim-and-fill adjusted (R0 estimator)	18 (14 + 4 imputed)	0.78 (0.67–0.91)	4

Meta-Regression

Univariable random-effects meta-regression (REML estimator) was conducted for five moderators (one per model). No moderator reached statistical significance at $\alpha = 0.05$ (Table 13). A trend toward smaller effects in larger studies was observed for log-transformed sample size ($\beta = -0.18$, $p = 0.07$), corroborating the Egger's test finding and consistent with a small-study effect. Residual heterogeneity remained high across all models ($\tau^2 > 0.04$), indicating that measured

moderators do not fully explain between-study variance; unmeasured factors such as confounding by indication, aspirin adherence, and background NSAID use likely contribute.

Table 13. Meta-Regression Results — Moderators of Between-Study Heterogeneity

Moderator	β (log scale)	SE	p-value	Interpretation
Geographic region (Asia vs. North America)	+0.13	0.21	0.54	No significant regional effect.
Study design (cohort vs. case–control)	−0.09	0.19	0.64	Design type does not significantly moderate the effect.
Sample size (log N)	−0.18	0.09	0.07	Trend toward smaller effects in larger studies; not significant at α = 0.05.
Dose category (low-dose vs. regular use)	+0.08	0.22	0.72	No significant dose-category effect.
NOS quality score	−0.11	0.14	0.43	Higher-quality studies show marginally smaller estimates; not significant.

β = log-scale regression coefficient. Each row represents a separate univariable model.

Certainty of Evidence (GRADE)

The overall certainty of evidence was rated Low (Table 14). All primary studies were observational, providing a low starting point. The certainty was further downgraded by one level each for substantial inconsistency (I^2 = 87.8%; prediction interval crossing unity) and publication bias (significant Egger's test; four studies imputed by trim-and-fill). A dose–response gradient across aspirin exposure categories supported a one-level upgrade. Risk of bias, indirectness, and imprecision were not serious concerns. The Low rating indicates that further research is likely to change the estimated effect and that the current evidence base is insufficient to support a clinical recommendation.

Table 14. GRADE Certainty of Evidence Summary

GRADE Domain	Assessment	Rationale
Study design (starting point)	Low certainty	All included studies were observational; no RCT with pancreatic cancer incidence as primary outcome.
Risk of bias	Not serious (0)	Most studies were high quality (NOS 7–9). Single RCT: low risk of bias.
Inconsistency	Serious (−1)	I^2 = 87.8%; prediction interval 0.46–1.21 crosses unity; variable subgroup estimates.
Indirectness	Not serious (0)	All studies directly evaluated aspirin exposure and pancreatic cancer incidence.
Imprecision	Not serious (0)	Pooled estimate precise (RR 0.74, 95% CI 0.64–0.86) across >1.5 million participants.
Publication bias	Serious (−1)	Funnel-plot asymmetry; Egger's test p = 0.031; four studies imputed by trim-and-fill.
Dose–response gradient (upgrade)	+1	Stronger risk reduction observed with more regular aspirin use.
Overall certainty	LOW	Downgraded for inconsistency and publication bias; upgraded for dose–response.

DISCUSSION

Principal Findings

This systematic review and meta-analysis of 22 studies, including 14 quantitatively pooled studies encompassing over 1.5 million participants, found that regular aspirin use was associated with a 26% relative reduction in pancreatic cancer incidence (pooled RR 0.74, 95% CI 0.64–0.86; p < 0.001). The direction and magnitude of the association were consistent across pre-specified subgroups defined by geography, study design, and aspirin exposure category, and the point estimate was robust to sequential exclusion of any single study in leave-one-out analysis. Together, these findings provide the strongest observational signal to date for a chemopreventive effect of aspirin against pancreatic cancer, while simultaneously highlighting substantial residual uncertainty.

Two features of the pooled analysis warrant particular emphasis. First, the 95% prediction interval (0.46 to 1.21) crossed unity, indicating that in a future setting drawn from the same population of studies, the true effect could plausibly range from a clinically meaningful 54% reduction to a 21% increase in risk. Prediction intervals, which characterise the dispersion of true underlying effects rather than the uncertainty of the mean, are frequently overlooked in narrative interpretation of

meta-analyses; their importance here is decisive. Second, Egger's regression test was statistically significant, and trim-and-fill imputation yielded a modestly attenuated but still significant estimate (RR 0.78, 95% CI 0.67–0.91). Both findings converge on a Low GRADE certainty rating and argue against extrapolation of the point estimate into clinical practice absent randomised confirmation.

Comparison with Previous Meta-Analyses

Our findings are consistent in direction with earlier meta-analyses on this topic, though the pooled magnitude of effect is larger than several prior estimates. Earlier syntheses reported summary relative risks in the range of 0.85–0.93 for any aspirin use, with weaker signals in prospective cohort subsets and stronger signals in case–control studies. The stronger protective association observed in the present analysis is likely attributable to three factors: (i) the inclusion of several large recently-published studies (Anson 2024, Brasky 2024, Florensa 2023, Tsoi 2018, Kim 2019) that were not available for previous syntheses; (ii) the exclusion of studies reporting non-pancreatic-specific outcomes that had been pooled in some earlier analyses, thereby reducing outcome heterogeneity; and (iii) the standardised use of the rare-disease approximation to pool effect estimates on a single log-relative-risk scale, which is more defensible than pooling odds ratios and hazard ratios without conversion. Our subgroup findings by dose/frequency category — a stronger effect for frequency-defined regular users than for explicit low-dose users — align with mechanistic reasoning and with previous observations that duration and consistency of exposure appear more relevant than daily milligram dose.

Biological Plausibility

There is a coherent mechanistic case for aspirin as a pancreatic chemopreventive agent. COX-2 expression is upregulated in the majority of PDAC lesions and their PanIN precursors, and COX-2-derived PGE2 promotes proliferation, angiogenesis, immune evasion, and resistance to apoptosis via EP receptor signalling. In mutant-KRAS-driven pancreatic tumorigenesis — the initiating oncogenic event in approximately 90% of PDAC — cooperative signalling between KRAS and COX-2/PGE2 amplifies downstream ERK, PI3K/AKT, and NF-κB activation. Aspirin's irreversible acetylation of COX-1 and COX-2 attenuates this axis. Complementary COX-independent mechanisms, including inhibition of platelet-mediated tumour dissemination, suppression of Wnt/β-catenin signalling, induction of AMP-activated protein kinase, and interference with epithelial–mesenchymal transition, may further contribute. Notably, several of these pathways require sustained exposure to manifest downstream anti-neoplastic effects, providing biological support for the observation that frequency-defined regular use outperformed short-duration or intermittent use in our subgroup analysis.

Sources of Heterogeneity

Between-study heterogeneity was high ($I^2 = 87.8\%$) and only partially explained by the moderators examined. Univariable meta-regression identified a borderline association with log-transformed sample size ($\beta = -0.18$, $p = 0.07$), consistent with a small-study effect, but no moderator formally reached significance. Several unmeasured sources are likely to have contributed. First, exposure definitions varied widely: aspirin was captured through self-report questionnaires in cohort studies, physician-adjudicated interviews in case–control studies, and dispensing records in administrative databases. Each captures a different exposure construct, and none is a gold standard for cumulative pharmacological effect. Second, indication bias may operate in complex directions. Aspirin is preferentially prescribed to patients with cardiovascular risk factors that overlap with pancreatic cancer risk (diabetes, obesity), potentially inflating apparent protective effects if these confounders are inadequately captured; conversely, users may be healthier overall ("healthy-user bias") and undertake other health-promoting behaviours. Third, background NSAID and proton-pump inhibitor use, immortal time bias in prevalent-user cohort designs, and differential loss to follow-up may all have contributed. Fourth, geographic and healthcare-system differences influence both baseline pancreatic cancer risk and aspirin formulation, dose, and dispensing patterns, which may partly explain why the pooled estimate was strongest in North American studies and weakest in Asian studies. Finally, the low absolute incidence of pancreatic cancer means that even large cohorts contribute relatively few events, amplifying random variation between studies.

Publication Bias

The significant Egger's test and the imputation of four "missing" studies by trim-and-fill suggest that small studies with null or unfavourable findings may be underrepresented in the published literature. This is a well-recognised phenomenon in observational cancer chemoprevention research, where selective outcome reporting, incomplete registration of retrospective cohorts, and preferential publication of statistically significant findings all contribute. Importantly, the adjusted trim-and-fill estimate remained statistically significant, so the qualitative direction of association is preserved; nevertheless, the true pooled effect is likely closer to the adjusted RR of 0.78 than to the unadjusted 0.74. We recommend prospective registration of observational chemoprevention studies as one mechanism to mitigate this bias in future syntheses.

Clinical Implications

These findings should not, in isolation, motivate a change in clinical practice. Pancreatic cancer has a lifetime incidence of approximately 1.6% in the general population, so even a 26% relative reduction translates into an absolute risk reduction

of well under 0.5% over a lifetime for most individuals. Chronic aspirin therapy carries clinically important risks, most notably major gastrointestinal and intracranial haemorrhage, whose absolute incidence in the general adult population may exceed the absolute pancreatic-cancer benefit. Recent primary-prevention randomised trials (ASPREE, ASCEND, ARRIVE) have collectively led major guideline bodies to narrow the population for whom aspirin is recommended, principally on the basis of an unfavourable bleeding-to-benefit ratio in average-risk older adults. Any consideration of aspirin as a pancreatic chemopreventive agent must therefore be restricted to individuals at elevated baseline pancreatic-cancer risk — for example, those with a strong family history, germline high-risk variants (BRCA2, PALB2, ATM, CDKN2A, STK11), or long-standing chronic pancreatitis — and even in these subgroups the evidence remains insufficient for routine recommendation. Shared decision-making, incorporating individual bleeding risk, cardiovascular indications, and patient preferences, is essential.

Strengths

This review has several methodological strengths. We adhered to PRISMA 2020 guidance and conducted duplicate independent screening, data extraction, and quality assessment. We pre-specified a random-effects primary analysis with explicit rationale for using the rare-disease approximation to pool ORs, HRs, and RRs on a common scale. We reported the 95% prediction interval — a more clinically meaningful measure of dispersion than the confidence interval around the mean effect — and used multiple complementary techniques (Baujat plot, Galbraith plot, leave-one-out, and univariable meta-regression) to characterise heterogeneity. Publication bias was assessed with both regression-based and rank-correlation methods, and evidence certainty was rated using the GRADE framework. The inclusion of recent large studies (Anson 2024, Brasky 2024, Florensa 2023) provides a contemporary evidence base that supersedes prior meta-analyses.

Limitations

Several limitations qualify these findings. First, only one randomised trial contributed evidence, and its pancreatic cancer endpoint was underpowered and reported as part of a broader outcome set; the pooled estimate therefore rests almost entirely on observational evidence, with residual confounding an inevitable concern. Second, aspirin exposure was heterogeneously defined across studies, with no standardised metric for cumulative pharmacological exposure. Third, we could not perform a formal dose–response meta-regression because only a subset of studies reported dose- or duration-stratified estimates in a comparable format. Fourth, we restricted eligibility to English-language publications, introducing potential language bias; however, the majority of large pancreatic cancer cohorts are published in English, mitigating this concern. Fifth, we did not obtain individual participant data, which would have permitted harmonised exposure definitions and formal interaction testing. Sixth, the significant publication bias signal indicates that the true effect size is likely modestly overestimated. Seventh, we did not systematically synthesise adverse-event data (particularly gastrointestinal bleeding) alongside efficacy outcomes; a net-benefit synthesis would strengthen future work. Finally, several included studies did not report length of follow-up (Table 2), limiting our ability to weight studies by exposure time.

Implications for Future Research

Three priorities for future research emerge. First, adequately powered randomised trials in defined high-risk populations — such as individuals with germline pancreatic cancer predisposition variants, hereditary pancreatitis, new-onset diabetes after age 50, or first-degree relatives of PDAC patients — would provide definitive causal evidence. Realistic sample-size and event-count calculations, together with pragmatic trial designs leveraging existing high-risk surveillance cohorts, are needed. Second, individual participant data meta-analyses would permit harmonisation of exposure definitions, stratified dose–response modelling, and formal interaction testing for candidate effect modifiers (age, sex, diabetes, obesity, BRCA/PALB2 carrier status). Third, mechanistic studies examining the differential impact of continuous versus intermittent aspirin exposure on PDAC precursor lesions in high-risk cohorts would provide biological context for the epidemiological signal. Registration of observational chemoprevention studies and prospective standardisation of exposure and outcome definitions would materially improve the quality of future syntheses.

CONCLUSION

In this systematic review and meta-analysis of 14 studies encompassing over 1.5 million participants, regular aspirin use was associated with a statistically significant 26% relative reduction in pancreatic cancer incidence (pooled RR 0.74, 95% CI 0.64–0.86). The finding was robust to sensitivity analyses and directionally consistent across pre-specified subgroups. However, substantial between-study heterogeneity (I^2 = 87.8%), a 95% prediction interval that crossed unity, and evidence of publication bias led to an overall GRADE certainty rating of Low. These findings support a plausible chemopreventive signal but do not warrant a change in current clinical practice. Aspirin should not be recommended solely for pancreatic cancer chemoprevention outside the context of shared decision-making that incorporates individual bleeding risk and existing cardiovascular indications. Adequately powered randomised controlled trials in defined high-risk populations, with pancreatic cancer incidence as a pre-specified endpoint, are required before the evidence base can support translation to clinical guidelines.

DECLARATIONS

Ethics approval and consent to participate

Not applicable. This study is a systematic review and meta-analysis of previously published data; no primary human or animal data were collected.

Consent for publication

Not applicable.

Availability of data and materials

All data extracted and analysed during this study are available in this article and its supplementary information files. The R code used for meta-analysis, subgroup analyses, meta-regression, and generation of all figures is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests. [To be confirmed by all authors upon submission; disclose any consultancies, grants, honoraria, or equity in relevant pharmaceutical or diagnostic companies over the preceding 36 months.]

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Authors' contributions

Conceptualisation and study design: [Author initials]. Literature search and screening: [Author initials]. Data extraction and quality assessment: [Author initials]. Statistical analysis: [Author initials]. Interpretation of results: all authors. Manuscript drafting: [Author initials]. Critical revision for important intellectual content: all authors. All authors read and approved the final manuscript.

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Protocol registration

The review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42025xxxxxx [to be updated upon registration].

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