Title

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Journal

United European Gastroenterology Journal, 14(3)

ISSN

2050-6406

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Publication Date

2026-04-01

DOI

10.1002/ueg2.70209

United European Gastroenterology Journal

WILEY | ueg journal

ORIGINAL ARTICLE OPEN ACCESS

The Joint Global Epidemiology of Pancreatic Cancer and Pancreatitis: Co-Occurrence Patterns, Shared Risk Factors, and Projections to 2040

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Received: 17 December 2025 | **Revised:** 5 March 2026 | **Accepted:** 16 March 2026

Keywords: global burden of disease | global epidemiology | pancreatic cancer | pancreatitis | pancreatology

ABSTRACT

Background: Pancreatic cancer and pancreatitis cause substantial mortality and morbidity, yet their joint global burden, epidemiology and determinants are rarely assessed together. We quantified their joint incidence burden, identified co-occurrence patterns, and examined shared risk exposures across countries.

Methods: Incidence rates for both diseases among adults aged ≥ 25 years across 204 countries and territories were obtained from the Global Burden of Disease (GBD) 2021 study. Temporal trends were assessed through estimated annual percent changes (EAPC). Country-level co-occurrence clusters were identified using Gaussian mixture modeling. Random forest models with Shapley additive explanations were used to investigate associated risk exposures. Non-seasonal time-series models were used to forecast incidence to 2040.

Results: High-income countries predominantly clustered as dual-high for both conditions and showed modest to rapidly increasing incidence, whereas most sub-Saharan African countries were dual-low and largely stable. Many middle-SDI (Sociodemographic index) settings remained low but increased moderately over time. Smoking, alcohol use, high body-mass index, and diets high in red and processed meat were shared risk factors, with higher exposure levels in high-SDI regions. Projections indicate that pancreatic cancer incidence will continue to rise globally through 2040, driven mainly by high- and high-middle SDI regions, while pancreatitis incidence will remain comparatively stable.

Conclusion: Co-occurrence of pancreatic cancer and pancreatitis follows a strong sociodemographic gradient that parallels the distribution of modifiable risk exposures. Integrated strategies combining targeted surveillance with lifestyle and metabolic risk reduction are needed to mitigate the growing joint burden of pancreatic diseases.

1 | Introduction

Pancreatic cancer and pancreatitis together account for a substantial and growing global disease burden. Pancreatic cancer is one of the most lethal malignancies worldwide and ranks as the sixth leading cause of cancer-related death [1, 2]. According to GLOBOCAN 2022 estimates, more than 510,000 new cases and 467,000 deaths have occurred globally, while the overall 5-year survival remains at approximately 10% [2, 3]. Data from the Global Burden of Disease (GBD) 2017 study further indicate that pancreatic cancer deaths and disability-adjusted life years (DALYs) have more than doubled since 1990, with the highest age-standardized incidence and mortality rates observed in high-income regions [4]. In parallel, pancreatitis, encompassing both acute and chronic forms, is a major cause of gastrointestinal morbidity and hospitalization [5, 6]. Meta-analyses of

Key Summary

- Summarise the established knowledge on this subject
  - Pancreatic cancer and pancreatitis both represent a growing disease burden worldwide.
  - Epidemiological and clinical studies have reported associations between pancreatitis and pancreatic cancer, supported by overlapping pathological mechanisms.
- What are the significant and/or new findings of this study?
  - Pancreatic cancer and pancreatitis show distinct country-level co-occurrence clusters with a strong sociodemographic gradient, with dual-high patterns in high/high-middle SDI and dual-low patterns in many sub-Saharan African countries.
  - Shared risk exposures including smoking, alcohol use, high BMI, and diets high in red/processed meat align with these co-occurrence patterns and are more prevalent in higher-SDI settings.
  - Forecasts to 2040 indicate continued increases in pancreatic cancer incidence while pancreatitis remains comparatively stable, suggesting persistent disparities.

population-based cohort studies have reported incidence rates of approximately 33.7 and 9.6 per 100,000 person-year for acute and chronic pancreatitis, respectively [7]. Collectively, these conditions impose a considerable clinical and economic burden, particularly in aging populations and in regions undergoing rapid epidemiological transition.

Pancreatitis and pancreatic cancer are clinically and biologically interconnected. Chronic pancreatitis is a well-established risk factor for pancreatic cancer, with substantial evidence showing elevated pancreatic cancer risk among patients with chronic pancreatitis [8, 9]. A Meta-analysis from 13 studies reported pooled effect estimates for pancreatic cancer with 16.16 in patients with chronic pancreatitis within the 2 years from their diagnosis, with risk remaining elevated thereafter [8]. Moreover, acute pancreatitis, particularly non-biliary acute pancreatitis, has also been associated with increased pancreatic risk. Large population-based matched-cohort studies indicated a higher risk of pancreatic cancer among patients with an episode of acute pancreatitis [10, 11]. Mechanistically, recurrent pancreatic inflammation promotes acinar-to-ductal metaplasia, progressive fibrosis and accumulation of oncogenic driver mutations and tumor-suppressor gene alterations, thereby creating a microenvironment conducive to malignant transformation [10, 12]. Pancreatic cancer and pancreatitis also have several shared modifiable risk factors, including smoking, heavy alcohol consumption, obesity, and gallstone diseases [13, 14]. Moreover, longitudinal studies have documented disease progression from pancreatitis to pancreatic cancer in a subset of patients [15, 16]. Collectively, these overlapping exposures, shared biological pathways and temporal relationships suggest that pancreatitis and pancreatic cancer represent points along a continuum of chronic pancreatic injury and carcinogenesis.

Despite strong associations between the two pancreatic diseases, existing studies have largely investigated each condition separately, which leaves critical gaps in understanding the co-occurrence patterns, shared risk exposures, and geographical and sociodemographic disparities at the global scale. Bridging these gaps is essential for moving beyond fragmented, disease-specific programs toward integrated prevention strategies that encompass shared risk reduction and risk-stratified surveillance of high-risk populations. Therefore, we used data from GBD 2021 to conduct a systematic analysis of the global, regional and national burden of pancreatic cancer and pancreatitis, along with characterizing their global co-occurrence patterns across sociodemographic contexts and decomposing the contribution of major risk exposures. We further projected both disease burdens to 2040 to anticipate future healthcare demands. By identifying where the joint burden is highest and which modifiable risks drive it in specific settings, our findings provide insights to support targeted prevention, guide earlier detection in high-risk populations, and inform more efficient resource allocation for pancreatic disease control worldwide.

2 | Methods

2.1 | Data Source

Incidence rates (IR) of pancreatic cancer and pancreatitis and risk exposure metrics for adults aged ≥ 25 years across 204 countries/territories were obtained from the Global Burden of Disease (GBD) 2021 study. Age-standardized incidence rate (ASIR) were calculated with corresponding weight for each age group. GBD 2021 is a systematic global health initiative to estimate the burden of 371 diseases and 88 attributable risk factors across 204 countries and territories. Detailed estimation methodologies and data sources were reported in previous publications by the GBD 2021 collaborators [17, 18]. Risk exposure was quantified using summary exposure values (SEVs), which weight exposure prevalence by severity relative to disease burden. Pancreatic cancer was defined by ICD-10 C25.0–C25.7 and ICD-9157.0–157.9; pancreatitis (acute and chronic) by ICD-10 K85–K86 and ICD-9577.0–577.1. We also extracted the Sociodemographic Index (SDI), a composite measure based on fertility in women < 15 years, educational attainment (≥ 15 years), and lag-distributed income per capita. All data are publicly available via the GBD Results tool on the Global Health Data Exchange. The study followed GATHER guidelines, and all analyses and visualizations were performed with RStudio (v4.4) [19].

2.2 | Temporal Trends and Co-Occurrence Patterns of Pancreatic Cancer and Pancreatitis

Estimated annual percent changes (EAPCs) were used to estimate the temporal trends of pancreatic cancer and pancreatitis across the 204 countries and territories between 1990 and 2021. EAPC summarizes the average annual percentage change by fitting a log-linear regression model to the time series. We interpreted the trends as follows: an increasing trend was defined when both limits of the 95% CI of the EAPC were greater than 0; a decreasing trend was defined when both limits of the 95% CI were less than 0; otherwise, the trend was

considered stable. Statistical significance was evaluated with a significance level of $\alpha = 0.05$. Detailed methodology and formulas are reported in Supporting Information S1: Appendix 1.

To characterize co-occurrence patterns of pancreatic cancer and pancreatitis across locations, we applied Gaussian mixture model (GMM) clustering. For each country or territory, we constructed a four-dimensional profile based on: (i) the ASIR of pancreatic cancer and pancreatitis in 2021 and (ii) the corresponding EAPCs from 1990 to 2021 for both diseases. Before clustering, each variable was standardized to a z-score to place them on a comparable scale and prevent undue influence from differences in units or variance. We fitted GMMs with different number of components and compared model fit using the Bayesian information criterion (BIC). The model with the lowest BIC was selected, while also considering the epidemiological interpretability and stability of the resulting clusters. GMM clustering was chosen in preference because it (i) allows clusters to have different shapes, orientations, and variances through flexible covariance structures; (ii) provides probabilistic (soft) cluster assignments that quantify uncertainty in cluster membership; and (iii) is well suited to capturing heterogeneous co-occurrence profiles driven jointly by current incidence levels and long-term temporal trends.

2.3 | Risk Factor Analysis With Machine Learning Approaches

We used a predictive risk modeling approach rather than the GBD comparative risk assessment framework. We screened all GBD risk factors and excluded exposures lacking biological or epidemiologic plausibility for pancreatic cancer or pancreatitis based on expert review and a targeted literature search, yielding 28 candidate risks (Supporting Information S1: Table 1). For each disease, we fitted random forest (RF) regression models including all candidate exposures. Hyperparameters were selected via k-fold cross-validation by minimizing prediction error, and model performance was summarized using fold-wise cross-validated metrics and metrics computed from pooled out-of-fold predictions. To interpret models and rank exposures, we applied Tree SHAP (Sharpley Additive Explanation models) to compute SHAP values, which attribute each prediction to additive feature contributions. We summarized importance using mean absolute SHAP values across locations and examined SHAP dependence plots to assess the direction and shape of associations. SHAP results were interpreted as hypothesis-generating and were subsequently examined with our regression models.

Risk exposures with high SHAP importance were advanced to regression analyses. We used negative binomial regression to estimate relative risks (RRs) for pancreatic cancer and pancreatitis, modeling location-specific incident case counts as a function of selected exposures and including the log population as an offset. All models adjusted for key ecological covariates, including SDI and GBD super-region. Collinearity among selected exposures was assessed using variance inflation factors (VIFs). To evaluate robustness, we conducted sensitivity analyses using cumulative lagged exposure measures (2011–2021) and re-estimated models after excluding influential observations identified by standard influence diagnostics. This combined machine-learning and regression framework has been applied in prior ecological and global burden analyses to support hypothesis generation and risk prioritization [20, 21]. Detailed methods, model diagnostics and supplementary results are provided in Supporting Information S1: Appendix 1.

2.4 | Projection and Forecasting the Disease Burden Till 2040

Autoregressive integrated moving average (ARIMA) models were used to project the disease burden through 2040. For each location, the data from 1990 to 2021 was modeled as a non-seasonal ARIMA (p, d, q) process, where p denotes the autoregressive order, d the degree of differencing applied to achieve stationarity, and q the moving-average order. Candidate model orders were considered across locations, and the final specification for each series was selected by minimizing the Akaike Information Criterion (AIC) following maximum-likelihood estimation. Model adequacy was assessed using residual diagnostics, including the Ljung–Box test, to evaluate remaining autocorrelation in the residuals. To evaluate predictive performance and robustness across forecasting horizons, we conducted rolling-origin (walk-forward) back-testing using an expanding training window. Specifically, models were repeatedly refit using observations from 1990 to year t, and h-step-ahead forecasts were generated for $t + 1$ to $t + h$, with horizons $h = 5$, 10, and 15 years and annual advancement of the forecast origin. Forecast accuracy was summarized across all folds using mean absolute error (MAE) and root mean squared error (RMSE).

3 | Results

3.1 | Overview of the Global Burden and Trend of Pancreatic Cancer and Pancreatitis

In 2021, the global ASIR of pancreatic cancer among adults aged ≥ 25 years was 11.50 (95% UI: 10.59–12.16) per 100,000 population. Country-specific ASIRs varied markedly, ranging from 0.40 (95% UI: 0.30–0.52) per 100,000 in Mozambique to 51.35 (95% UI: 37.48–68.40) per 100,000 in Monaco (Figure 1A). High-income regions, including high-income North America, Europe, and Australasia, showed the highest incidence rates, whereas most low-SDI regions reported comparatively low burdens.

The global ASIR of pancreatitis in 2021 was 52.64 (95% UI: 45.57–60.42) per 100,000 population. The lowest country-specific ASIR was observed in Zambia (23.76, 95% UI: 19.15–29.79), while the highest was observed in the Russian Federation (173.44, 95% UI: 142.20–204.01) (Figure 1B). The regional distribution of pancreatitis largely paralleled that of pancreatic cancer, with high-income regions, particularly high-income North America and Eastern Europe, having the greatest

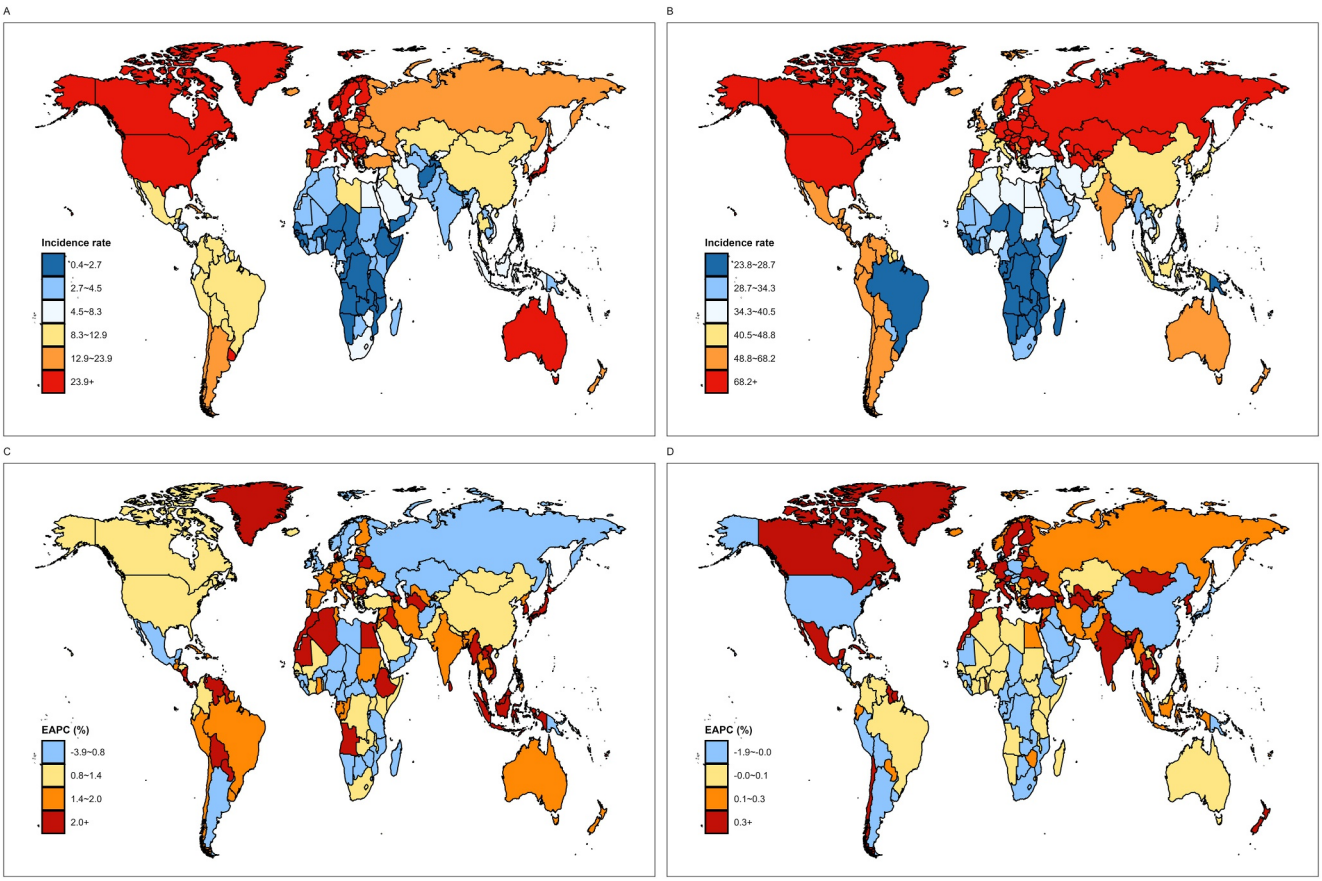

FIGURE 1 | The incidence rate of (A) pancreatic cancer and (B) pancreatitis across 204 countries and territories in 2021; The estimated annual percent changes (EAPC) of (C) pancreatic cancer and (D) pancreatitis across 204 countries and territories, 1990–2021.

burden, whereas low-SDI countries, especially those in Africa, reported the lowest incidence rates.

Temporal trends in pancreatic cancer incidence showed broadly increasing patterns across most settings (Figure 1C). Over the past 32 years, only 10 countries have exhibited declining IRs of pancreatic cancer, including the United Arab Emirates, Qatar, Swaziland, Nigeria, Madagascar, Afghanistan, Lesotho, Tajikistan, San Marino, and Mozambique. The fastest increases were observed in countries in Oceania, the Middle East, Europe, and southern Latin America. Turkmenistan, the Northern Mariana Islands, Cabo Verde, and Georgia had the largest estimated annual percent changes (EAPCs), each exceeding 5% per year.

Temporal trends in pancreatitis incidence across 204 countries and territories are shown in Figure 1D. Overall, several European and South Asian countries reported the highest positive EAPCs. In contrast, Poland, China, Afghanistan, Slovenia, and the United States showed the greatest declines in incidence, with EAPCs less than −0.4% per year. Conversely, Singapore and Chile experienced the steepest increases, with EAPCs greater than 1% per year. The detailed IR and EAPCs of pancreatic cancer and pancreatitis across the 204 countries and territories are reported in Supporting Information S1: Table 2.

3.2 | Co-Occurrence Patterns of Pancreatic Cancer and Pancreatitis

Gaussian mixture model clustering identified four distinct co-occurrence patterns of pancreatic cancer and pancreatitis based on the incidence rates and EAPCs for both diseases (Figure 2A). Cluster 1 (24 countries) comprised settings with high incidence rates but only modestly increasing trends for both diseases. This pattern was common in high-income North America, parts of Eastern Europe, and China. Cluster 2 (58 countries), concentrated in Southeast Asia, Oceania, and the Middle East, was characterized by low incidence rates and moderate increases in both pancreatic cancer and pancreatitis. Cluster 3 (77 countries) showed a pattern of both high incidence and rapidly increasing trends for the two diseases, spanning much of Europe, South Asia, and Latin America. Cluster 4 (45 countries), primarily located in sub-Saharan Africa, exhibited low incidence rates with largely stable temporal trends for both conditions.

The co-occurrence patterns displayed a clear socioeconomic gradient (Figure 2B). Cluster 4 (low and stable co-occurrence patterns) was the predominant pattern among low-SDI countries, with 82.4% of countries and territories in low-SDI regions exhibiting this pattern. The prevalence of Cluster 1 (high and modestly increasing) and Cluster 3 (high and rapidly increasing) increased with higher SDI levels, with 29.3% and

65.9% of high-SDI countries exhibiting these patterns, respectively. Co-occurrence patterns were more heterogeneous in low-middle to high-middle SDI regions, with Cluster 2 and Cluster 3 more prevalent in these regions.

3.3 | Associated Risk Factors With Pancreatic Cancer and Pancreatitis

Our random forest and SHAP analyses indicated substantial overlap in the most influential risk exposures for pancreatic cancer and pancreatitis (Figure 3). The RF models demonstrated stable predictive performance (Supporting Information S1: Table 3). Because variable importance rankings showed a clear plateau beyond the top 15 predictors, subsequent interpretation focused on the top 15 exposures for each outcome. At the population level, smoking, high alcohol use, elevated body mass index (BMI), high fasting plasma glucose (FPG), and diets high in sodium, processed meat, and red meat; a diet high in whole grains ranked among the most influential factors for pancreatic cancer. For pancreatitis, the highest-ranked exposures were high alcohol use, smoking, elevated BMI, diets high in processed and red meat, high low-density lipoprotein cholesterol (LDL-C), and a diet low in whole grains. In negative binomial regression, seven exposures were significantly associated with pancreatic cancer and six with pancreatitis (Figure 4). Five risk factors were shared across both outcomes, including smoking, high alcohol use, elevated BMI, and diets high in processed and red meat. High FPG showed the strongest association (RR = 1.244 95% CI 1.169–1.319) with pancreatic cancer, whereas high LDL-C was specific to pancreatitis. Smoking and alcohol use were associated with larger relative risks for pancreatitis (RR = 1.229 and 1.192, respectively) than for pancreatic cancer (RR = 1.196 and 1.148), while higher intake of processed and red meat exhibited modest but consistent

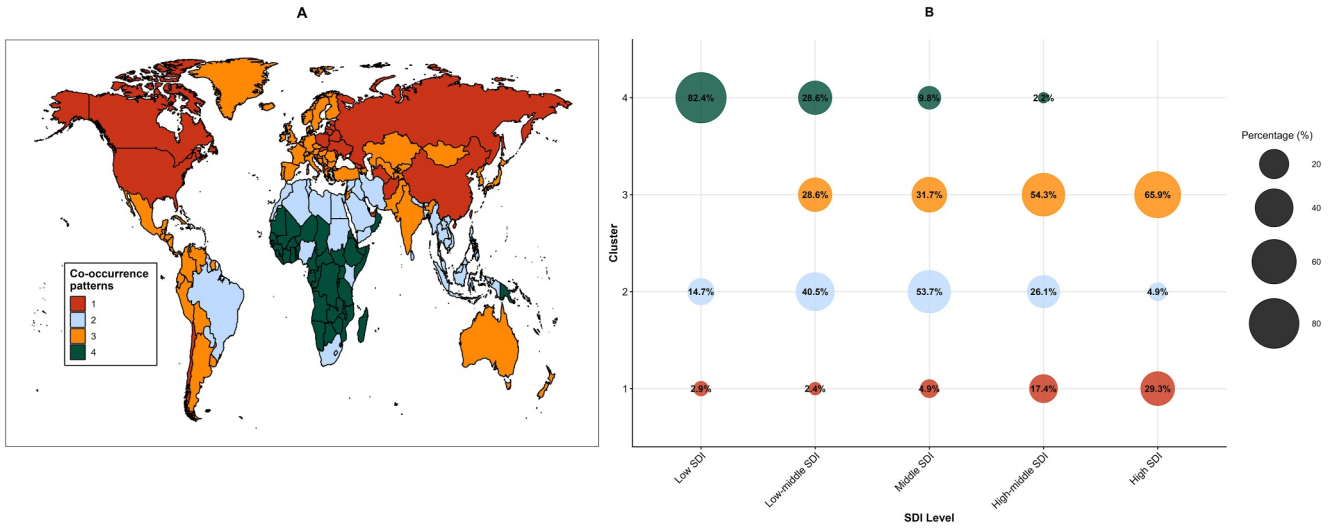

FIGURE 2 | (A) The co-occurrence patterns of pancreatic cancer and pancreatitis across 204 countries and territories; (B) The distribution of co-occurrence patterns across sociodemographic index (SDI) levels. (*Percentages denote the proportion of countries/territories within each SDI stratum assigned to the corresponding cluster*).

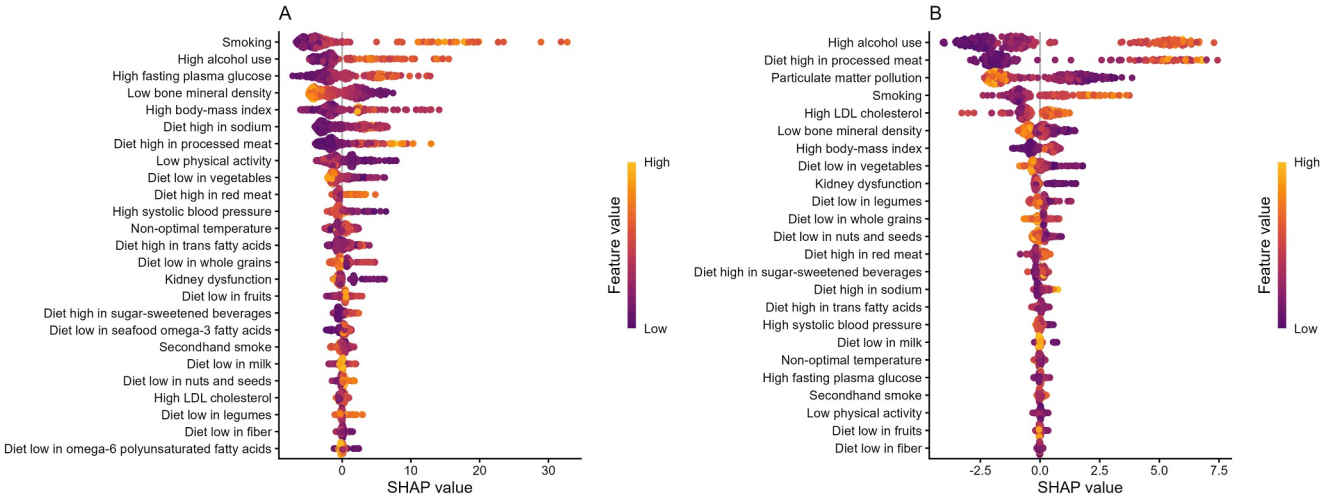

FIGURE 3 | (A) The Sharpley Additive Explanation (SHAP) summary plot of risk factors associated with pancreatic cancer; (B) SHAP summary plot of risk factors associated with pancreatitis.

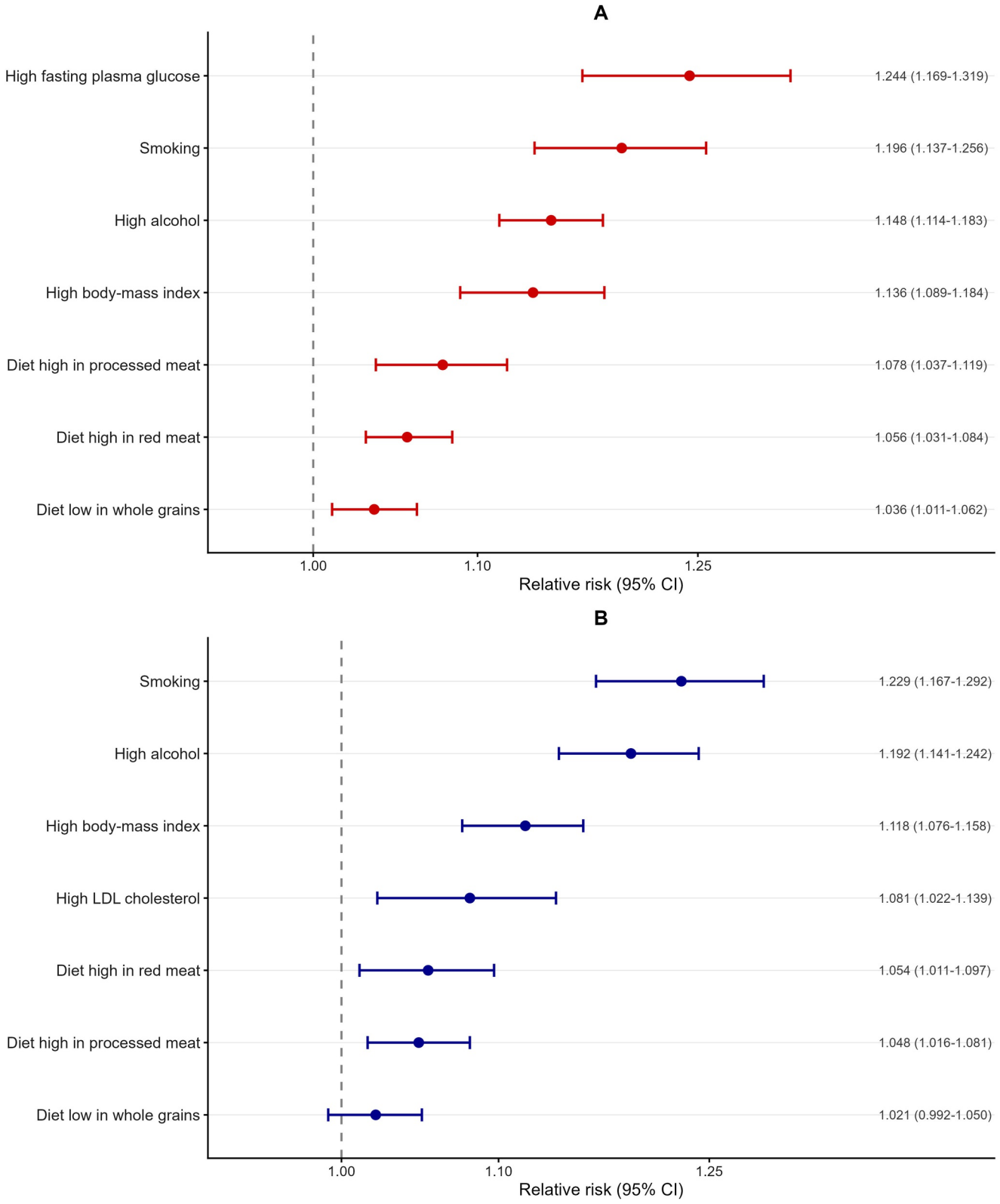

FIGURE 4 | (A) Relative risk of risk factors associated with pancreatic cancer; (B) Relative risk of risk factors associated with pancreatitis.

associations with both conditions (Figure 4). Sensitivity analyses yielded concordant findings when using cumulative lagged exposures (2011–2021) and after excluding influential outliers (Supporting Information S1: Tables 4 to 6).

Figure 5 maps the global distribution of these exposures. Most were more prevalent in high-SDI regions: high BMI, high FPG, high LDL-cholesterol, and diets high in red/processed meat clustered in North America, Europe, Australasia, and parts of

Latin America and the Middle East. Smoking and alcohol burdens were also highest in Europe, North America, and Oceania, but remained low across much of sub-Saharan Africa and South Asia. Diet low in whole grains was most prominent in Southeast Asia, Australasia, and several European countries. Overall, low-SDI countries, particularly in sub-Saharan Africa, were concentrated in the lowest exposure categories, paralleling their dual-low co-occurrence patterns.

3.4 | Projection and Forecast Burden of Pancreatic Cancer and Pancreatitis Till 2040

ARIMA projections indicate that sociodemographic disparities in the burden of pancreatic cancer and pancreatitis are likely to persist, and in some settings to widen by 2040 (Figure 6). The ARIMA model diagnostics and rolling-origin performance metrics are reported in Supporting Information S1: Table 7.

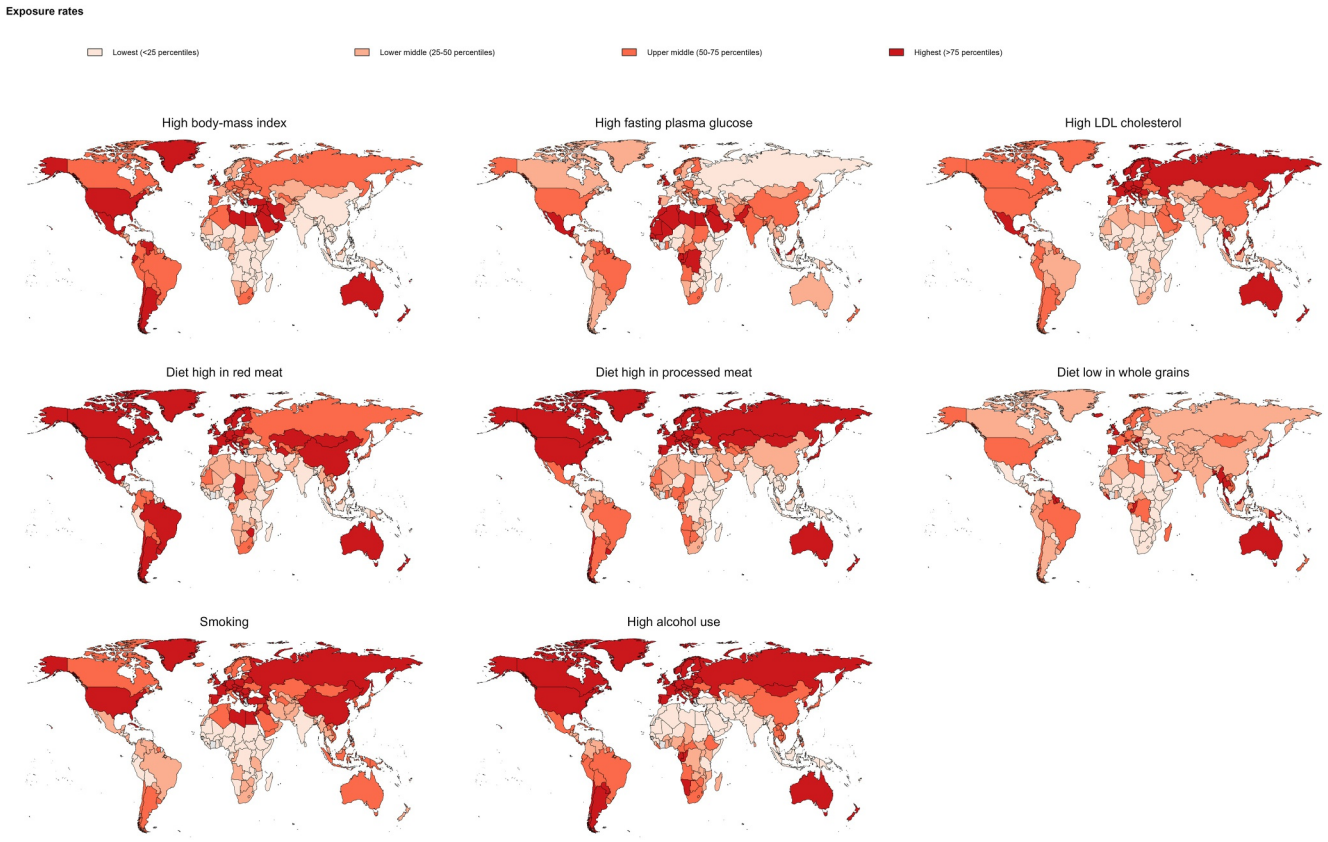

FIGURE 5 | The exposure rates of risk factors across 204 countries and territories.

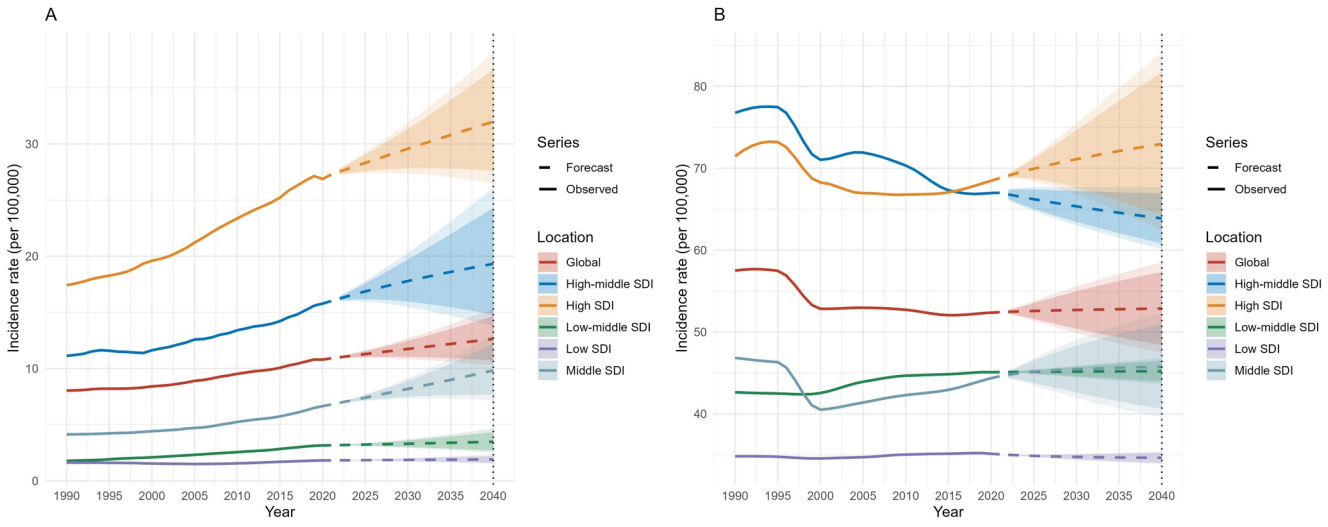

FIGURE 6 | (A) The projected incidence rate of pancreatic cancer till 2040; (B) The projected incidence rate of pancreatitis till 2040.

Globally, the IR of pancreatic cancer among adults aged ≥ 25 years is projected to increase to 12.86 (95% CI: 10.56–15.16) per 100,000 population by 2040, continuing the upward trend observed in recent decades. High-SDI and high-middle-SDI regions are projected to maintain increasing trends, whereas forecasts in low- and low-middle-SDI regions remain comparatively stable over the projection period.

By contrast, the global IR of pancreatitis is forecast to remain approximately stable, reaching 52.87 (95% CI: 47.48–58.49) per 100,000 population by 2040 (Figure 6). High and high-middle SDI regions are projected to retain the highest incidence levels, while low SDI regions are likely to retain low and stable incidence rates.

4 | Discussion

Our study provides a comprehensive assessment of the joint global epidemiology, co-occurrence patterns, and associated risk factors of pancreatic cancer and pancreatitis, as well as forecasts of their future burden through 2040. We observed clear socio-demographic gradients, with high SDI countries, particularly those in North America and Europe, bearing the highest burden of both conditions, while low-SDI countries, especially in Africa, predominantly exhibited a dual-low co-occurrence pattern. These co-occurrence profiles closely mirrored the distribution of major risk exposures, which were highly concentrated in high-SDI settings. Moreover, our projections indicate that these disparities in disease burden are likely to persist, which highlights the urgent need for coordinated, targeted prevention strategies worldwide.

Our findings were highly consistent with previous global assessments, indicating that the highest incidence rates of both pancreatic cancer and pancreatitis are concentrated in high-SDI regions, where population aging and the cumulative exposure to key lifestyle and metabolic risk factors are particularly prominent [4, 14]. Notably, countries with high and high-middle SDI levels were more likely to fall into co-occurrence patterns characterized either by dual-high incidence with only moderate temporal increases or by dual-high incidence with rapidly rising trends. The distinct changing patterns within high SDI countries likely reflect the disparities in the accessibility and quality of prevention programs, risk factor management and healthcare infrastructure. For example, *Pancreatic Cancer Europe* has highlighted unequal approaches to prevention, screening, diagnostics and treatment across European countries, identifying unstandardized cancer care and substantial variation in investment and policy focus on pancreatic cancer as emerging challenges [22, 23]. These disparities are particularly salient for pancreatitis, where alcohol remains a major driver and the alcohol-attributable burden is disproportionately concentrated in Eastern Europe, consistent with longstanding high per capita consumption and heavy episodic drinking patterns [24]. At the same time, country examples suggest that stronger prevention and care pathways can coincide with declining pancreatitis incidence. For example, a large U.S. claims-based analysis reported decreasing adult acute pancreatitis incidence from 2007 to 2014 and a concurrent decline in chronic pancreatitis incidence, plausibly reflecting shifts in risk-factor profiles and improvements in clinical management pathways [25]. Similarly, in China, a marked decline in the age-standardized pancreatitis burden was reported over the past 2 decades, which has been linked to healthcare advances and broader improvements in prevention and management [26]. Together, these findings reinforce that upstream risk-factor control is essential for reducing the burden of pancreatic diseases in higher-SDI settings, yet substantial disparities in prevention capacity and implementation persist across countries.

On the other hand, the lowest incidence rates of both conditions were consistently reported in Sub-Saharan African regions. While a historically lower prevalence of certain risk factors may contribute to lower incidence in some settings, these estimates should be interpreted cautiously because they may also reflect under-ascertainment resulting from limited diagnostic capacity, fragmented cancer registration, and competing health priorities. Recent reviews have highlighted that pancreatic cancer in sub-Saharan Africa is characterized by late presentation, restricted access to cross-sectional imaging and pathology, and incomplete vital and cancer registries [27]. Notably, several countries in South and Southeast Asia and Oceania exhibited rapid increases in both pancreatic diseases, which may reflect changing underlying risk profiles alongside improvements in case detection and reporting over time. These trends are consistent with a broader epidemiological transition in many low-SDI countries, characterized by rapid urbanization, shifts toward energy-dense, ultra-processed diets, and declining physical activity, which together are driving sharp increases in overweight, obesity and type 2 diabetes [28, 29]. Collectively, these observations suggest that the current dual-low co-occurrence patterns in many low-SDI countries may mask a substantial and growing underlying burden, underscoring the need to strengthen non-communicable disease surveillance, risk factor control and diagnostic capacity in these settings.

We identified similar risk-exposure profiles associated with pancreatic cancer and pancreatitis incidence at the population level. Our results are largely concordant with existing individual-level cohort and meta-analytic evidence [30, 31]. Smoking and alcohol use were well-established risk factors for pancreatic diseases. Data from the International Pancreatic Cancer Case–Control Consortium (PanC4) reported odds ratios for pancreatic cancer of approximately 2.2 among current cigarette smokers and 1.6 among individuals consuming ≥ 9 drinks per day [30, 32]. Consistent with this, meta-analyses have demonstrated substantially higher risks of both acute and chronic pancreatitis among heavier smokers and drinkers [33, 34]. Westernized dietary patterns, particularly diets rich in red and processed meat, have also been associated with higher risks of both pancreatic cancer and pancreatitis [35, 36]. On the other hand, recent large-scale population-based studies indicated that healthier dietary patterns, including diabetes-prevention diets, Mediterranean-style diets and higher overall diet quality scores are linked to lower pancreatic cancer risk [37–39]. Obesity provides another key mechanistic link, promoting chronic low-grade inflammation, altering adipokine and insulin signaling, and impairing or deregulating autophagy, thereby creating a biological milieu that favors the initiation and progression of pancreatic disease [40, 41]. A large pooled analysis of 32 prospective cohort studies reported that pancreatic cancer risk

increases by roughly 10% for each 5-unit increment in BMI, while data from previous GBD studies also reported a sustained risen burden of obesity-attributed pancreatic cancer burden [42, 43]. Diabetes, pancreatitis, and pancreatic cancer are linked by complex, partly bidirectional relationships. Meta-analyses indicate that diabetes, and prediabetes are associated with a higher risk of incident pancreatic cancer [44, 45]. Pancreatic cancer can also induce or worsen dysglycaemia, likely via paraneoplastic metabolic and inflammatory mechanisms rather than simply pancreatic tissue destruction [46]. Diabetes/hyperglycaemia is also associated with pancreatitis, with evidence often stronger for acute than chronic pancreatitis. Accordingly, associations between high fasting glucose and pancreatitis may partly reflect a greater contribution of acute pancreatitis within aggregated pancreatitis outcomes [47, 48]. Overall, the convergence of risk factors for pancreatitis and pancreatic cancer highlights a critical opportunity for targeted prevention strategies, shifting the focus to systematically modifying the common upstream drivers of pancreatic pathology.

Our study has several implications for integrated, targeted prevention strategies. Our results support prioritizing risk-stratified approaches in settings where the joint burden of pancreatitis and pancreatic cancer is high or increasing, particularly in high-SDI countries. Given that population-based screening is not recommended for average-risk adults, these settings are where targeted surveillance is most likely to yield meaningful benefits. In particular, high-risk individuals, especially patients with non-biliary acute pancreatitis and those with chronic pancreatitis, may warrant consideration for structured surveillance and expedited diagnostic evaluation, given evidence that targeted programs can increase detection of earlier-stage, and improve prognosis outcomes [49]. On the other hand, in many low-income settings, strengthening infrastructure for routine disease monitoring (e.g., improved case ascertainment, registry capacity, and diagnostic access) is essential to enable timely identification of pancreatitis and pancreatic cancer and to support implementation and evaluation of prevention programs. Moreover, our findings highlight the importance of primary prevention efforts targeting shared modifiable risks for population-level health gains. Tobacco control and smoking cessation, along with harmful alcohol-use reduction, should remain core components of pancreatic disease prevention. In parallel, rising metabolic risks, particularly obesity and diabetes, call for integrated prevention and chronic-care pathways that link risk-factor management with early identification and treatment. This is especially relevant for middle-SDI countries, where the burden is increasing rapidly but management of these risk exposures often lag behind [50]. Finally, emerging imaging and data-driven risk stratification tools, including machine learning algorithms and multi-omics, may further refine risk assessment and screening, but they require rigorous external validation, assessment of real-world performance and evaluation of cost-effectiveness across populations before broad adoption [51, 52]. Taken together, these implications support integrated pancreatic disease control strategies that combine upstream risk reduction, improved surveillance capacity, and targeted early-detection pathways tailored to local context.

Several limitations should be considered. First, GBD estimates integrate heterogeneous data sources and modeling, and may underestimate the true burden in settings with limited diagnostic capacity and incomplete registration, particularly in low-SDI countries. Such differential data completeness may bias incidence and EAPC estimates and, in turn, influence cluster assignment and the apparent temporal stability of the dual-low cluster observed in parts of sub-Saharan Africa. Second, pancreatitis was defined as the aggregate of acute and chronic pancreatitis, which may mask subtype-specific epidemiology, temporal patterns, and risk profiles. Acute pancreatitis is typically episodic and etiology-dependent, and any excess pancreatic cancer diagnoses may be concentrated shortly after an acute event, partly reflecting reverse causation or diagnostic intensity. In contrast, chronic pancreatitis reflects persistent inflammatory injury and is associated with a more sustained elevation in pancreatic cancer risk and a distinct exposure profile. Aggregating these subtypes may therefore dilute subtype-specific trends and obscure associations with exposures that differentially influence acute versus chronic disease. This is particularly relevant for BMI and diet-related exposures, which may show heterogeneous associations with acute pancreatitis versus chronic pancreatitis, as pooled data could attenuate or misattribute these associations. Third, analyses were conducted at the national level and therefore do not capture potentially large subnational variation in burden, risk exposures, or healthcare access. Fourth, our machine-learning and regression analyses were based on country-level ecological data. Therefore, the identified relationships reflect population-level associations rather than causal effects, and individual-level inferences cannot be made. Fifth, the cross-country comparability of exposure estimates may be imperfect, particularly for dietary and alcohol-related measures, which may differ in reporting practices across settings. As the risk exposures are estimated as prevalence metrics from pooled evidence, variations in the underlying data coverage and quality across countries may influence the precision and validity of these exposure estimates. Lastly, our forecasting was based on time-series patterns in historical incidence rates and did not incorporate mechanistic drivers or scenario-based changes. Future trajectories could deviate substantially if prevention policies, diagnostic practices, or surveillance intensity changes, which are effects that may differ by SDI strata. In lower-SDI settings, expansion of diagnostic capacity and cancer registration could increase case ascertainment and raise observed incidence even without proportional changes in underlying risk, whereas in higher-SDI settings, strengthened upstream risk prevention could attenuate longer-term increases.

In conclusion, our study systematically examined the joint burden, co-occurrence patterns and associated risk factors of pancreatic cancer and pancreatitis, and projected their future incidence to 2040. High-SDI countries, including high-income North America and much of Europe, consistently exhibited dual-high co-occurrence profiles, whereas lower-SDI settings, particularly sub-Saharan Africa, predominantly showed dual-low patterns that closely paralleled the global distribution of shared risk exposures. These findings underscore the need for strengthened, context-specific prevention strategies that integrate targeted disease surveillance with comprehensive lifestyle and metabolic risk-reduction policies to reduce the joint burden of pancreatic diseases worldwide.

Author Contributions

Laiang Yao conceived, developed this study design and collected, analyzed, interpreted the data, and wrote and revised the manuscript. Cuiyue Wang, Fansheng Meng and Shuai Shao provided technical support, and critical feedback for the revisions of this study. Xiangming Xu provided project administration, validation, and wrote and revised the manuscript. All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript.

Funding

This project is supported by the Natural Science Foundation of Shandong Province, China (Grant No. ZR2024QH551).

Ethics Statement

The Global Burden of Disease Study obtained ethical approval from the University of Washington. Our study did not require ethical approval.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in the Global Health Data Exchange at https://gbd2021.healthdata.org/gbd-results.

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Supporting Information

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