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Temporal trends in cross-country inequalities of early-onset pancreatic cancer: a comprehensive analysis for the global burden of disease study 2021

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By 2040, pancreatic cancer is expected to become the second leading cause of cancer-related deaths in the U.S., with early-onset pancreatic cancer (EOPC) cases rising among adolescents and young adults. This study uses the global burden of disease (GBD) 2021 dataset to examine global, regional, and national EOPC trends and predicts the burden through 2050. The analysis covers EOPC burden from 1990 to 2021, focusing on age-standardized prevalence rate (ASPR), incidence rate (ASIR), mortality rate (ASMR), and disability-adjusted life years rate (ASDR). Annual percentage change (APC) and average annual percentage change (AAPC) were calculated via joinpoint regression. Clustering and frontier analysis based on the sociodemographic index (SDI) assessed the link between development levels and health outcomes. We used WHO-recommended health equity methods to quantify EOPC burden disparities and applied a Bayesian age-period-cohort (BAPC) model to project trends. In 2021, EOPC cases rose to 42,254, a 73% increase from 1990, while deaths reached 26,996, up 57%. Although ASIR, ASMR, and ASDR declined, ASPR rose (EAPC = 0.1). Central and Eastern Europe had the highest EOPC burden, with the fastest growth in Australasia (EAPC = 2.78) and Western Sub-Saharan Africa (EAPC = 2.25). Males had about double the burden of females, though female prevalence increased. The widening gap in health burden between low- and high-SDI regions is especially concerning. While EOPC currently affects high-SDI countries the most, there is a clear trend over time showing a gradual shift of EOPC burden towards low-SDI countries. By 2050, ASIR, ASPR, ASMR, and ASDR are projected to stabilize, with cases increasing until 2036, then decreasing. High-SDI countries bear a disproportionately high EOPC burden, with significant diagnostic and management challenges, particularly in Central and Eastern Europe. Rising global EOPC prevalence highlights the need to identify burden differences and risk factors across countries to develop targeted prevention and control strategies.

Keywords Early-onset pancreatic cancer, Global burden of disease study 2021, Epidemiological trends, Future predictions, Sociodemographic index analysis, Health inequalities

Pancreatic cancer (PC) is a highly malignant gastrointestinal tumor with a five-year survival rate of less than 12%[1,2]. PC is projected to become the second leading cause of cancer-related deaths in the United States by 2040[3]. Over the past 30 years, the number of new cancer cases in individuals under 50 has increased by 79%[4]. Early-onset pancreatic cancer (EOPC), diagnosed below age 50, has significantly increased[5–8]. Pancreatic ductal adenocarcinoma (PDAC) remains the predominant subtype of EOPC. However, pancreatic neuroendocrine tumors (PanNETs), though less common overall, constitute a relatively higher proportion of cases in younger

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patients. Early-onset PanNET cases are often associated with hereditary syndromes, such as multiple endocrine neoplasia type 1 (MEN1). A study reported that the incidence of PanNETs was 42.6% among patients aged 50 years or younger, compared to 34.5% in those over 50 years[9–11].

EOPC cases are mostly sporadic, with non-genetic factors such as alcohol consumption, smoking, and high body mass index (BMI) potentially playing crucial roles[12–14]. Compared to late-onset pancreatic cancer (LOPC), EOPC often exhibits more aggressive tumor biology, leading to a disproportionately high disease burden, especially in years of potential life lost (YPLL)[15]. This burden is particularly high in Asia and Central Europe, reaching 37% and 40% respectively[16].

The Global Burden of Disease (GBD) study, initiated in 1991, uses data from 328,938 different sources in its latest iteration to provide a comprehensive empirical assessment of global health[17,18]. Previous studies have assessed the burden and trends of EOPC only up to 2019[19,20]. The COVID-19 pandemic from 2019 to 2021 caused a significant setback in global health over the past 71 years, disrupting cancer screening and diagnosis, and interrupting care, thereby exacerbating global healthcare inequalities[18,21–24]. Although some studies based on national databases found that surgical mortality and survival rates of PC patients were not significantly affected during the COVID-19 pandemic, there has been no comprehensive analysis based on updated metrics to assess the epidemiological trajectory and predict long-term outcomes of EOPC populations[25–27]. The distribution of all-causes and communicable, maternal, neonatal, and nutritional diseases (CMNNDs) burden were more concentrated in low sociodemographic index (SDI) countries. However, the burden of non-communicable diseases was concentrated in high-SDI countries, including cancers[28,29].In high-income countries, EOPC has also emerged as a significant contributor to the disease burden. Consequently, current studies are fragmented and outdated.

This study comprehensively updates the global, regional, and national burden of EOPC from 1990 to 2021 within the GBD2021 framework. It examines age and sex distributions and explores the relationship between disease burden and sociodemographic development levels through frontier analysis. Additionally, we predict the burden status of EOPC by 2050, offering a unique perspective on current and future challenges. This study aims to fill the evidence gap in the global prevention and control of EOPC, improve the health outcomes of young patients, and guide health resource allocation.

Methods

Study population

The data for EOPC in this study are derived from GBD2021, which shows the latest trends of 21 GBD regions and 204 countries and territories at regional, national, and local levels from 1990 to 2021. In previous studies, EOPC is defined as occurring in patients aged 15–49[30,31]. We retrieved data on the incidence, prevalence, mortality, and disability-adjusted life years (DALY) of pancreatic cancer patients aged 15–49 from the GBD database, covering the period from 1990 to 2021. These metrics were adjusted for various populations worldwide using a standard population[32]. All this data is accessible for free access through the Global Health Data Exchange (https://ghdx.healthdata.org/gbd-2021/sources), which provides the world's most comprehensive catalog of surveys, censuses, vital statistics, and other health-related data[15].

Group description

After obtaining the age-standardized incidence rate (ASIR), age-standardized prevalence rate (ASPR), age-standardized mortality rate (ASMR), and age-standardized DALY rate (ASDR), we calculated the annual percentage change (EAPC) for these metrics. EOPC patients were divided into seven age groups: 15–19, 20–24, 25–29, 30–34, 35–39, 40–45, and 45–49 years. We compared the disease burden across different age groups and genders.

Joinpoint regression analysis

In assessing temporal trends of disease burden, this study employed the Joinpoint regression model, a robust analytical tool widely utilized for dissecting temporal variations in disease epidemiology. The Joinpoint model operates by identifying "joinpoints" within the dataset, effectively partitioning the time series into distinct linear segments. In our analysis, these joinpoints correspond to pivotal years marking significant shifts in the epidemiological trajectory of EOPC. The model employs maximum likelihood estimation to optimize the fit of linear trends within each segment while constraining the number of joinpoints to prevent overfitting.

During the analysis, two key indicators are mainly focused on: the Annual Percent Change (APC) and the Average Annual Percent Change (AAPC). The APC quantifies the annual rate of change in EOPC indicators between consecutive time points, providing precise insights into the direction and magnitude of trends within each segment. For instance, a positive APC with a 95% confidence interval (CI) lower bound greater than 0 indicates a statistically significant upward trend, whereas a negative APC with a 95% CI upper bound less than 0 signifies a downward trend. The AAPC, on the other hand, integrates data across the entire study period (1990–2021), offering a comprehensive assessment of the average annual change over time.

SDI and frontier analysis

SDI evaluates regional or national social and demographic development. It combines per capita income, average educational attainment of those over 15, and fertility rate under 25. SDI values range from 0 to 1, with regions classified into five categories. Low SDI areas, below 0.45, have low income, limited education, and high fertility. Low-middle SDI regions, between 0.45 and 0.61, show some economic and educational progress but still have relatively high fertility. Middle SDI regions (0.61–0.69) display more balanced development, while high-middle SDI areas (0.69–0.81) have high income, better education, and lower fertility. High SDI regions, 0.81 and above, are characterized by advanced economies, high-quality education, and low fertility. SDI values for each country can be found in the IHME data section of the GBD database, widely used in global health to study disease and healthcare disparities.

In this study, frontier analysis measures the gap between expected and actual EOPC burden. First, an expected EOPC burden model is built for each SDI-classified region, considering historical data from similar-development regions, healthcare infrastructure, screening capabilities, and lifestyle risk factors. The actual EOPC burden is based on our study data. Comparing the two reveals regions with higher or lower-than-expected EOPC burden. For areas with a large gap, we analyze factors like healthcare policies, environmental exposures, and genetic predispositions. These insights help formulate targeted health policies to reduce the gap, such as improving early-detection or promoting lifestyle changes in regions with a higher-than-expected EOPC burden[33,34].

Health inequalities and decomposition analysis

Monitoring health inequalities is essential for evidence-based health planning, as it can inform policies and programs aimed at reducing disparities in health outcomes. In this study, we employed two widely used metrics—the Slope Index of Inequality (SII) and the Concentration Index (CI)—to evaluate the distributional inequality of the EOPC burden across countries. The SII was calculated by regressing age-standardized DALYs rates of EOPC against a relative position scale linked to sociodemographic development, which was defined by the midpoint of the population's cumulative distribution ordered by SDI. To account forheteroskedasticity, a weighted regression model was applied. The CI was determined by integrating the area under the Lorenz curve, constructed using the cumulative percentage of EOPC DALYs rates, as well as the cumulative relative population distribution ranked by SDI.

Decomposition analysis broke down the changes in EOPC mortality into population growth, aging, and epidemiological changes, quantifying each factor's impact on disease burden. If $r < 0.05$, the difference was considered statistically significant[35]. All analyses were performed using joinpoint 5.2.0 (released June 4, 2024) and R software version 4.4.0 (released April 24, 2024).

Bayesian age-period-cohort model analysis

This study aims to provide an in-depth analysis of the incidence trends of EOPC by employing a Bayesian Age-Period-Cohort (BAPC) model. Grounded in Bayesian theory, this model innovatively integrates three critical dimensions—age, period, and cohort—into a unified analytical framework.

1. Age effect: Captures individual physiological changes over time and the cumulative impact of prolonged exposure to various carcinogenic risk factors.
2. Period effect: Encompasses macro-level factors that uniformly influence the entire population during specific time intervals, including advancements in medical technology, evolving societal environments, and shifts in public health policies.
3. Cohort effect: Focuses on individuals born in the same period, accounting for shared life experiences during their formative years that may influence EOPC risk.

The model utilizes Markov Chain Monte Carlo (MCMC) algorithms to iteratively sample from the posterior distribution of parameters. Through this process, precise estimates of age, period, and cohort effects are derived, enabling robust predictions of EOPC incidence trends under varying future conditions.

Patient and public involvement statement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Global burden of EOPC

Globally, the number of EOPC cases in 2021 was estimated at 42,254 (95% CI 38,611–5,893), representing a 73% increase from 24,480 cases (95% CI 23,000–26,034) in 1990 (Table S1). The ASPR increased from 1.04 per 100,000 (95% CI 1.03–1.06) in 1990 to 1.09 (95% CI 0.81–1.38) in 2021, with an EAPC of 0.1 (95% CI 0.07–0.12) (Table S2). Notably, while the case number and ASPR for males were nearly twice those for females, the EAPC for males showed a declining trend, whereas the EAPC for females exhibited an increasing trend (Fig S1). Mortality data indicated that EOPC caused 26,996 deaths in 2021 (95% CI 24,493–29,598), a 57% increase from 17,193 deaths (95% CI 16,069–18,432) in 1990 (Table S3). The number of DALYs due to EOPC increased from 832,544 (95% CI 777,154–893,199) in 1990 to 1,285,174 (95% CI 1,164,116–1,407,685) in 2021, a 54% increase. However, the ASDR decreased over the past 30 years (EAPC = −0.3; 95% CI −0.37 to −0.24), with females showing a more significant decline than males (Table S4).

Differences in the burden of EOPC by sex and age group

Figure S2 illustrates the heterogeneity in EOPC burden trends by gender and age group globally in 2021. EOPC incidence, prevalence, mortality, and DALYs increase with age, peaking at 45–49 years. EOPC cases below 30 years are minimal and grow slowly. The EOPC burden rises rapidly from age 30, peaking at 45–49 years. Across all age groups, males have higher incidence, prevalence, mortality, and DALYs than females. Notably, the gender difference is minimal between ages 15–29, but from age 30, male cases surge, with the burden difference between genders becoming increasingly significant with age.

Regional and National burden of EOPC

At the regional level in 2021, Western Europe (2.69, 95% CI 1.69–3.69) and Australasia (2.68, 95% CI 1.39–3.96) had the highest ASPRs among the 21 GBD regions (Table S1). Eastern Europe and Central Europe had the highest ASIR, ASDR, and ASMR but were among the only three regions showing a slight decrease in prevalence from 1990 to 2021 (EAPC = -0.84 and − 0.53, respectively). Globally, EOPC prevalence generally increased, with Australasia (EAPC = 2.78) and Western Sub-Saharan Africa (EAPC = 2.25) showing the most significant growth. Western Sub-Saharan Africa also had the highest increases in incidence, mortality, and DALYs. Conversely, South Asia and Western Sub-Saharan Africa had the lowest EOPC burdens in 2021, consistent with the spatial distribution in 1990. Compared to 1990, Eastern Europe, Central Europe, and High-income Asia Pacific saw the fastest declines in ASIR, ASDR, and ASMR (Fig. S3–S6).

At the national level, detailed incidence, prevalence, mortality, and DALYs in 204 countries and regions in 2021 are shown in Fig. 1, revealing significant variations in EOPC burden among countries. The top five countries with the highest prevalence in 2021 were Saint Lucia, Equatorial Guinea, Guam, Gambia, and Andorra.

Association of burden in EOPC with SDI, frontier analysis and cross-country inequality analysis

We investigated the association between ASR and the SDI in 204 countries and regions with different SDI levels in 2021. At the regional level, there was a strong positive correlation between ASPR and SDI ($R = 0.89$, $p < 2.2e{-16}$), which was statistically significant (Fig. 2). Notably, although ASIR ($R = 0.74$, $p < 2.2e{-16}$), ASMR ($R = 0.63$, $p < 2.2e{-16}$), and ASDR ($R = 0.62$, $p < 2.2e{-16}$) also showed a positive correlation with SDI, they exhibited different growth patterns compared to ASPR. Initially, they increased with rising SDI, peaking in Eastern Europe at an SDI of approximately 0.7 (ASIR = 2.1/100,000, ASPR = 2.5/100,000, ASMR = 1.9/100,000, ASDR = 92.5/100,000). With further increases in SDI, ASIR, ASMR, and ASDR declined rapidly, a pattern more pronounced in males, while females showed relatively stable growth. Additionally, the positive correlation trend between ASR and SDI was more significant in females. Cluster analysis of the 204 countries and regions confirmed these patterns at the national level (Fig. S7–S8).

To further assess the effectiveness of EOPC prevention and control efforts under the current level of social development in a country and identify potential areas for reducing disease burden, we conducted a frontier analysis of SDI with ASIR, ASMR, ASPR, and ASDR using GBD data from 1990 to 2021 (Fig. 3). In the figure, the black boundary line represents the countries and regions with the best improvement in the four disease

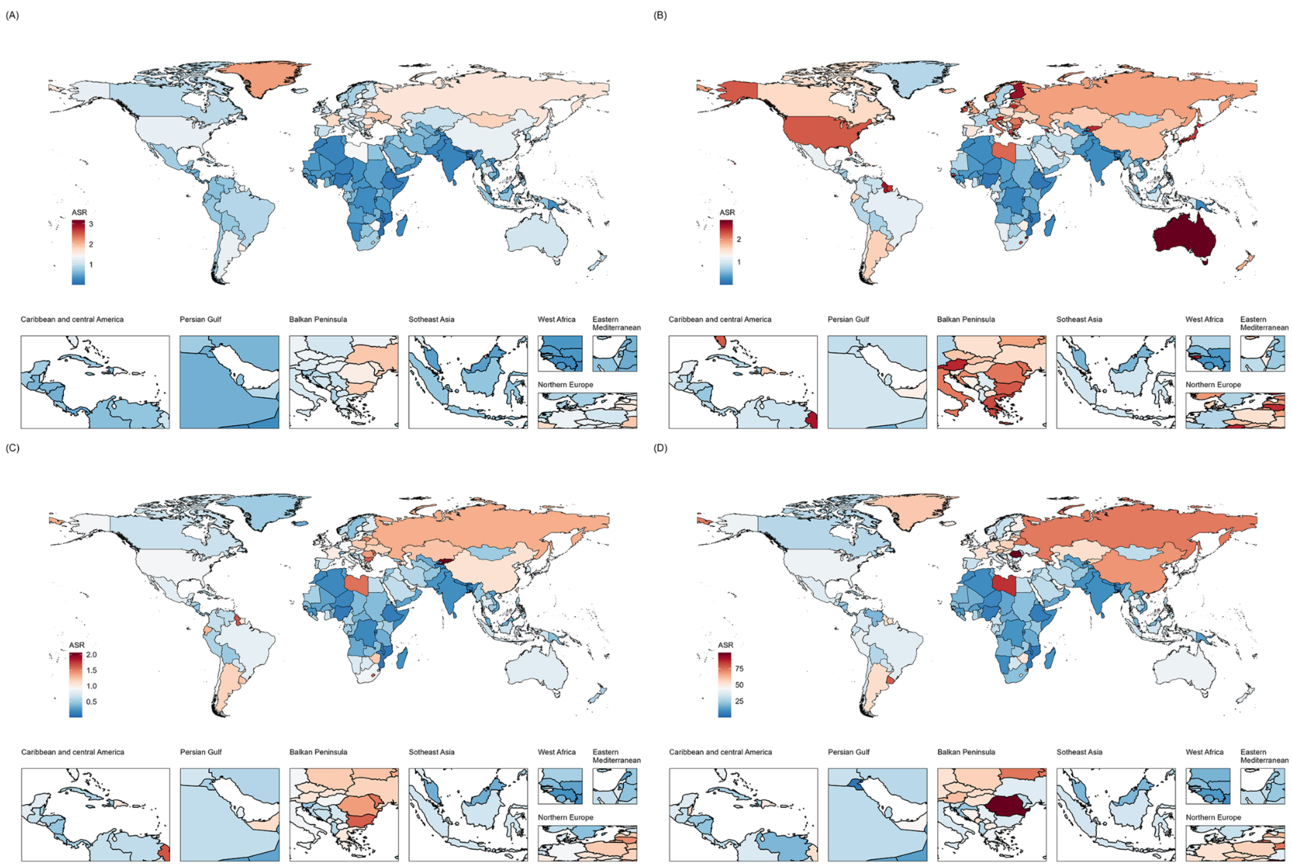

Fig. 1. Global distribution of early-onset pancreatic cancer burden in 2021. (**A**) Age-standardized incidence rates; (**B**) Age-standardized prevalence rates; (**C**) Age-standardized mortality rates; (**D**) Age-standardized disability-adjusted life-years rates.

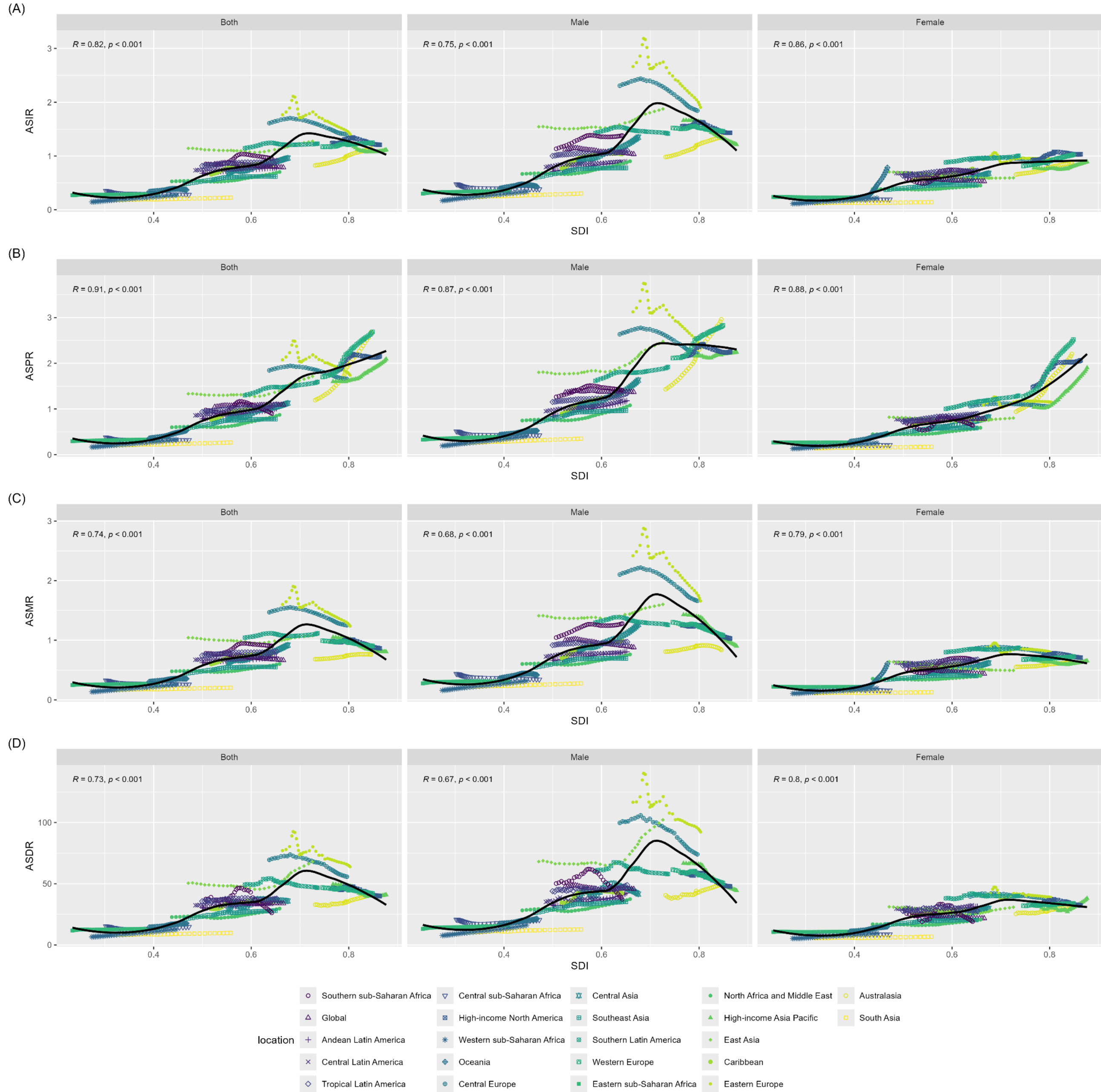

Fig. 2. Regional sex-specific associations of early-onset pancreatic cancer with SDI, 1990–2021. (**A**) Age-standardized incidence rates; (**B**) Age-standardized prevalence rates; (**C**) Age-standardized mortality rates; (**D**) Age-standardized disability-adjusted life-years rates. SDI, sociodemographic index.

burden indicators at the same SDI level. The distance of other countries from the upper boundary line represents the effective difference, indicating the gap between their current disease burden and the best achievable burden status. For example, in terms of ASDR, the top 10 countries with the most significant effective difference (range: 65.66–99.52) included Romania (99.52), Libya (85.47), Northern Mariana Islands (83.57), Armenia (81.1), Uruguay (78.33), Belarus (73.88), China (69.03), Palau (68.12), Saint Lucia (67.38), and Eswatini (65.66) (Tables S5-S8). These countries had much higher EOPC DALYs compared to other countries with comparable sociodemographic resources. Conversely, the top 10 countries with the smallest effective difference in ASDR (range: 0-5–03) were Somalia (0), Niue (1.31E-09), Tokelau (4.42E-06), Niger (2.24), Mozambique (2.71), Nigeria (3.80), Ethiopia (3.82), Kuwait (4.06), Bangladesh (4.82), and Malawi (5.03).

Generally, countries with higher SDI have more socio-demographic resources at their disposal, and the effective difference tends to be smaller. It is noteworthy that some developed countries, such as Japan, Ireland, and Norway, showed an increased EOPC burden and an increased effective difference that did not match their level of social prosperity. Conversely, some countries with previously perceived low social development levels,

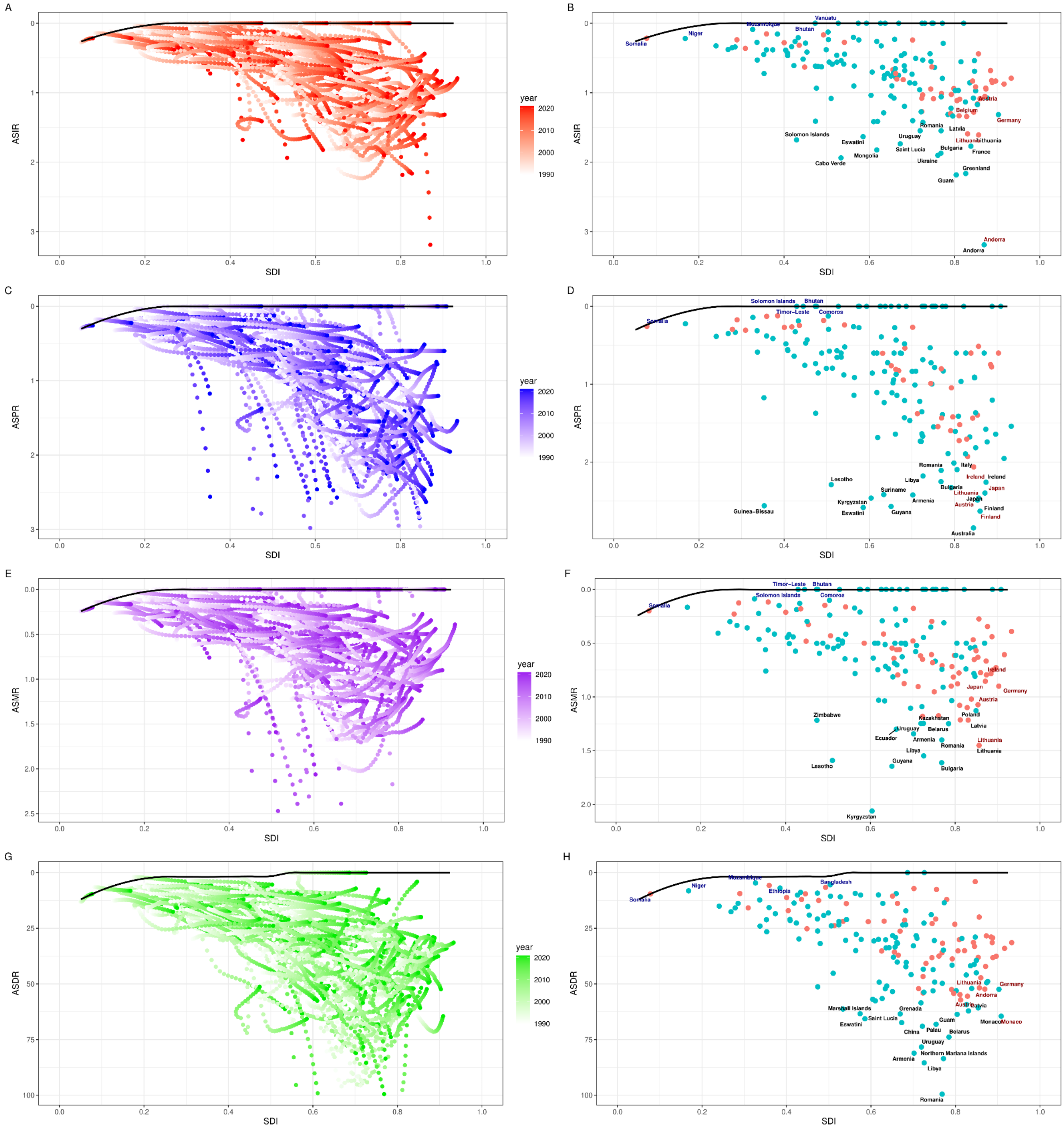

Fig. 3. The frontier analysis in (**A**) and (**B**) applies ASIR, in (**C**) and (**D**) uses ASPR, in (**E**) and (**F**) employs ASMR, and in (**G**) and (**H**) utilizes ASDR. In graphs (**A, C, E**, and (**G**), the gradual deepening of colors over time represents the year change from 1990 to 2021. In figures (**B, D, F**, and **H**), "increase" means the 2021 EOPC standardized rate in a country exceeds that in 1990, while "decrease" is the reverse. Additionally, the 15 countries with the largest ASR-frontier value gap (EF) for EOPC are highlighted in black, and the 5 countries with SDI < 0.5 and the smallest EF are in blue. The five countries with an SDI greater than 0.85 and the largest EF values are marked in red. ASIR, age-standardized incidence rate; ASPR, age-standardized prevalence rate; ASMR, age-standardized mortality rate; ASDR indicates age-standardized disability-adjusted life-years rate; and SDI, sociodemographic index.

such as Somalia, Solomon Islands, and Timor-Leste, performed surprisingly well in controlling the EOPC burden.

There was a clear indication of both absolute and relative inequalities in EOPC burden associated with SDI, with these disparities widening over time (Fig. 4). Notably, the distribution of DALYs has increasingly shifted towards countries with lower sociodemographic development levels. As SDI increased, the crude DALY rate also rose, and the SII values were higher, indicating a concentration of disease burden in countries with higher SDI. The slope index of inequality demonstrated a disparity of 34.46 DALYs per 100,000 population between the

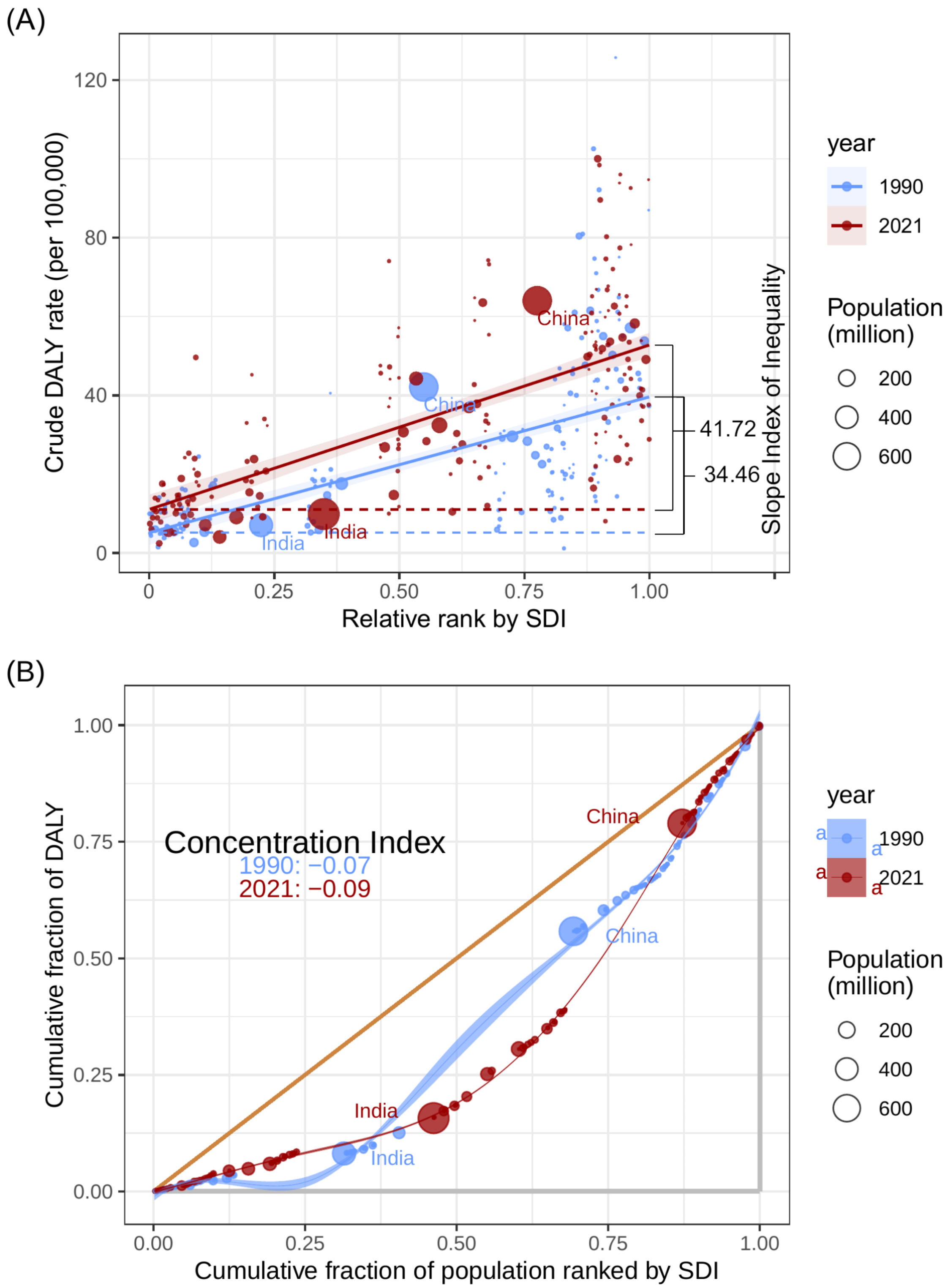

Fig. 4. Health inequality regression curves (**A**) and concentration curves (**B**) for the DALYs of EOPC, 1990 and 2021. DALYs, disability-adjusted life-years.

highest and lowest SDI-ranked countries in 1990, which further increased to 41.72 DALYs per 100,000 in 2021. In addition, the concentration index, which measures the relative inequality gradient, changed from − 0.07 in 1990 to − 0.09 in 2021, suggesting a progressively uneven distribution of EOPC burden favoring countries with lower SDI rankings.

Drivers of EOPC epidemiology: population growth, aging, and epidemiologic changes

To quantify the potential drivers of changes in EOPC disease burden, we used case decomposition analysis to estimate the relative contributions of aging, population growth, and epidemiological changes (reflecting potential changes in incidence and mortality rates standardized by age and population) to epidemiological patterns (Fig S9). Overall, the incidence of EOPC increased significantly globally and in each SDI quintile, with the most significant increase in middle SDI regions. Regarding the global increase in the incidence of EOPC from 1990 to 2021, the contributions of aging and population growth were 44.9% and 77.27%, respectively, while epidemiological changes decreased by 22.17%. Aging contributed the most to incidence growth in high SDI regions (113.49%) and high-middle SDI regions (96.59%) but almost disappeared in low SDI regions (1.60%). Population growth's driving effect on epidemiological changes was most evident in low SDI regions (82.16%). Over the past 31 years, epidemiological changes have shown a downward trend globally and in high SDI and high-middle SDI regions but an upward trend in low SDI and low-middle SDI regions.

Notably, in East Asia, at both global and regional levels, the trends in the incidence of EOPC among males and females were not significantly different, except in high-income Asia Pacific where gender differences were observed: the number of male cases decreased, mainly due to epidemiological changes (150.87%), while the number of female cases increased, primarily due to aging (423.88%).At the regional level, we observed significant epidemiological pattern differences.

Notably, most GBD regions showed an increasing trend in the incidence of EOPC, consistent with the global trend and that of each SDI quintile, except for Central Europe and High-income Asia Pacific, which showed slight negative growth. Although aging led to an increase in EOPC cases in each region, the growth rate in East Asia, Southeast Asia, and Eastern Europe far exceeded other regions. While population growth was the primary driver of increased cases in most regions, the contribution was most significant in South Asia, North Africa, and the Middle East. In Central Europe, Eastern Europe, and High-income Asia Pacific, observed population declines could offset some of the aging-driven increases in EOPC cases. Additionally, only four regions exhibited a decline in epidemiological changes, including Eastern Europe, Western Europe, High-income North America, and Southern Latin America, contributing to the decline in the incidence of EOPC by 212.14%, 103.46%, 27%, and 24.81%, respectively.

Future forecasts of global burden of disease in EOPC

We used the BAPC model to predict global EOPC burden trends by gender until 2050 (Fig. S10). The ASIR, ASPR, ASMR, and ASDR of EOPC in all populations are expected to remain relatively stable, with a slight downward trend, projected to decline to 0.59/100,000, 0.74/100,000, 0.51/100,000, and 25.96/100,000, respectively, by 2050. This decline pattern is consistent in both males and females, with females reflecting this stability more markedly. Additionally, over time, the number of age-standardized EOPC cases in the general population shows an initial annual increase, followed by a decline after 2036, a trend more pronounced in males. By 2050, we estimate there will be 32,820 EOPC cases and 22,795 deaths globally, with males consistently predominating.

Discussion

As one of the most aggressive malignant tumors, the global burden of pancreatic cancer has doubled over the past 25 years, sounding an alarm for healthcare systems[36]. The inadequate early diagnosis and treatment systems for pancreatic cancer and societal biases often lead to dismal clinical outcomes for EOPC. Although EOPC represents a relatively small proportion of all cases, it imposes a substantial disease burden but has not received sufficient attention. The COVID-19 pandemic, starting in 2019, consumed considerable medical and instrumental resources from various countries, presenting significant challenges for the surgical treatment and chemotherapy required for pancreatic cancer patients, which are critical due to high mortality risks and adverse events[37].

Currently, studies on the global burden of EOPC remain at the GBD2019 data level and have significant research gaps in predicting future trends and conducting frontier and decomposition analyses[19–21]. Therefore, this study uses the recently updated GBD2021 data to provide the latest measurements and comprehensive descriptions of the global, regional, and national burden of EOPC.

Our study examines the global, regional, and national burden distribution of EOPC by age, gender, and SDI group. In 2021, the global number of EOPC cases reached 42,254 (95% CI 38,611–5,893), a 73% increase from 1990, and the number of deaths reached 26,996 (95% CI 24,493–29,598), a 57% increase from 1990. From 1990 to 2021, the ASIR, ASMR, and ASDR of EOPC decreased, while ASPR showed an upward trend (EAPC = 0.1). This epidemiological picture of a surge in absolute case numbers but a decline in age-standardized rates reflects the overall improvement of modern healthcare systems, with encouraging progress in EOPC prevention and intervention, although significant gaps remain in identifying and caring for high-risk populations.

At the regional and national levels, EOPC also exhibits unique geographic variations in disease burden. The ASIR, ASDR, and ASMR of EOPC were highest in Eastern Europe and Central Europe, while ASPR was most prominent in Western Europe (2.69, 95% CI 1.69–3.69) and Australasia (2.68, 95% CI 1.39–3.96). These regions should be prioritized for future EOPC monitoring. This is consistent with findings based on the GBD2017 database[38]. Behavioral factors may play a crucial role in the shifting EOPC burden due to socio-economic and cultural differences among populations[39]. Consideration must be given to the quality of cancer life registration systems in low-income countries. Host mechanism research on the gut microbiome has become a focal point in the pathogenesis of many early-onset gastrointestinal cancers. For example, the high intake of red or processed meat in Western diets, high alcohol consumption in European countries, and rising obesity and diabetes rates may enhance population susceptibility to behavioral risk factors in these regions. Smoking is also a known major environmental exposure factor for EOPC. In recent years, high-income countries have made significant progress in tobacco control, leading to a decline in smoking rates, but smoking rates remain high among adolescents and young adults in East Asia, low SDI regions, and middle SDI regions[40]. The rapid industrialization and economic globalization have led to dietary shifts in many Asian countries, increasing exposure to risk behaviors and factors[41]. Policymakers in these high-burden countries and regions should focus on educational efforts for adolescents and young adults, control alcohol and tobacco consumption, promote moderate exercise, healthy diets, and maintain metabolic health to reduce the EOPC burden among obese and diabetic populations. In North Africa and the Middle East, additional measures to control substance abuse are needed[42].

While our study reports a global decline in age-standardized EOPC incidence and mortality rates, this trend contrasts with rising rates observed in high-resource settings such as the U.S. (as reflected in SEER data). This discrepancy may stem from methodological differences between GBD and registry-based studies, as well as contextual factors such as the U.S.-specific rise in obesity and metabolic disorders, advanced diagnostic capabilities, and improved cancer registration systems. Importantly, GBD's aggregation of EOPC subtypes (e.g., PDAC and PanNETs) may obscure PDAC-specific mortality trends, which dominate in the U.S. Future studies should prioritize subtype-stratified analyses to reconcile these differences.

Frontier analysis revealed that some high SDI developed countries underperformed in EOPC burden control compared to their level of social prosperity, such as Japan, Ireland, and Norway. Conversely, some low-income countries, like Somalia, Solomon Islands, and Timor-Leste, performed exceptionally well. Future research could further explore the policies of leading countries for controlling EOPC and the barriers faced by lagging countries.

One of our findings is that males consistently exhibit about twice the burden of EOPC as females across incidence, prevalence, mortality, and DALY metrics. This gender disparity may relate to lifestyle differences between young males and females. Previous studies have indicated that smoking, alcohol consumption, high BMI, and a family history of pancreatic tumors are major risk factors for EOPC, more prominently associated with males, contributing to the rising incidence of pancreatic cancer since the 20th century. Besides lifestyle factors, estrogen in females may confer a protective effect on pancreatic cells, potentially reducing the risk of malignant transformation. This protective role may partly account for the relatively lower incidence of pancreatic cancer in women of reproductive age, with a notable increase following menopause, as estrogen levels decline. Although this mechanism remains incompletely understood.Numerous studies have highlighted the role of estrogen in safeguarding pancreatic cells, primarily through estrogen-related receptors (ERRs)[43–45]. Furthermore, Natale et al. provided significant insights into nonclassical estrogen signaling, demonstrating that the G protein-coupled estrogen receptor (GPER) may exert tumor-suppressive effects in the context of pancreatic cancer[46].

However, the ASPR among female EOPC patients shows an increasing trend, while it remains stable among males, warranting attention in health monitoring. Adolescents and young adults have potential biological differences from adults, meaning that the disease mechanisms and treatment strategies for the same type of cancer might be unique[33]. Besides these non-genetic risk factors, emerging research indicates that EOPC has a distinct genomic landscape compared to LOPC[47,48]. EOPC patients have a lower frequency of KRAS mutations but a higher prevalence of SMAD4 gene mutations, which has been validated in larger cohorts. EOPC also exhibits specific patterns in gene expression, such as upregulation of the Hedgehog, TGFβ, and hypoxia pathways[14]. Given the low incidence and high screening costs of pancreatic cancer, effectively identifying high-risk populations to benefit more from screening is crucial for early diagnosis and treatment of EOPC. Current initial screening methods for high-risk populations include early imaging tests, fasting blood glucose, and HbA1c tests. However, there is a lack of large-scale cohort studies and risk assessment models for EOPC, and future promising developments include radiomics, liquid biopsy, and genetic sequencing.

Previous studies have shown that differences in social development levels significantly affect the incidence and clinical outcomes of EOPC patients[49]. Our study found that from 1990 to 2021, high SDI and high-middle SDI regions bore most of the global EOPC burden and exhibited a downward trend in incidence, mortality, prevalence, and DALY ASRs. Notably, ASRs peaked in Central Europe, Eastern Europe, and East Asia when the SDI was around 0.7. In contrast, middle SDI regions, low-middle SDI regions, and low SDI regions showed an upward trend in EOPC ASR. Moreover, SDI was significantly positively correlated with ASRs in both the overall population and male and female populations. This contrasts with the burden trends reported for other adolescent and young adult cancers[50–52]. This phenomenon may result from more advanced healthcare systems and technologies in high SDI countries, greater awareness of PC prevention and screening among young populations, and higher probabilities of reporting EOPC cases through physical examinations using CT or tumor marker tests. However, high SDI regions can also more promptly and accurately identify high-risk populations and implement treatment strategies. Therefore, in the long term, managing and controlling EOPC in high SDI and high-middle SDI regions will help reduce their high disease burden. Meanwhile, high-risk populations in low-middle SDI and low SDI regions deserve more attention and a more significant allocation of healthcare resources.

EOPC has become a significant public health concern, particularly in high-income countries, where it imposes a disproportionately high burden. Notably, while EOPC currently affects high-SDI countries the most, there is a clear trend over time showing a gradual shift of EOPC burden towards low-SDI countries. Additionally, the concentration index moved from −0.07 in 1990 to -0.09 in 2021, indicating an evolving concentration of EOPC burden in low-SDI countries. These findings highlight the need for targeted public health interventions that address the current high burden in affluent countries while preparing for the anticipated rise in EOPC cases within resource-limited regions.

Decomposition analysis showed that population growth and aging are the main drivers of the global and regional increase in EOPC burden, contributing 44.9% and 77.27% to the incidence from 1990 to 2021, respectively, while epidemiological changes (early detection and diagnosis of EOPC, thereby effectively reducing incidence) reduced by 22.17%, failing to offset the growth brought by population growth and aging. Notably, aging had a particularly significant impact on middle SDI regions, especially East Asia, combined with behavioral choices, increasing population exposure to EOPC risk factors. This may be related to the large population base in

East Asia. Therefore, considering the inevitability and difficulty of eliminating aging factors, relevant countries should focus on primary prevention and screening measures for adolescents and young adults to raise health awareness among high-risk populations, improving prognosis for this group to the greatest extent.

Our study has many strengths. To our knowledge, this is the first study to provide the latest estimates and comprehensive review of the EOPC burden based on GBD2021 data. However, like many GBD burden assessments, this study also has inherent limitations. First, the incompleteness and unavoidable quality issues of GBD data sources affect the assessment of the EOPC burden. Some low-income countries with limited health resources lack robust vital registration and cancer registration systems, leading to sparse, non-representative data and high barriers to data sharing, especially in countries severely impacted by COVID-19 lockdowns. Improvements in cancer registries and medical imaging over the study period likely contributed to the observed increase in EOPC incidence. Therefore, the increase in younger patients may be partly due to better recognition of these subtypes, rather than a true rise in disease burden.Additionally, ascertainment bias represents one of the primary limitations of this study. In less developed countries, insufficient monitoring systems, incomplete data collection, and inconsistent diagnostic standards may lead to findings that do not accurately reflect true differences. Variations in reporting methods and case definitions in these regions may introduce unknown ascertainment biases, necessitating cautious interpretation of the results. Despite using robust statistical methods to correct the model-fitted data with real-world deviations, the estimates of EOPC cases still have uncertainty intervals.Future GBD studies should prioritize the development of standardized data collection methods across regions and implement targeted strategies to enhance the reliability of data from less developed countries.

Moreover, since GBD data is modeled based on past trend analyses and covariate predictions, there is a lag, so this study does not reflect the potential impact of COVID-19 on the EOPC burden, including excess mortality, delays from diagnosis to surgery, interrupted care, and deteriorating baseline physical condition[53]. COVID-19 impact data will be included in future iterations of the GBD database, providing a clearer understanding of the pandemic's long-term impact on the EOPC burden. Additionally, although GBD provides the most comprehensive disease burden data to date at the global, regional, and national levels, there is a lack of detailed assessments of local levels and urban-rural differences. This heterogeneity of estimates hinders epidemiological analysis across regions and populations[54]. In future research, to balance this limitation, GBD developers will conduct more extensive global collaborations, include more data sources at smaller administrative levels, and combine racial distributions, social backgrounds, and environmental factors from different regions to improve data representativeness and usability[55,56]. Finally, since GBD data does not stratify EOPC cases by detailed histological subtype, possible multiple endocrine tumors may bias EOPC incidence estimates.Future updates of the GBD database with more granular data on cancer subtypes would allow for more accurate evaluations of the disease burden.

GBD's estimates of adolescent and young adult cancer burdens highlight a massive burden of excess and premature deaths among young people, which are severely underestimated compared to widely recognized infectious diseases (e.g., AIDS and other sexually transmitted diseases)[52,57,58]. Therefore, GBD collaborators advocate that, from a global perspective, to improve the prognosis of this particular population of PC patients, we can refer to the WHO's recently promoted framework for global action on childhood cancer, prioritizing the inclusion of adolescent and young adult cancers, including EOPC, into the WHO cancer control plan and universal health coverage, providing supportive physical and mental care and high-quality healthcare for EOPC patients[52,59]. Additionally, several single-center studies have shown that diagnosed EOPC patients often do not receive evidence-based treatment according to pancreatic cancer guidelines but receive more additional treatments than older PC patients[60–62]. For instance, reconstructive surgery for organ function restoration should consider long-term durability and potential impacts on appearance, partner relationships, and reproductive function[47]. Therefore, developing specific EOPC treatment guidelines is urgent.

Conclusion

Over the past 30 years, amid population expansion and aging, the rising global, regional, and national burden of EOPC has become an important public health challenge. The EOPC burden is particularly heavy in high SDI and high-middle SDI regions. The widening gap in health burden between low- and high-SDI regions is especially concerning. Risky behaviors and economic instability may play a potential role in this burden. Given the significant geographic and population heterogeneity in the EOPC burden, the targeted identification, prevention, and treatment of high-risk adolescents and young adults are urgent. This study provides new insights for policy formulation and the rational allocation of healthcare resources related to EOPC management, aiming to reduce inequalities in health outcomes.

Data availability

The datasets supporting the conclusions of this article are available in the Global Health Data Exchange (GHDx) query tool (https://ghdx.healthdata.org/gbd-2021).

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Author contributions

LLH wrote the paper. LJH generated the figures. YA and GWZ edited the paper. Each author contributed to the paper and approved the final version submitted for publication. All authors contributed to the article and approved the submitted version.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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